Peripheral nervous system and histone acetylation-related alterations of gene expression in non-lesional psoriatic skin

Dóra Romhányi

PhD Thesis

Szeged

2024

University of Szeged

Albert Szent-Györgyi Medical School

Department of Dermatology and Allergology

Doctoral School of Clinical Medicine

Peripheral nervous system and histone acetylation-related alterations of gene expression in non-lesional psoriatic skin

PhD Thesis

Dóra Romhányi

Supervisor:

Dr. Gergely Groma

Szeged

2024

TABLE OF CONTENT

LIST OF PUBLICATIONS

List of publications related to the thesis

1. Dóra Romhányi, Kornélia Szabó, Lajos Kemény, Endre Sebestyén and Gergely Groma Transcriptional Analysis-Based Alterations Affecting Neuritogenesis of the Peripheral Nervous System in Psoriasis. Life (Basel, Switzerland) 12, no. 1 (2022): 111.

https://doi.org/10.3390/life12010111

IF:3,2

2. Dóra Romhányi, Kornélia Szabó, Lajos Kemény and Gergely Groma Histone and Histone Acetylation-Related Alterations of Gene Expression in Uninvolved Psoriatic Skin and Their Effects on Cell Proliferation, Differentiation, and Immune Responses International Journal of Molecular Sciences 24, no. 19 (2023): 14551

https://doi.org/10.3390/ijms241914551

IF:4,9

List of publications not related to the thesis

1. Márta Kotormán, Dóra Romhányi, Bence Alpek, Orsolya Papp and Katalin Márton Fruit Juices Are Effective Anti-Amyloidogenic Agents. Biologia Futura 72, no. 2 (2021): 257–62.

https://doi.org/10.1007/s42977-020-00064-y. (The journal is supported by the Department of Biological Sciences of the Hungarian Academy of Sciences)

IF:-

LIST OF ABBREVIATIONS

ACTB	Actin Beta
AKT	AKT Serine/Threonine Kinase1
ANP32E	Acidic Nuclear Phosphoprotein 32 Family Member E
Arhgef11	Rho Guanine Nucleotide Exchange Factor 11
AQP3	Aquaporin 3
ATAC	Ada-two-A-containing
BRD8	Bromodomain Containing 8
CAF1	Chromatin assembly factor-1
CBP/CREBBP	CREB-binding protein
CDK1	Cyclin Dependent Kinase 1
CHAF1A	Chromatin Assembly Factor 1 Subunit A
CHD4	Chromodomain Helicase DNA Binding Protein 4
Cfl1	Cofilin 1
Cfl2	Cofilin 2
CGRP	Calcitonin gene-related protein
CSPG	Chondroitin Sulfate Proteoglycan
Crmp1	Collapsin Response Mediator Protein 1
CTBP1	C-Terminal Binding Protein 1
CXCL12	C-X-C Motif Chemokine Ligand 12
CXCR4	C-X-C Motif Chemokine Receptor 4
DCC	DCC Netrin 1 Receptor
DET	Differentially Expressed transcript
DNA	Deoxyribonucleic Acid
EGR2	Early Growth Response 2
eIF4E	Eukaryotic Translation Initiation Factor 4E
ELP3	Elongator Acetyltransferase Complex Subunit 3
EP300	E1A Binding Protein P300
ErbB2	Erb-B2 Receptor Tyrosine Kinase 2

FACT	FAcilitates Chromatin Transcription
Farp2	FERM, ARH/RhoGEF and Pleckstrin Domain Protein 2
FDR	False Discovery Rate
Fes	FES Proto-Oncogene, Tyrosine Kinase
FOXO3A	Forkhead Box O3
FOXP3	Forkhead Box P3
Fyn	FYN Proto-Oncogene, Src Family Tyrosine Kinase
FZD3	Frizzled Class Receptor 3
FZD5	Frizzled Class Receptor 5
GATAD2A	GATA Zinc Finger Domain Containing 2A
GO	Geneontology
GNAT	GCN5-related N-acetyltransferases
H	Healthy
H2AC18	H2A Clustered Histone 18
H4C14	H4 Clustered Histone 14
H2AZ1	H2A.Z Variant Histone 1
H3-3A	H3.3 Histone A
H3-3B	H3.3 Histone B
H3K27ac	histone H3 lysine 56 acetylation
H3K56ac	histone H3 lysine 56 acetylation
H3K9ac	histone H3 lysine 9 acetylation
H4K16ac	histone H4 lysine 16 acetylation
H4K5	histone H4 lysine 5 acetylation
H4K8	histone H4 lysine 8 acetylation
HAT	Histone acetyltransferase
HDAC	Histone deacetylase
HDAC1	Histone Deacetylase 1
HDAC2	Histone Deacetylase 2
HDAC3	Histone Deacetylase 3

HDAC4	Histone Deacetylase 4
HDAC5	Histone Deacetylase 5
HDAC6	Histone Deacetylase 6
HDAC8	Histone Deacetylase 8
HDAC11	Histone Deacetylase 11
HIRA	Histone cell cycle regulator
HSPA2	Heat Shock Protein Family A (Hsp70) Member 2
ID	Identity
IL-1β	Interleukin 1 Beta
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-9	Interleukin 9
IL-10	Interleukin 10
IL-12	Interleukin 12
IL-17A	Interleukin 17A
IL-23	Interleukin 23
ING3	Inhibitor of Growth Family Member 3
IPA	Ingenuity Pathway Analysis
KANSL1	KAT8 Regulatory NSL Complex Subunit 1
KAT2A	Lysine Acetyltransferase 2A
KAT5	Lysine Acetyltransferase 5
KAT8	Lysine Acetyltransferase 8
Ki-67	Marker Of Proliferation Ki-67
L1CAM	L1 Cell Adhesion Molecule
L	Lesional
Limk2	LIM Domain Kinase 2
LPS	Lipopolysaccharide
MACROH2A1	MacroH2A.1 Histone
Mapk3	Mitogen-Activated Protein Kinase 3

MBIP	MAP3K12 Binding Inhibitory Protein 1
MBP	Myelin Basic Protein
MCRS1	Microspherule Protein 1
mDC	myeloid dendritic cells
Mknk1	MAPK Interacting Serine/Threonine Kinase 1
Mlc1	Modulator of VRAC Current 1
MPZ	Myelin Protein Zero
Msrb1	Methionine Sulfoxide Reductase B1
MTA1	Metastasis Associated 1
MYST	Moz, Ybf2/Sas3, Sas2, Tip60
NCOR	Nuclear Receptor—Co-repressor
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NGF	Nerve growth factor
NL	Non-lesional
NPM1	Nucleophosmin 1
Nrp1	Neuropilin 1
Nrp2	Neuropilin 2
NSL	Non-specific lethal
NTN1	Netrin1
NURD	NUcleosome Remodeling and Deacetylase
ORF	Open Reading Frame
P53	Tumor Protein P53
Paks	P21 (RAC1) Activated Kinases
PARP1	Poly(ADP-Ribose) Polymerase 1
pDC	plasmacytoid dendritic cell
PI3K	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase
PLP1	Proteolipid Protein 1
PMP22	Peripheral Myelin Protein 22
PRX	Periaxin

PLXNA3	Plexin A3
PLXNB1	Plexin B1
PLXNB3	Plexin B3
PLXND1	Plexin D1
PMP22	Peripheral Myelin Protein 22
PWP1	PWP1 Homolog, Endonuclein
RAC1	Rac Family Small GTPase 1
RAF	Raf-1 Proto-Oncogene, Serine/Threonine Kinase
RBBP4	RB Binding Protein 4, Chromatin Remodeling Factor
Rock2	Rho Associated Coiled-Coil Containing Protein Kinase 2
RNA	Ribonucleic Acid
Rnd1	Rho Family GTPase 1
ROBO1	Roundabout Guidance Receptor 1
ROBO2	Roundabout Guidance Receptor 2
RTN4	Reticulon 4
SAGA	Spt-Ada-Gcn5 acetyltransferase
SEMA3A	Semaphorin 3A
SEMA3B	Semaphorin 3B
SEMA3D	Semaphorin 3D
SEMA3E	Semaphorin 3E
SEMA3E	Semaphorin 3F
SEMA3G	Semaphorin 3G
SEMA4D	Semaphorin 4D
SEMA5A	Semaphorin 5A
SEMA6A	Semaphorin 6A
SEMA6D	Semaphorin 6D
SET	SET Nuclear Proto-Oncogene
Shc	SHC Adaptor Protein
SIN3A	SIN3 Transcription Regulator Family Member A

SIRT5	Sirtuin 5
SIRT6	Sirtuin 6
SLIT2	Slit Guidance Ligand 2
SMRT	Silencing Mediator for Retinoid and Thyroid receptor
SP	Substance P
SPHK2	Sphingosine Kinase 2
SRA	Sequence Read Archive
STAT3	Signal Transducer and Activator of Transcription 3
TADA2B	Transcriptional Adaptor 2B
TBL1X	Transducin Beta Like 1 X-Linked
Th1	T helper 1
Th17	T helper 17
Th22	T helper 22
TLR	Toll Like Receptor
TNFα	Tumor Necrosis Factor
TMM	trimmed mean of M-values
TPM	Transcripts Per Million
Treg	Regulatory T cell
UBN1	Ubinuclein 1
UNC5A	Unc-5 Netrin Receptor A
VPS72	Vacuolar Protein Sorting 72 Homolog
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
WNT5A	Wnt Family Member 5A

1. INTRODUCTION

1.1 Psoriasis

Psoriasis is a multifactorial, polygenetic chronic inflammatory disease[1] affecting 2-3% of the world's population[2]. Psoriasis is characterized by an altered immunological response to biotic and abiotic stressors, leading to keratinocyte hyperproliferation and massive immune cell infiltration, resulting in the appearance of psoriatic plaques[3]. The most common form of psoriasis is plaque psoriasis, characterized by well-defined, silvery, scaly plaques **(Figure 1.)**, appearing mainly on the scalp, elbows, knees, and sacrum[4].

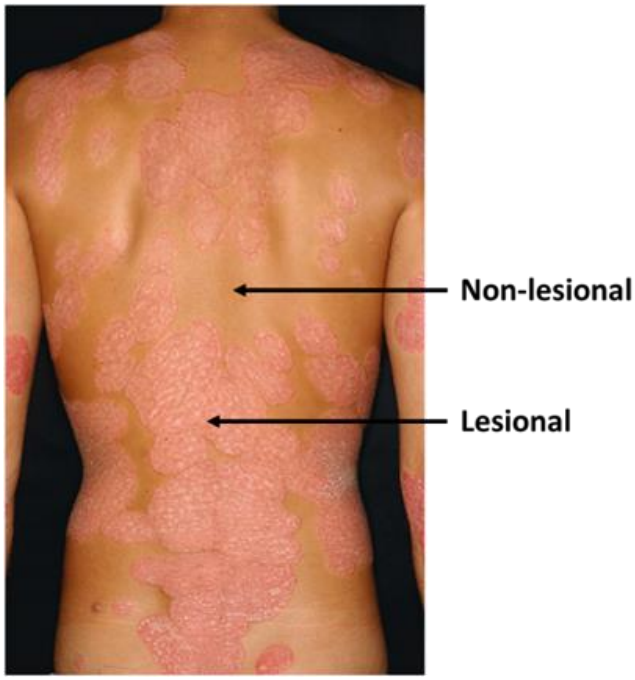


Figure 1. Skin symptoms of psoriasis. (From the archive of the Department of Dermatology and Allergology in Szeged.)

The currently accepted immunopathological theory is presented in **Figure 2**. Briefly, in response to biotic and/or abiotic stress stimulation, keratinocytes release antimicrobial peptides and their self-nucleotides, which result in the secretion of type I interferon through plasmacytoid dendritic cell activation (pDC)[5,6]. This triggers the maturation and activation of myeloid dendritic cells (mDC), which secrete TNF-α, IL-12, and IL-23 cytokines[7]. This leads to the differentiation of naïve T cells into Th1, Th17, and Th22 cells. The Th17/IL-23 axis plays a main role in plaque

psoriasis pathogenesis[8]. Cytokines secreted by Th17 cells, (e.g. IL-17A), further enhance the release of antimicrobial peptides and chemokines from keratinocytes, leading to epidermal infiltration of various immune cells[9]. This leads to the formation of microbial abscesses and keratinocyte hyperproliferation[10] **(Figure 2.)**.

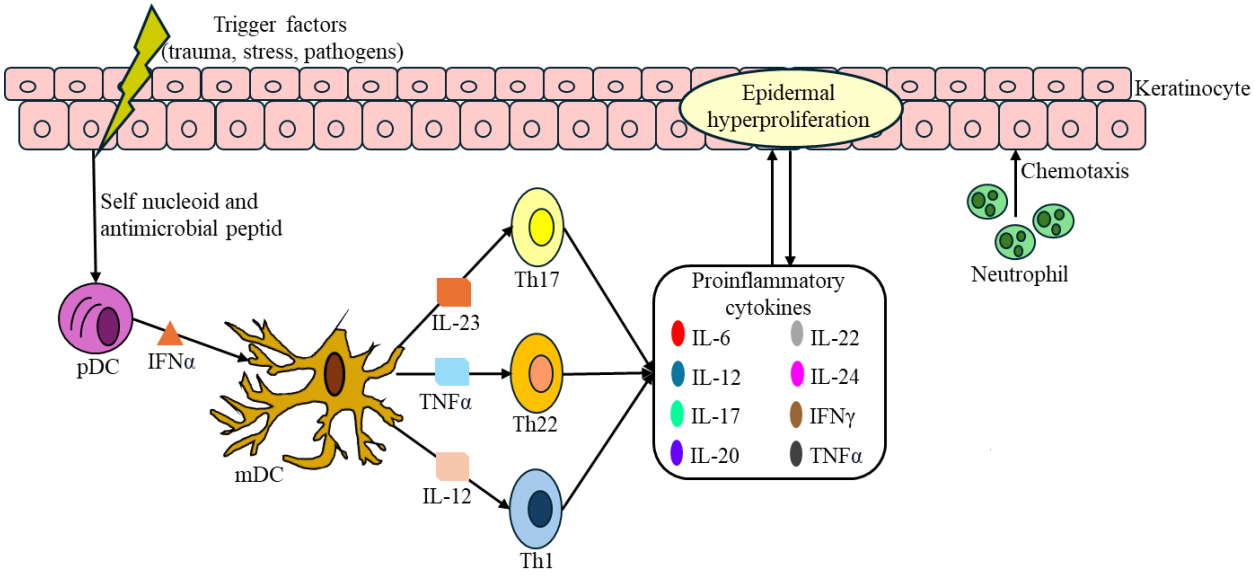


Figure 2. Schematic representation of psoriasis immunopathogenesis. (Based Kurpet K, Chwatko G 2022.[11])

1.2. Alterations of the non-lesional skin in psoriasis

Molecular alterations and abnormalities are present already in the macroscopically healthy-looking non-lesional skin. These molecular alterations can be classified into two major groups: "predisposing" alternations that contribute to the formation of lesions and "protective" alterations that participate in the maintenance of the non-lesional stage[12].

The asymptomatic non-lesional skin has a disrupted epidermal barrier, reduced lipid synthesis[13], elevated pH levels[14], and impaired angiogenesis[15] compared to healthy skin. The non-lesional skin also shows structural alterations in the dermal-epidermal junction, including basement membrane abnormalities[16,17], altered integrin expression by basal keratinocytes[18], and modified expression of specific extracellular matrix components[19,20].

Compared to healthy skin, the non-lesional skin has increased expression of innate immunity-related genes, and increased activation of IL-17 signaling pathways[21,22], consistent with the appearance of activated dendritic[23] and T cells[22]. In addition, altered expression of anti-

inflammatory regulators[24], stress-inducible non-coding RNAs[25,26] and transcription factors[27] affecting anti-inflammatory processes is also detectable in non-lesional skin compared to healthy individuals.

1.3. Abnormalities of the peripheral nervous system in psoriasis

One of the widely known characteristics of non-lesional skin is the Koebner phenomenon, the development of lesions in response to mechanical provocations or stress[28] likely due to elevated immune response and increased keratinocyte proliferation[13,29]. External, potentially dangerous stimuli are not only sensed by keratinocytes but also by cutaneous axons of neurons, among other cells. Keratinocytes become activated by these insults, produce pro-inflammatory cytokines[30], and may activate and modulate neuronal functions[31]. An example of this is the altered thermosensation in psoriatic tissues[32].

Several studies report remission of lesional plaques in patients with psoriasis in areas affected by peripheral nervous system dysfunction[33-36]. In addition, psoriatic plaque lesions reappear with restoration of peripheral nerve function[35-37].

Apart from the nervous system-related injuries, several case series showed near-complete remission of psoriatic lesions following botulinum toxin treatment[38,39] that further supports the role of the nervous system both in the formation, as well as in the maintenance of psoriatic plaques. In a psoriasiform animal model, botulinum toxin treatment was suggested to exert its effect through the inhibition of neuropeptides[40]. In 1986, researchers suggested the influence of cutaneous neurons and neuro-immune factors in the pathogenesis of psoriasis[41]. Since then, numerous studies indicated the role of neuropeptides both in the inflammatory and proliferative processes in psoriasis pathogenesis[42,43]. Therefore, we may consider psoriasis, in part, as a neurogenic inflammatory disease[43] at least in a subgroup of patients. Studies reported increased expression of several neuropeptides in the lesional (L) skin, including CGRP (calcitonin gene-related protein)[44-46], NGF (nerve growth factor)[47], and SP (substance P)[48,49]. Apart from their neural functions, these molecules also display proinflammatory activities and thereby contribute to inflammation[50], highlighting an important role of the nervous system in psoriasis pathomechanism.

The majority of psoriatic patients are troubled by itch at their lesional skin[51,52]. In these areas, neurogenic pro-inflammatory mediators, e.g., CGRP, NGF, and SP can contribute to itching (pruritus) development[53-55]. Moreover, patients may also suffer from aching, burning, cramping,

stinging, tenderness, and tingling at the lesional areas[56], suggesting that cutaneous neuronal sensation mechanisms are affected at multiple levels.

Furthermore, abnormal morphology of nerve endings can be observed in the psoriatic lesions[57]. Although the cell bodies of the nerve cells are not located in the skin, a massive RNA transport and translation takes place in axon terminal regions located in the skin[58,59]. Moreover, in our previous psoriatic proteomic analysis, we have identified altered expression of several proteins related to neurogenesis and myelination[60]. However, the molecular mechanisms underlying the functional and structural abnormalities associated with the nervous system characteristic of psoriatic skin are still largely unknown. Nevertheless, recent studies have shown that cutaneous nerve fibers are closely associated with keratinocytes and immune cells, and play a significant role in the pathogenesis of the disease at least in a subgroup of patients[61].

The large number of abnormalities present already in non-lesional skin suggests epigenetic alterations of various cells present in the skin, which may affect the function of cutaneous nerve fibers. The interaction of cutaneous cells with nerve fibers is likely to be the most relevant in the epidermis where neuronal projections are only partially myelinated or completely demyelinated. Therefore, epigenetic dysregulation of skin cells including "myelin substituting" keratinocytes may negatively affect the structure and/or function of cutaneous nerve fibers in psoriasis.

1.4. Epigenetic regulations

The chromatin is composed of DNA and histones[62]. Two major types of chromatin can be distinguished: the gene-poor, transcriptionally less active heterochromatin, and the gene-rich euchromatin, which is accessible for transcription[63,64]. The basic unit of the chromatin is the nucleosome, composed of DNA and a core histone octamer[65]. The histone octamer is composed of H2A, H2B, H3, H4 core histones[66,67], while higher-order chromatin structures are interconnected by the H1 linker histone[68,69].

The role of epigenetics is to maintain the inherited cellular gene expression profile without modifying the DNA sequence[70,71]. Epigenetic modifications can affect the DNA as well as the histones. The major DNA-related epigenetic regulatory modification is DNA methylation[72]. During the epigenetic modification of histones, three major regulatory layers could be distinguished[73] (**Figure 3.)**. Histones can be substituted by histone variants[74]. Based on their role in replication, replication-dependent (also known as canonical) and replication-independent (also known as non-

canonical) histone variants can be distinguished[75] (**Figure 4**.). The first layer of histone-related epigenetic modification involves histone chaperones, which transport, exchange, and incorporate histone variants, thereby modifying the histone composition of the nucleosome sites[76] (**Figure 3.)**. The second layer is the histone (and histone variant) composition of the nucleosome determined by these chaperones[77] (**Figure 3.)**. Histones and their variants are encoded by different genes in the human genome[75], providing a large number of combination possibilities for the histone composition of the nucleosomes in the chromatin **(Figure 4.)**. While the third layer comprises post-translational modifications of histones at their N-terminal histone tail[78,79].

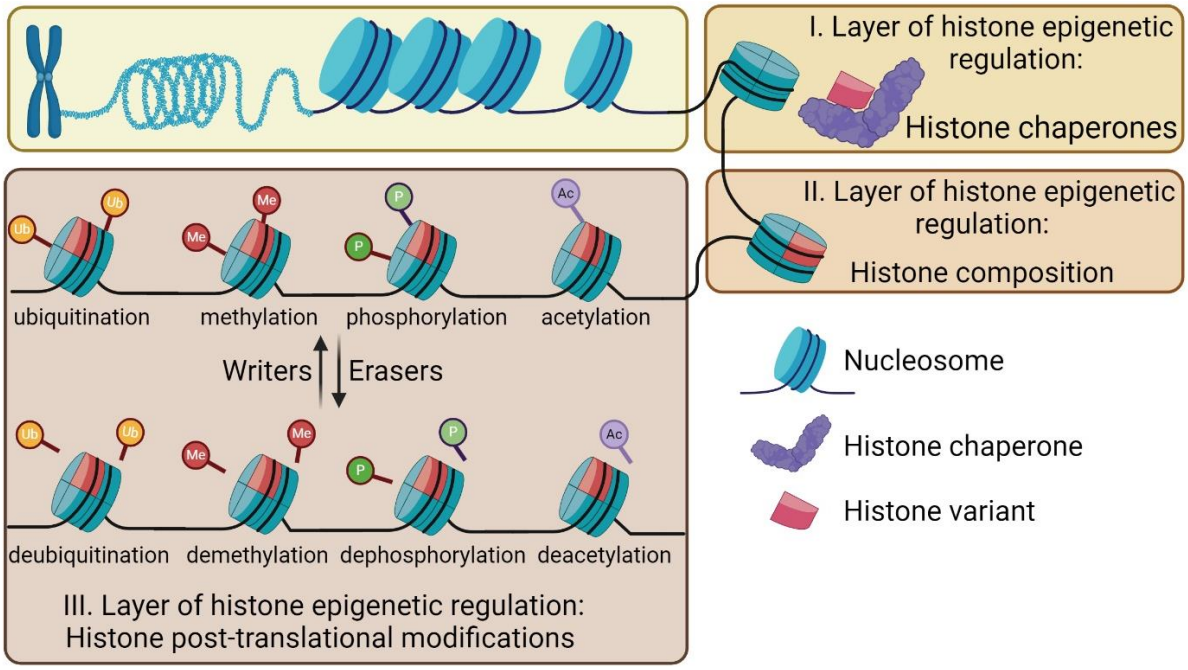


Figure 3. The three major regulatory layers of histone epigenetic modification.

Histones and their variants may differ not only in the length of the histone tail[80,81], but also in the number and position of post-translational modification sites[82-84] **(Figure 3.)**. Major differences between replication-dependent and replication-independent histone variants are summarized in **Table 1**[81,85,86]. The sum of these three regulatory layers allows an extremely fine-tuning of regulation. This complex epigenetic regulation of histones is indispensable in the regulation of cell type-specific gene expression, allowing tissue-specific proliferation, differentiation, and the proper formation of cellular responses to various internal and external stimuli[87,88].

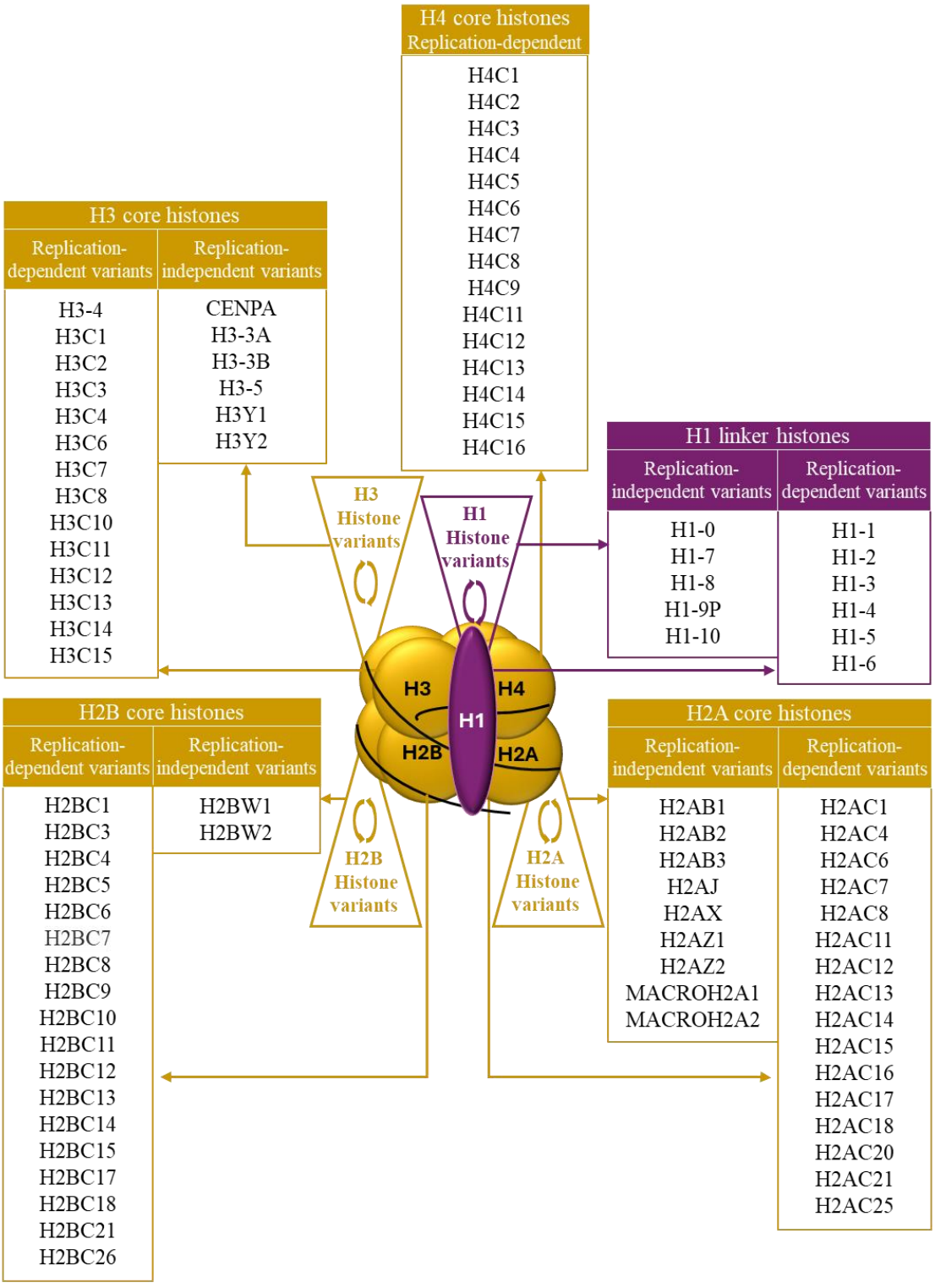


Figure 4. Human histones and their variants (Based on Amatori S. et.al.,2021[75]).

General overview of the differences between replication-dependent and replication-independent histone variants		
	Replication-dependent variants	**Replication independent variants**
Expression-timing	Replication-dependent	Replication-independent
Sequence identity	High	Low
Functional relationship	Isoform	Specialised function
Transcript stabilisation	Stem-loop	poly(A) tail
Gene distribution	Clusters	Scattered

Table 1. Major differences of histone variants.

Histone post-translational modifications are highly diverse, including well-characterized modifications like acetylation, phosphorylation, methylation, and ubiquitination, as well as less-known ones like biotinylation and dopaminylation, among others[82]. One of the major epigenetic post-translational modifications of histones regulating transcription is acetylation[89]. Histone acetylation, carried out by histone acetyltransferases (HATs)[90], leads to transcriptional activation[91]. There are two major types of HATs, A- and B-type. A-type HATs acetylate chromatin-incorporated histones, whereas B-type HATs acetylate newly synthesized histones[92]. Type A HATs can be further classified into three main subfamilies: the CBP/CREBBP, GNAT, and MYST families[93,94]. Whereas, histone deacetylation carried out by four different classes of histone deacetylases (HDACs)[90,95] results in transcriptional repression[96].

1.5. Histone-related epigenetics of the skin and its alterations in psoriasis

Epigenetic modifications are strictly regulated in every tissue including the skin[97,98]. One of the major developmental epigenetic regulatory modifications is histone-acetylation. During epidermal development, H3 histone-associated acetylation (H3K27ac) gradually increases in basal cells but decreases in differentiating cells. In addition, the acetylation pattern of the H4 histone (H4K16ac) in the granular layer, is responsible for the maintenance differentiation state of the cells, preventing proliferation. The fully developed stratified epidermis shows a similar pattern with high levels of H3K27ac and H4K16ac in basal cells, both of which continuously decrease from the basal layer upwards in the differentiating cells[99] **(Figure 5.)**. In psoriatic lesional skin, altered levels of H3K27ac[100] suggest a disturbed epigenetic regulation that is likely to contribute to the abnormal

epidermal development characterized by hyperproliferation and abnormal differentiation of keratinocytes[101].

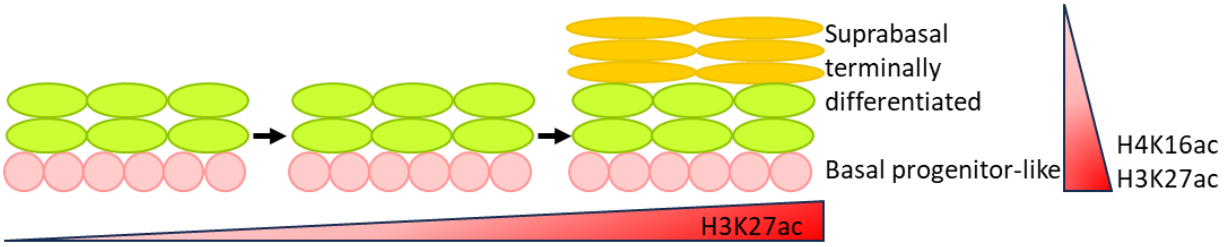


Figure 5. A schematic illustrates histone acetylation alternations during skin development as cells mature and undergo terminal specialization, culminating in a stratified epithelium. (Based on Shue YT. .t. al. 2020.[99])

The regulation of histone-acetylation also plays a key role in immune cell development and response. In psoriasis, altered H3 histone acetylation is known to promote Th17 cell differentiation[102]. Peripheral blood mononuclear cells, composed of several immune cell types including T-cell, monocytes, dendritic cells, and natural killer cells[103], are also known to have a significant role in the pathogenesis of psoriasis[104]. The peripheral blood mononuclear cells of psoriasis patients are characterized by hypoacetylation of histone H4 (compared to healthy controls), which displays a negative correction with the disease activity[105]. The histone acetylation pattern plays a key role in the function of innate immune cells, including the regulation of macrophage polarization[106]. In accordance with this, psoriasis is characterized by an altered M1/M2 macrophage ratio[107].

Currently, the literature mainly reports abnormal histone acetylation patterns in lesional psoriatic skin[100]. However, these histone acetylation patterns play a crucial role in epidermal development[99] and immune cell function[102,106], disturbances of which may already be present in non-lesional skin.

1.6. Transcriptome of Protein-Coding RNAs

Given the complex, multifactorial, and polygenic nature of psoriasis, one effective way to characterize mechanistic alterations at a global level is the comparison of healthy and psoriatic transcriptome data from full RNA sequencing.

RNAs can be divided into two broad groups: non-protein-coding RNAs and protein-coding RNAs[108,109]. Non-coding RNAs can be further subdivided into housekeeping RNAs, which are required for proper cellular function, and regulatory RNAs, which influence gene expression at multiple levels[110].

As a first step in protein synthesis, pre-RNA (5'cap; 3'polyA tail) is transcribed from DNA, from which introns are spliced out, creating thereby the canonical protein-coding transcript from which the canonical protein isoform is translated **(Figure 6.)**. As a result of alternative splicing, several transcript variants (also known as splice variants) can arise, in addition to the canonical protein-coding transcript, coded by the same gene[111,112]. Some exons can be excluded by exon skipping while others could be included by exon inclusion, creating transcript variants coding for alternative protein isoforms[113] **(Figure 6.)**. In addition, incorrect splicing can result in intron retention, leading to intron-encoded transcript variants. Some intron-encoded transcript variants could be translated, and the resulting alternative protein isoform may possess different functional properties or cellular localizations[114,115].

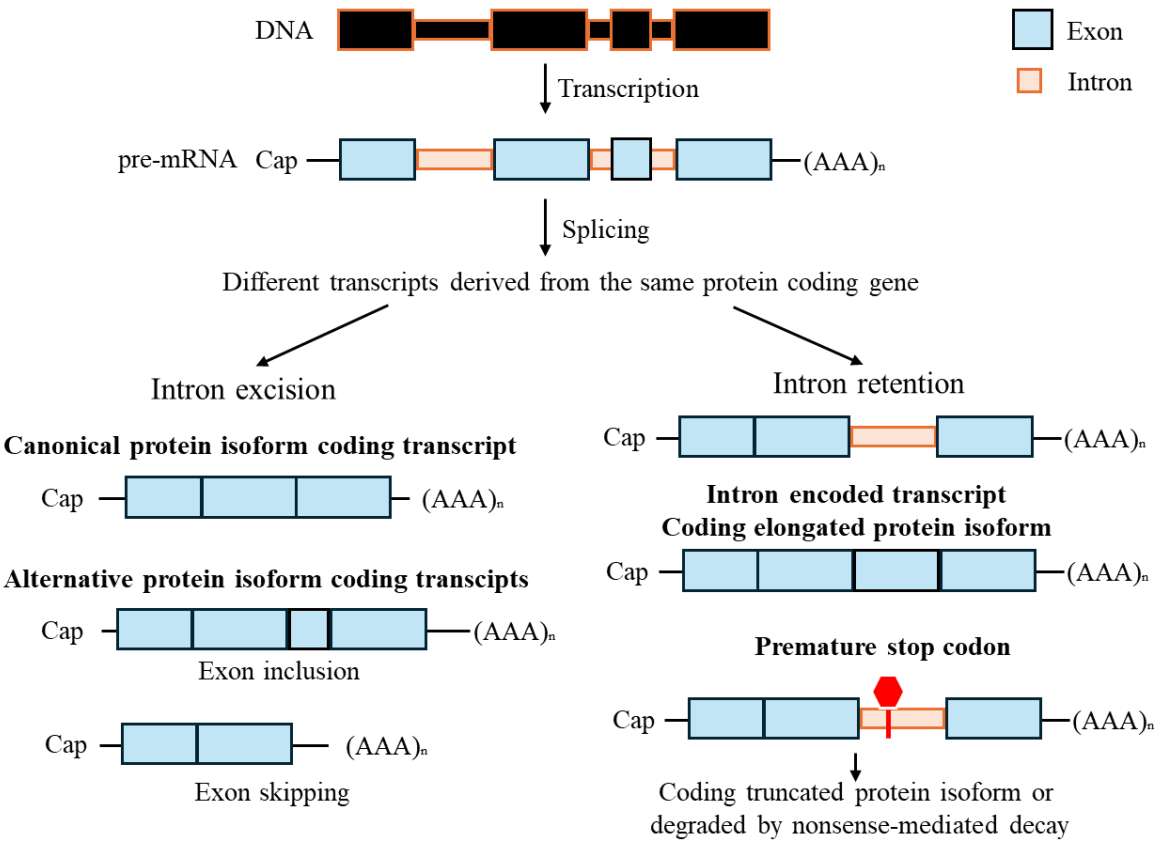


Figure 6. Major types of protein-coding transcripts.

In other cases, inappropriate intron excision is associated with a premature stop codon, inducing the appearance of truncated protein or nonsense-mediated decay[116] **(Figure 6.)**. In addition, there are protein-coding transcripts such as non-stop decay (lacking a stop codon)[117], which can result in an elongated isoform of the protein if translated; while processed transcripts lack an ORF (Open Reading Frame)[118,119]. In some cases, the processed transcript may still contain a short ORF or other functional element that can give rise to a short peptide or partially functional protein. Taken together, as a result of splicing different transcripts arising from the same gene are then translated into different protein isoforms. Such isoforms often exhibit different ligand binding properties, modifying the repertoire of their interaction partners, and resulting in different or even opposing biological functions[120]. Therefore, we decided to apply all protein-coding transcripts for our analysis of this study.

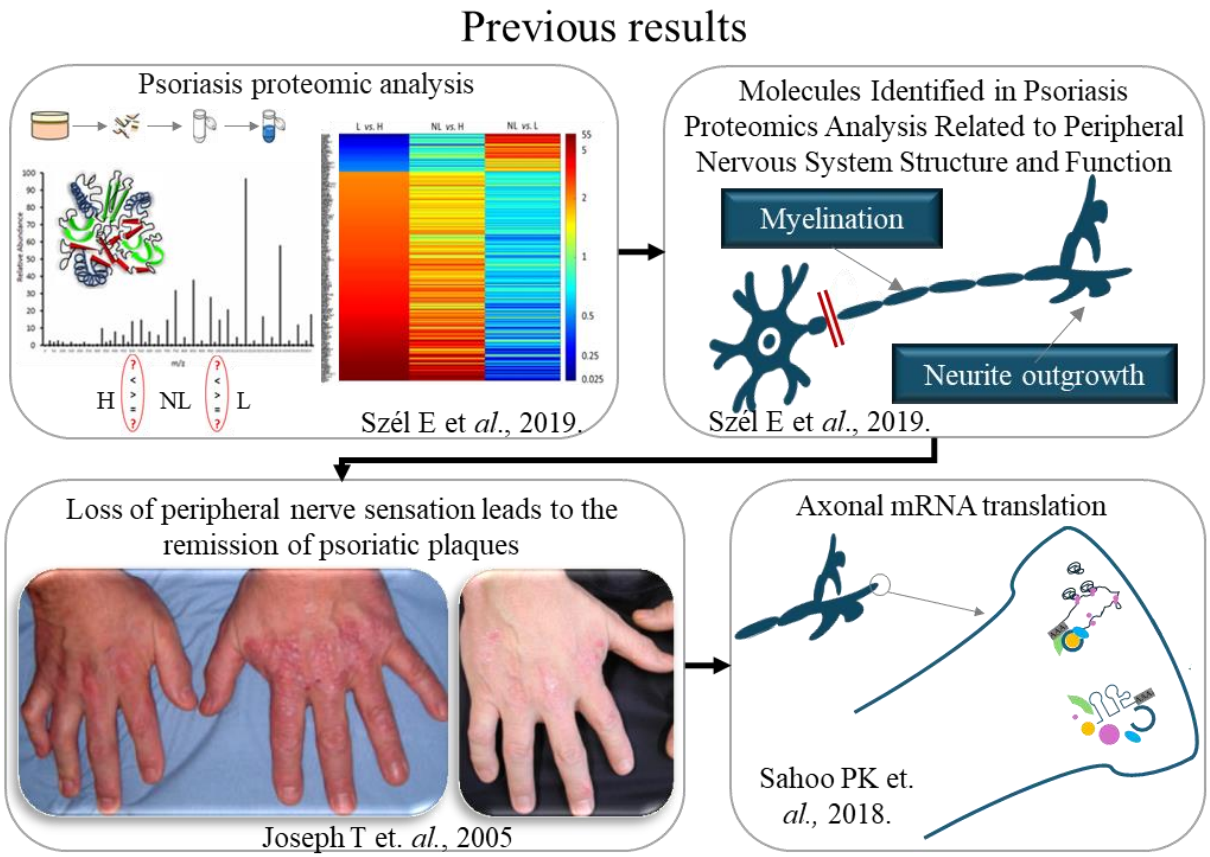
2. AIMS

I) To explore the molecular mechanisms underlying peripheral nervous system-related abnormalities in psoriatic skin and identify potential signaling pathways at the transcriptional level.

II) a, To map histone-related epigenetic regulatory abnormalities in non-lesional psoriatic skin, focusing on proteins that govern histone composition and acetylation.

b, To analyze the effect of the identified histone-related epigenetic abnormalities in shaping core psoriatic processes, emphasizing their effects on cell proliferation and immune responses.

Previous results leading to the concept and aims of our study are summarized in **Figure 7**.



(Figure 7. continued)

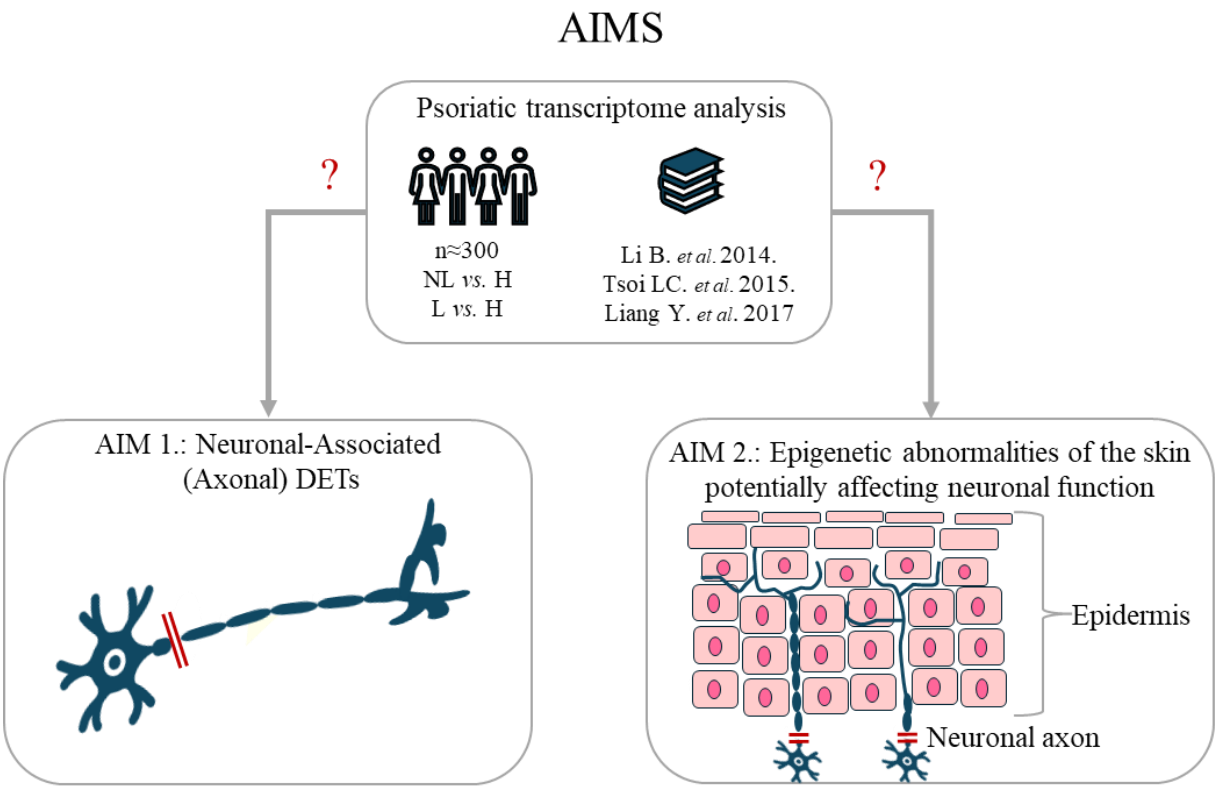


Figure 7. Schematic overview of previous results leading to the aims of our study.

3. MATERIAL AND METHODS

3.1. Criteria for combining the transcriptome sequencing data of from three published psoriatic datasets

To identify general alterations in psoriasis and to avoid any potentially non-disease related associations and differences, randomly engaged individuals of chronic plaque psoriatic patients and healthy donors were involved in the three studies[121-123] of which the combined database was generated from. For inclusion criteria, no preference of gender, age (apart from >18), or Psoriasis Area Severity Index scores (min. 1% of total body surface area) was put forward in any of the three studies, of which the RNA sequencing data were collected from. Similarly, skin punch biopsies (6 mm) were collected from various regions of the body (hip, buttlock, thigh, back, arm, flank, abdomen, elbow). A washout period of 1 week for patients on topical anti-psoriatic treatments and 2 weeks for those on any systemic anti-psoriatic treatments was set as general criteria prior to biopsy collection.

3.2. RNA sequencing data processing

The RNA sequencing datasets from three papers were uniformly reprocessed[121-123]. We downloaded the data from SRA (Sequence Read Archive, https://www.ncbi.nlm.nih.gov/sra, accessed on 15 November 2021) with study ID accession numbers SRP035988, SRP050971, and SRP055813 using SRA-tools (version 2.9.2, https://github.com/ncbi/sra-tools, accessed on 15 November 2021) and reprocessed all available samples. We quantified transcript level expression using Kallisto[124] (version 0.43.0) and the full GENCODE[118] v27 transcriptome annotation, available at https://www.gencodegenes.org (accessed on 15 November 2021). Kallisto was run with the following options: --bias --single -l 120 -s 20 -b 100.

3.3. Differential expression analysis

Transcript-level length-scaled TPM (Transcripts Per Million) expression estimates from Kallisto were imported into the R statistical environment (version 3.4.3, https://www.r-project.org; accessed on 15 November 2021), using the tximport[125] package (version 1.6.0). The data were TMM (trimmed mean of M-values) normalized and voom transformed. We used edgeR[126] (version 3.20.9) for the TMM normalization and the voomWithQualityWeights() function from limma[127,128] (version 3.34.9) for the voom transformation. We decided to use voomWithQualityWeights() to

combine transcript observation-level weights with sample-specific weights, as we did not want to discard samples with lower quality, but preferred to downweigh them in the analysis. Limma was also used to test for differential expression between lesional and non-lesional, lesional and healthy, or non-lesional and healthy sample groups. A linear model was fitted with the limma lmFit function, and the moderated t-statistics were calculated with the eBayes function. Transcripts were defined as differentially expressed if they had an FDR[128,129] (false discovery rate) corrected p-value < 0.05.

3.4. Analysis of DET-related to neuronal changes: functional annotation, enrichment analysis, and statistics

Differentially expressed transcripts (DETs) from non-lesional *vs.* healthy and lesional *vs*. healthy comparisons were analyzed using Ingenuity Pathway Analysis (IPA) software (IngenuityH Systems, www.ingenuity.com; accessed on 15 November 2021) to identify pathways that are enriched. DET sets were mapped to the HUGO gene symbols within IPA software and those that did not map to any HUGO gene were discarded. For the "Diseases and Biological functions" annotation, the p-value was calculated using Fisher's exact test[130] to measure the significance of DET enrichment of a given pathway. For the Gene Ontology enrichment analysis and visualization (Gorilla) tool, the enrichment analysis p-value was calculated according to the mHG or HG model[131]; p-value correction for multiple testing was done according to the Benjamini and Hochberg method[132] (FDR correction). Enrichment was defined as (b/n)/(B/N), where N: is the total number of genes, B: is the total number of genes associated with a given specific GO term, n: is the number of genes at the top of the user's input list or in the target set when appropriate, b: number of genes in the intersection.

3.5. Screening for histones and histone acetylation-related DETs

Differentially expressed transcripts (DETs) from the non-lesional *vs.* healthy comparison were analyzed using libraries of datasets downloaded from https://amigo.geneontology.org/amigo/term/ (accessed on 24–29 June 2023) and supplemented with literature data. To supplement downloaded GO datasets with additional associated genes from literature, data from the AMIGO database was compared with the PubMed (https://pubmed.ncbi.nlm.nih.gov/) literature database using keyword-based automated literature screens. Output publications were checked manually within the manuscript, as well as in Genecards database for additional genes related to the given GO term described process/mechanism. If

AMIGO database was found to be incomplete after a manual check based on the literature data, we combined the two results and included the literature-supported relevant data.

In the case of histones, the AMIGO GO term "Histone(s)" was not available, so after a keyword-based automated literature screen, we created the histone database based on literature data. This was based on an article containing the classification of histones, which, to the best of our knowledge, contains all currently known human histone variants (Amatori S. et.al., 2021[75]). These datasets were then combined, giving rise to the library of histones, histone chaperones, and histone (de)acetylation-related genes.

This library and the transcriptome database of differentially expressed transcripts of non-lesional psoriatic *vs.* healthy skin, (created by combining three published transcriptome analysis datasets,) were filtered to determine matches between the two datasets. The filtering used to determine matches between non-lesional *vs.* healthy and the downloaded dataset was performed in Python by applying intersection analysis. The output of this filtering was a library of histones, histone chaperones, and histone (de)acetylation-related genes differentially expressed in non-lesional psoriatic skin vs. healthy. This library served as an input for a third literature screen together with given mechanism(s) term(s) (listed below) as keywords to identify proliferation, differentiation, and immune response-related functions of (gene) dataset components. For this screen in PubMed the following keywords (listed in alphabetical order) were applied: Cell cycle, Dendritic cell, Differentiation, Epidermis, Immune, Immune cell, Innate immune, Inflammation, Hematopoietic and Hematopoiesis, Keratinocyte, Macrophage, Neutrophil, Pluripotency, Proliferation, Psoriasis, Self-renewal, Senescence, Skin, Stem cell, T cell.

All described screens and filtering(s) were conducted in a case-insensitive manner (both upper- and lower-case letters were considered) and alternative names/aliases of genes were taken into account.

A. Histone chaperone activity, Geneontology ID#: GO:0140713
   Database used for literature search: Pubmed (https://pubmed.ncbi.nlm.nih.gov/)
   Keywords used for literature search to supplement Geneontology dataset: Histone chaperone, Histone chaperone complex
   Applied literature for supplementation: De Koning L. et al., 2007[76]; Filipescu D. et al., 2013[133]; Lamaa A. et al., 2020[134]; Moreno-Andrés D.et al., 2020[135]

B. Histone acetylation, Geneontology ID#: GO:0016573
   Database used for literature search: Pubmed (https://pubmed.ncbi.nlm.nih.gov/)
   Keywords used for literature search to supplement Geneontology dataset: Histone acetylation, Histone acetyltransferase, Histone acetyltransferase complex

Applied literature for supplementation: Arede, L. 2020[136]; Di Cerbo V. et al., 2013[137], Fang Z. et al., 2021[138]; Herbst D. A. et. al., 2021[139]; Seo S. et al., 2002[140]; Yang Q. et al., 2018[141]

C. Histone deacetylation, Geneontology ID#: GO:0016575
Database used for literature search: Pubmed (https://pubmed.ncbi.nlm.nih.gov/)
Keywords used for literature search to supplement Geneontology dataset: Histone deacetylase, Histone deacetylase complex, Histone deacetylation
Applied literature for supplementation: Fang Z. et al., 2021[138]; Yang Q. et al., 2018[141]

The literature mining and monitoring strategy for histones, histone acetylation-related components, and DETs in non-lesional skin is summarized in **Figure 8**. Details of the datasets for histones and their variants are provided in **Figure 4.** Data related to histone chaperones and post-translational modifications associated with acetylation which includes merged information from the GO database and literature are presented in the Results part of the thesis.

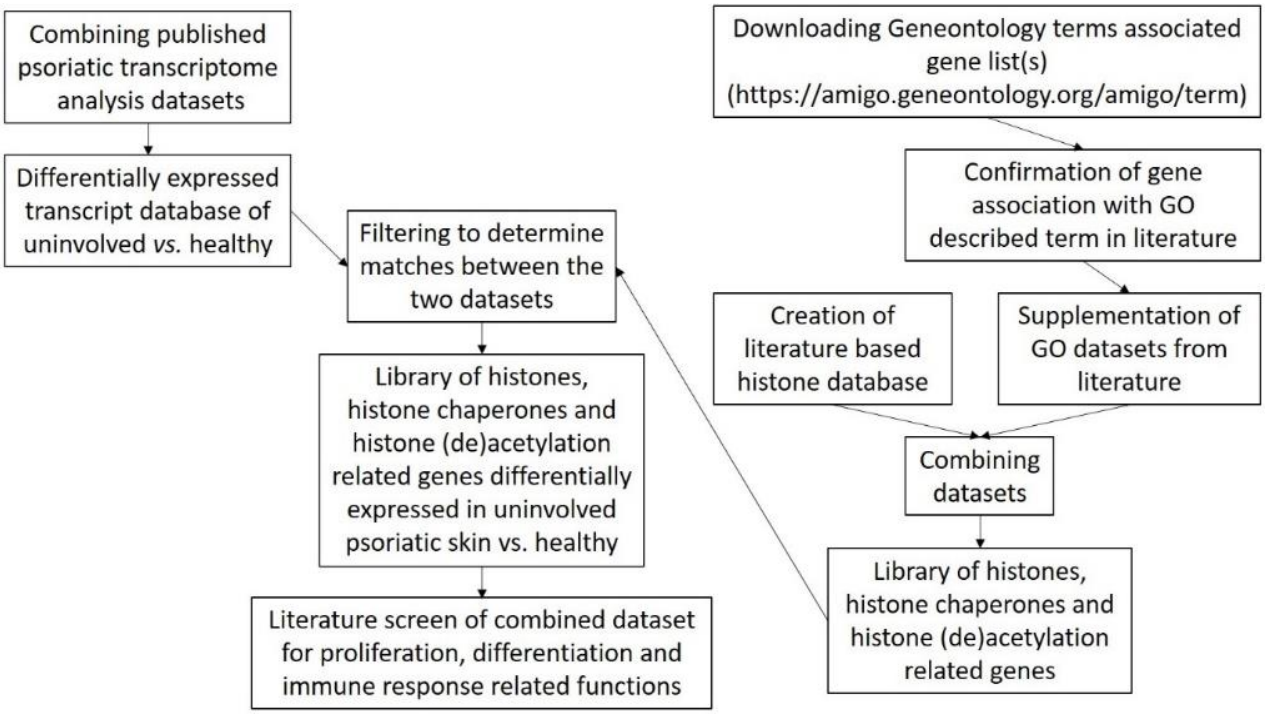


Figure 8. The strategy of literature mining to confirm GO term association of genes in literature, and to identify function(s) of GO terms associated and literature-supplemented genes was performed as described previously.

4. RESULTS

4.1. RESULTS PART 1.: Peripheral nervous system-related abnormalities in psoriasis

4.1.1. Peripheral nervous system-associated transcript expression alterations in psoriasis

Based on our transcriptome analysis, 2681 transcripts showed altered expression levels in the non-lesional and healthy skin comparison, whereas the number of transcripts with altered expression in lesional *vs.* healthy skin was 12314. Using the Ingenuity Pathway Analysis (IPA) software we identified DETs coded by 347 and 885 genes in association with nervous system development and function in non-lesional and lesional skin, respectively**.** These DETs are predicted to affect neuronal morphogenesis, including neuritogenesis, which represented the most specific group in the analysis (**Table 2.**).

Categories	Functions	Comparison	P-value	Number of Molecules
Nervous System Development and Function	Morphology of nervous system	NL *vs.* H	4.11E-17	236
		L *vs.* H	5.28E-32	637
Nervous System Development and Function,Neurological Disease	Abnormal morphology of	NL *vs.* H	4.95E-13	188
		L *vs.* H	2.80E-20	495
Nervous System Development and Function,Tissue Morphology	Morphology of nervous tissue	NL *vs.* H	1.11E-12	165
		L *vs.* H	5.25E-22	439
Nervous System Development and Function,Organismal Development,Tissue Development	Morphogenesis of nervous tissue	NL *vs.* H	4.70E-10	144
		L *vs.* H	4.46E-22	405
Cell Morphology,Cellular Assembly and Organization,Cellular Development,Cellular Function and Maintenance,Cellular Growth and Proliferation,Nervous System Development and Function,Organismal Development,Tissue Development	Neuritogenesis	NL *vs.* H	5.26E-10	142
		L *vs.* H	6.62E-22	399
Cell Morphology,Cellular Development,Cellular Growth and Proliferation,Nervous System Development and Function,Organismal Development,Tissue Development	Morphogenesis of neurons	NL *vs.* H	6.60E-10	143
		L *vs.* H	6.85E-22	403
Cellular Development,Cellular Growth and Proliferation,Nervous System Development and Function,Tissue Development	Development of neurons	NL *vs.* H	1.12E-09	177
		L *vs.* H	2.14E-24	517

Table 2. Functional annotation of nervous system-related DETs in non-lesional and lesional psoriatic skin. (H: healthy, L: lesional, NL: non-lesional skin)

4.1.2. Differentially expressed transcripts affecting axon-related alterations in non-lesional and lesional psoriatic skin

Since only neurites penetrate the skin, we wanted to gain further insight into how neuron projections are likely to be affected in the skin. For this, we performed gene ontology (GO) functional enrichment analysis using neuron projection GO:0043005 as a background in Gorilla

(Gene Ontology enrichment analysis and visualization tool; accessed on 15 November 2021.) on the neuritogenesis-associated DETs from the original IPA analysis. This analysis revealed biological processes linked to the regulation of neuron projection development and the semaphorin-plexin signaling pathway. According to our results, these pathways are likely to be affected already in the non-lesional skin, and to a greater extent in lesional samples, as suggested by a higher number of DETs in the latter group (**Table 3.**).

GO Term	Description	Comparsion	P-value	FDR q-value	Enrichment (N, B, n, b)
GO:0010975	regulation of neuron projection development	NL *vs.* H	1.98E-4	2.74E-2	1.72 (1442, 229, 139, 38)
		L *vs.* H	6.66E-10	2.79E-7	1.64 (1594, 260, 389, 104)
GO:0045664	regulation of neuron differentiation	NL *vs.* H	2.68E-4	3.35E-2	1.67 (1442, 249, 139, 40)
		L *vs.* H	6.63E-11	4.07E-8	1.64 (1594, 285, 389, 114)
GO:0071526	semaphorin-plexin signaling pathway	NL *vs.* H	4.09E-4	4.07E-2	5.19 (1442, 12, 139, 6)
		L *vs.* H	2.3E-5	1.37E-3	2.96 (1594, 18, 389, 13)

Table 3. Gene ontology (GO) functional enrichment analysis of DETs associated with neuritogenesis in non-lesional and lesional skin. (H: healthy, L: lesional, NL: non-lesional skin).

In addition, neuron projection morphogenesis, development, and guidance were predicted to be affected only in psoriatic lesions (**Table 4.)**. While among axon formation-associated regulatory processes, negative regulation of axonogenesis and axon guidance are predicted to be affected in psoriatic lesions (**Table 5.**).

GO Term	Description	Comparsion	P-value	FDR q-value	Enrichment (N, B, n, b)
GO:0048812	neuron projection morphogenesis	L *vs.* H	2.94E-10	1.43E-7	1.96 (1594, 138, 389, 66)
GO:0097485	neuron projection guidance		8.37E-7	9.17E-5	1.78 (1594, 124, 389, 54)
GO:0031175	neuron projection development		9.31E-7	9.74E-5	1.68 (1594, 159, 389, 65)
GO:0010976	positive regulation of neuron projection development		3.15E-6	2.54E-4	1.69 (1594, 141, 389, 58)
GO:0010977	negative regulation of neuron projection development		9.99E-5	4.76E-3	1.74 (1594, 87, 389, 37)

Table 4. Gene ontology (GO) functional enrichment analysis of DETs associated with neuritogenesis reveals neuron projection-related biological processes in lesional but not in non-lesional (H: healthy, L: lesional).

GO Term	Description	Comparsion	P-value	FDR q-value	Enrichment (N, B, n, b)
GO:0050770	regulation of axonogenesis	L *vs.* H	6.36E-7	7.32E-5	1.89 (1594, 102, 389, 47)
GO:0007411	axon guidance		8.37E-7	9.06E-5	1.78 (1594, 124, 389, 54)
GO:1902668	negative regulation of axon guidance		8.36E-5	4.2E-3	3.00 (1594, 15, 389, 11)
GO:0048843	negative regulation of axon extension involved in axon guidance		9.41E-5	4.56E-3	3.15 (1594, 13, 389, 10)
GO:0050771	negative regulation of axonogenesis		2.61E-4	1.07E-2	2.00 (1594, 45, 389, 22)
GO:0008045	motor neuron axon guidance		6.07E-4	2.21E-2	2.73 (1594, 15, 389, 10)
GO:0048841	regulation of axon extension involved in axon guidance		6.07E-4	2.2E-2	2.73 (1594, 15, 389, 10)
GO:1902667	regulation of axon guidance		9.35E-4	3.19E-2	2.50 (1594, 18, 389, 11)

Table 5. GO functional enrichment analysis of DETs associated with neuritogenesis reveals axon formation-related biological processes only in lesional psoriatic skin. (H: healthy, L: lesional).

Axon formation is strongly associated with Schwann cell myelination in the peripheral nervous system. Although functional enrichment analysis did not reveal any associated processes, skin tissue expression analysis (tissues.jensenlab.org; accessed on 15 November 2021) integrated into the STRING database (version:11.5; accessed on 15 November 2021) revealed certain associations. Four molecules (MBP, MPZ, PMP22, and EGR2) out of the DETs coded by 347 genes in non-lesional skin were assigned to Schwann cells (BTO:0001220, 4 of 6 molecules), and to myelin (MBP, MPZ, PMP22, and RTN4, BTO:0000894, 4 of 6 molecules) **(Figure 9.)**. A similar analysis also pointed out four (MBP, MPZ, EGR2, and PRX) Schwann cell-associated molecules in lesional skin samples (out of the DETs coded by 885 genes), while myelin-related molecules with DETs were MBP, MPZ, PLP1, and RTN4 **(Figure 9.)**. Our analysis suggests a common molecule that emerges is RTN4 (also known as Nogo), thus myelin-associated inhibitory regulation of axon formation via RTN4 appears to be a commonly affected mechanism in both non-lesional and lesional skin samples.

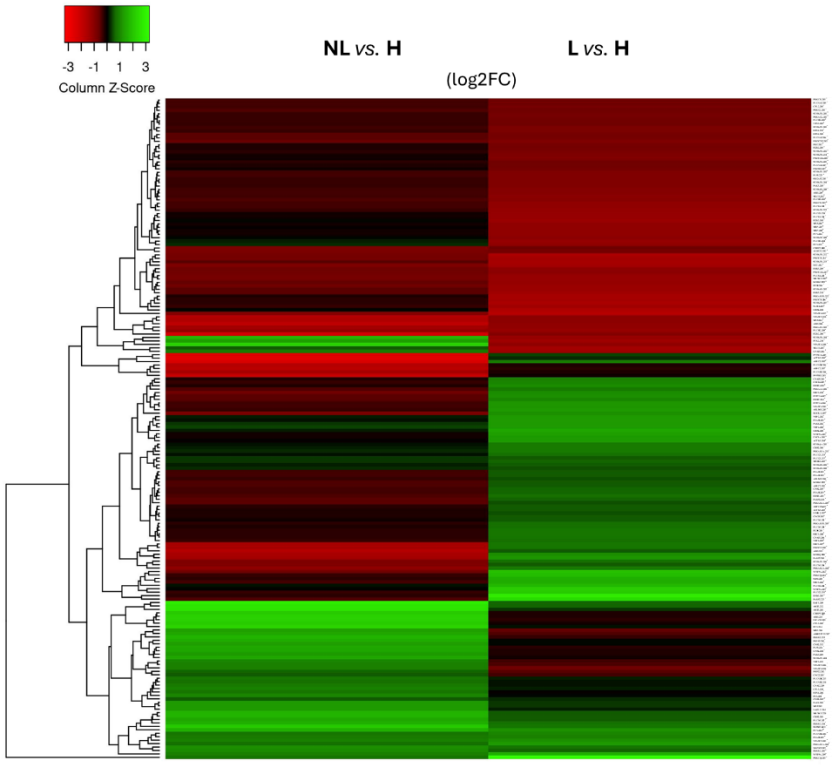


Figure 9. Heatmap of differentially expressed transcripts of neurogenesis- and myelination-related molecules in psoriasis. (H: healthy, NL: non-lesional/uninvolved, L: lesional skin; ¥: transcript variants showing differential expression in NL vs. H; *: transcript variants showing disparate expression levels in NL skin vs. H.)

4.1.3. Semaphorin-plexin signaling, an important regulator of axon formation, is differentially affected in non-lesional and lesional psoriatic skin

Since both IPA and GOrilla enrichment analysis suggested that Semaphorin-Plexin signaling is affected in psoriasis pathogenesis (Semaphorin Neuronal Repulsive Signaling Pathway: $p\text{-value}_{\text{NL vs. H}}$ = 1.52E-03 and $p\text{-value}_{\text{L vs. H}}$ = 1.45E-02 and **Table 3.,** respectively), we analyzed these pathways in depth. Type 3 semaphorins (Sema3) play a role in neurite formation by regulating axon attraction and repulsion. Among the Sema3 family members that inhibit axon extension, we found DETs coded by Sema3B and Sema3F genes both in non-lesional and lesional skin, while in lesional skin, we also detected Sema3D, Sema3E, and Sema3G with differential expression (**Figure 9. and 10.**). While Sema3A is not affected by DETs in non-lesional or lesional skin. Among semaphorin3 receptors and coreceptors, L1CAM, Nrp1and PlxnD1 are only affected by DETs in non-lesional skin, while in lesional samples gene expressional differences are associated with Nrp2 and PlxnA3 receptors (**Figure 9. and 10.**). Transcripts of the downstream

signaling molecules Fyn, Crpm1, Mapk3, Mknk1, and Paks are differentially expressed in both non-lesional and lesional skin. Fes and AKT expression are altered only in non-lesional skin, while DETs of eIF4E, Farp2, Limk2, MsrB1, PI3K, and Rnd1 are present in lesions (**Figure 9. and 10.**). These abnormalities may suggest that axon repulsion and the negative regulation of axon attraction are likely to be strongly affected in lesional in contrast to non-lesional skin, where PI3K-mediated negative regulation of axon attraction does not seem to be affected when compared to healthy skin samples.

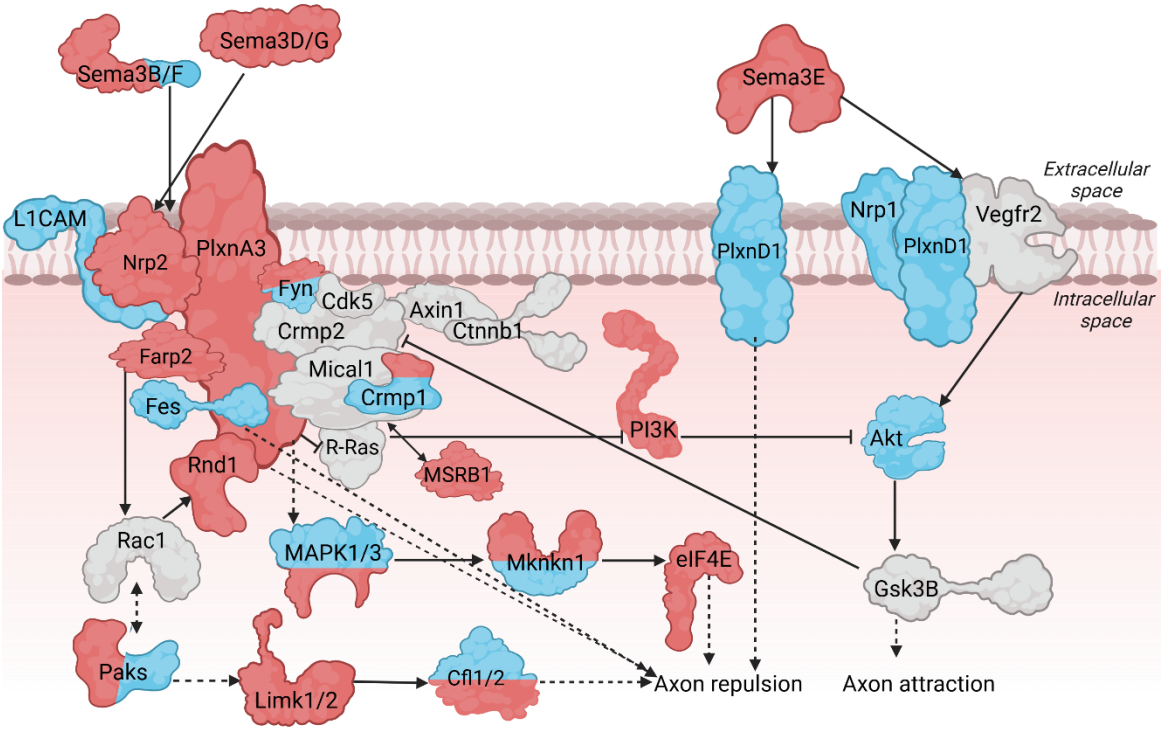


Figure 10. *In silico* model of how Sema3 signaling alterations regulate axon morphogenesis in non-lesional (blue) and lesional skin (red).

Sema4D is important in axon regeneration not only by modulating axon elongation but also by inhibiting neuronal myelination[142]. SEMA4D encoding DETs are present in lesional but not in non-lesional skin. Sema4D cell surface receptors (PlxnD1 and ErbB2), as well as downstream signaling proteins (Paks, Cfl1, and Cfl2) expression, are altered in non-lesional and lesional skin. Whereas in non-lesional skin, AKT, Arhgef11, and RAF, while in lesional samples Mlc1, PI3K, Rnd1, Rock2, and Shc are affected by DETs (**Figures 9. and 11.**). While Sema6A and 6D gene

expression is affected in lesions that share receptors of Sema3A, as well as CSPG, the receptor of Sema5A **(Figure 9.)**. These alterations may also affect axon repulsion.

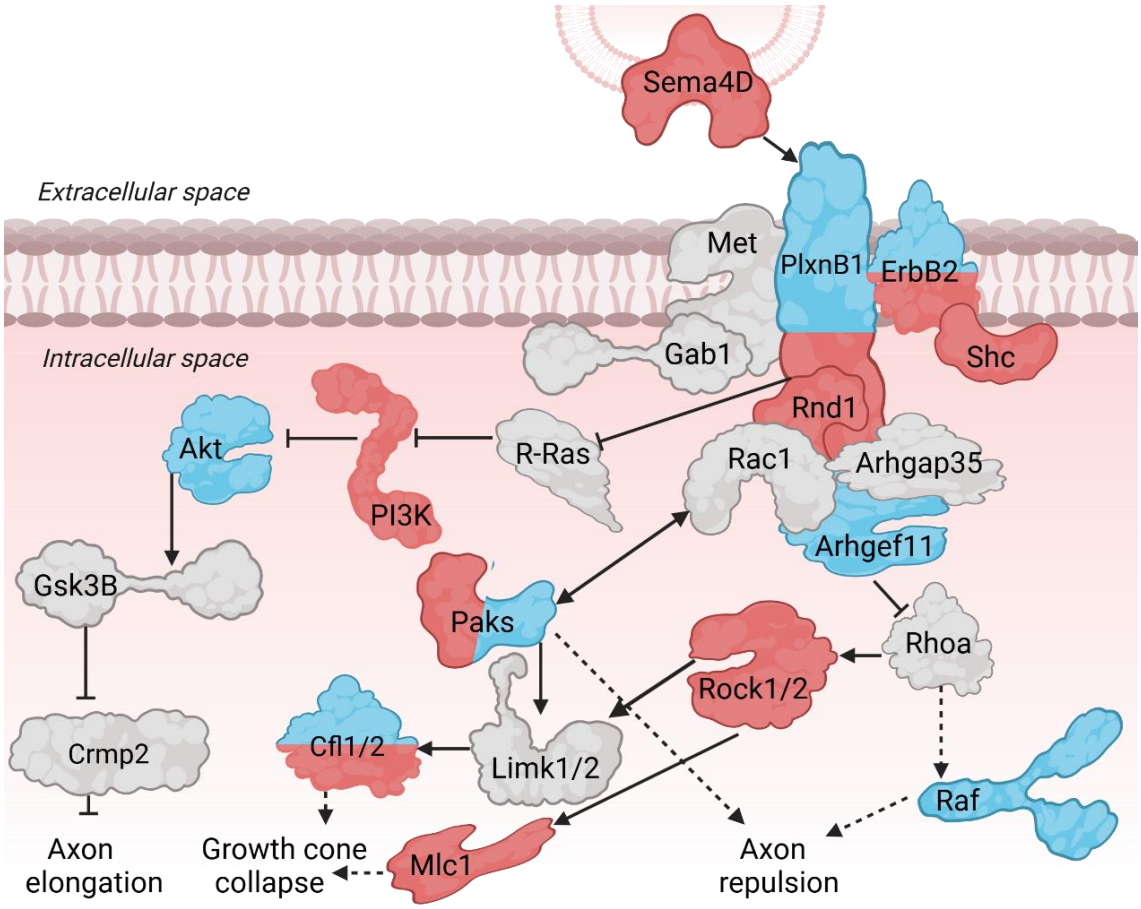


Figure 11. Schematic *in silico* model of the role Sema4D signaling in axon elongation/ repulsion in non-lesional (blue) and lesional skin (red).

4.1.4. ROBO-DCC-UNC5 signaling regulates axon formation and is differentially affected in non-lesional and lesional psoriatic skin

Axon dynamics is also regulated by Slit and Ntn signaling through Robo and Dcc, respectively. Slit and Ntn signaling via Robo and Dcc were found as part of the general canonical Axonal Guidance Signaling pathway term, which also included Wnt5a and semaphorins and were suggested to be affected both in non-lesional (NL) and lesional (L) skin (p-value NL *vs.* H = 3.21E-5 and p-value L *vs*. H = 5.03E-06, respectively). SLIT2 and its receptor ROBO2 are only affected in lesional skin, while ROBO1 expression is altered in non-lesional and lesional skin samples (**Figures 9. and 12.**). The expression of NTN1, as well as its receptors DCC (**Figures 9., 12. and**

13.) and UNC5A (**Figures 9. and 13.**) are affected in lesional but not in non-lesional skin, where only some of the downstream proteins may be differentially expressed.

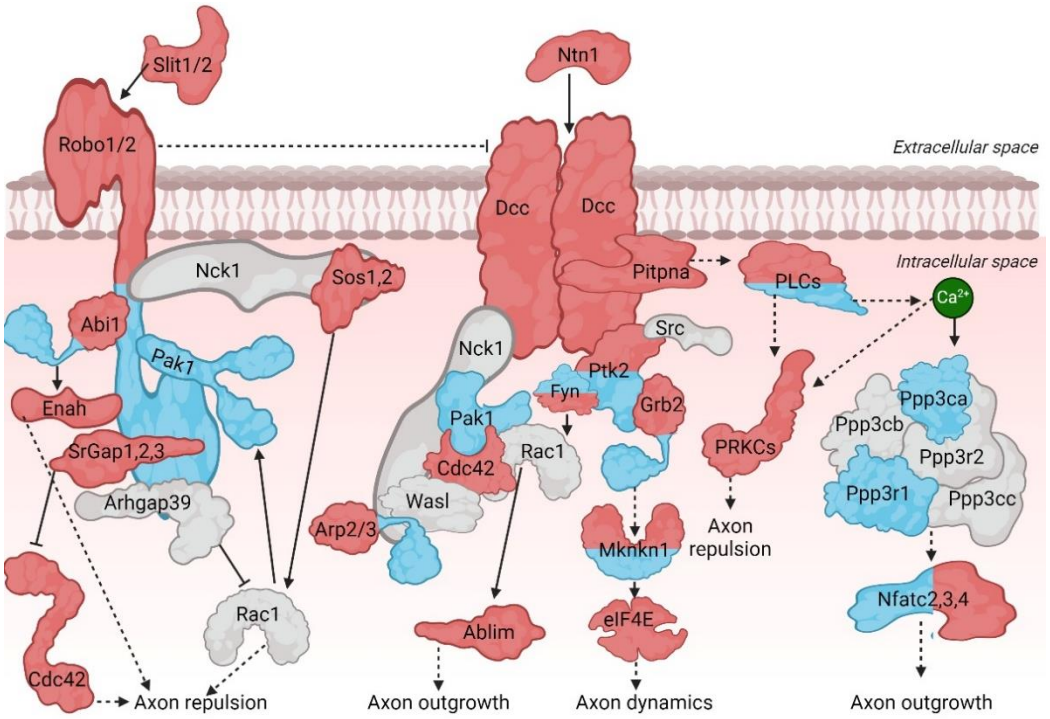


Figure 12. Schematic in silico model of Robo-DCC signaling-related axon outgrowth/repulsion regulation in non-lesional (blue) and lesional skin (red).

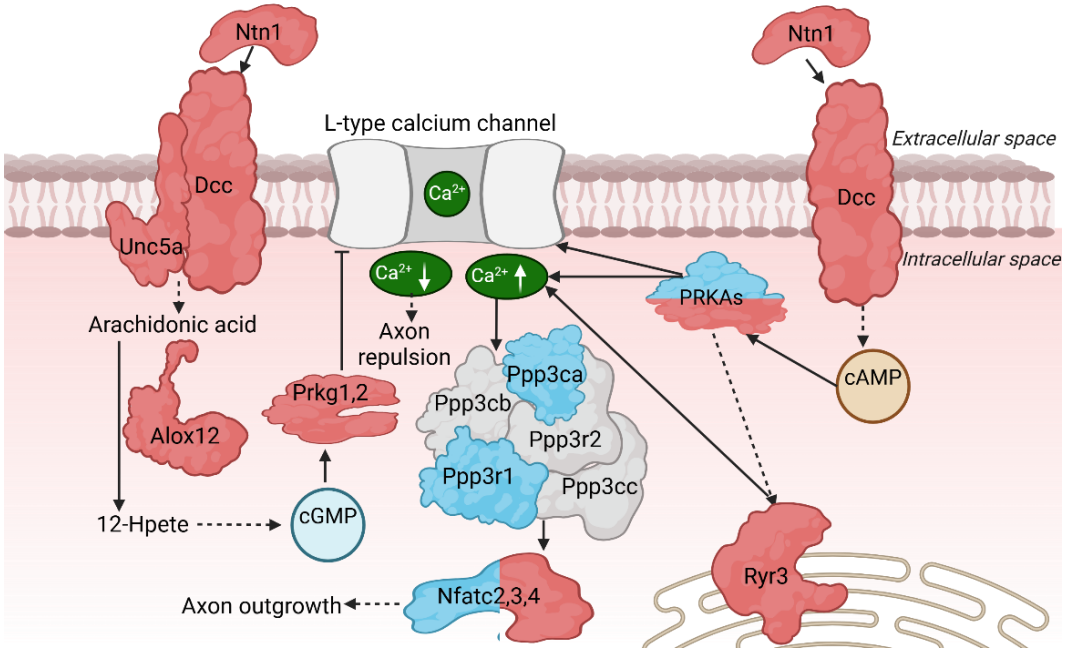


Figure 13. Schematic *in silico* model of UNC5A-DCC signaling-related axon outgrowth/repulsion regulation alterations in non-lesional (blue) and lesional skin (red).

4.1.5. Disturbed WNT5A signaling may influence cutaneous axon growth in psoriasis

We found that WNT5A is affected in psoriatic lesions, and the FZD3 and FZD5 receptor-mediated signaling pathway (also affected in lesional skin) may play a role in axon growth/repulsion (**Figures 9. and 14.**). In contrast, we only found DETs of downstream molecules in the non-lesional skin, and these were mostly affecting axon outgrowth (**Figure 9. and 14.**).

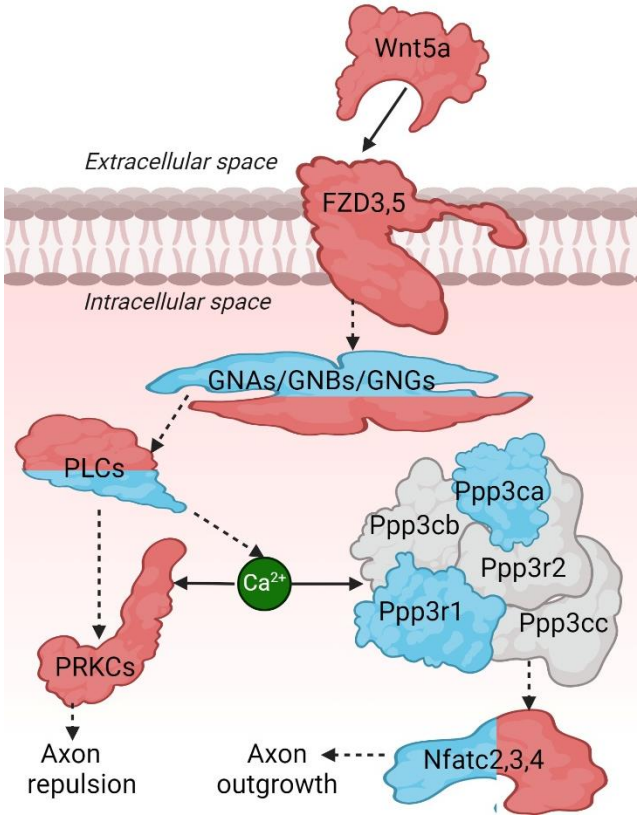


Figure 14. *In silico* model of the effect of Wnt5a signaling on axon growth and retention in psoriasis.

4.2. RESULTS PART 2.: Alterations of histone-related epigenetic regulation in psoriasis

The large number of differentially expressed transcripts identified in non-lesional skin that may affect cutaneous axon structure and function suggested dysregulation of epigenetic modifications. Therefore, we aimed to characterize transcriptional abnormalities of non-lesional skin in psoriasis that may affect the histone-related epigenetic regulatory system. Our analysis highlighted that all three layers of histone-related epigenetic regulation (**Figure 3.)** are affected by differentially expressed transcripts in non-lesion skin **(Figures 15. and 16.)**.

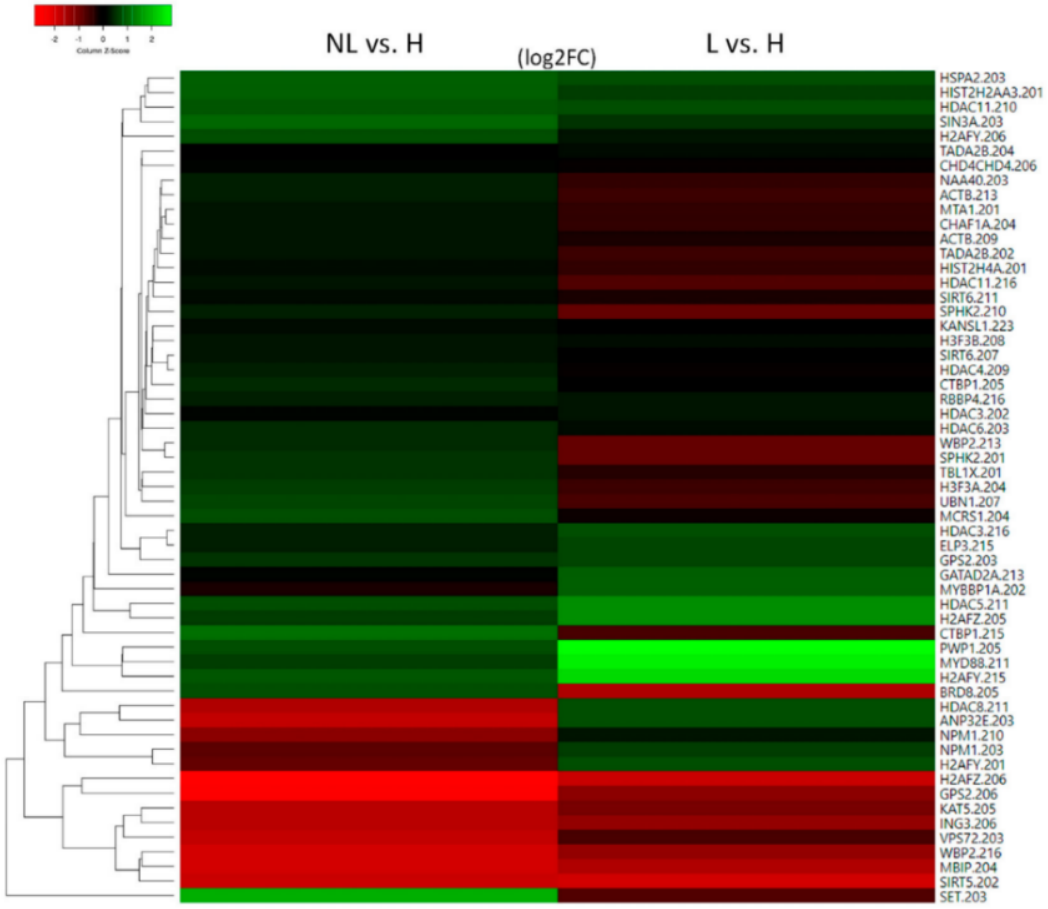


Figure 15. Heatmap of histones, histone chaperones, and histone acetylation-related molecules with altered expression in non-lesional (NL) psoriatic skin (left column) and their expression in lesional (L) skin (right column) compared to healthy (H) skin.

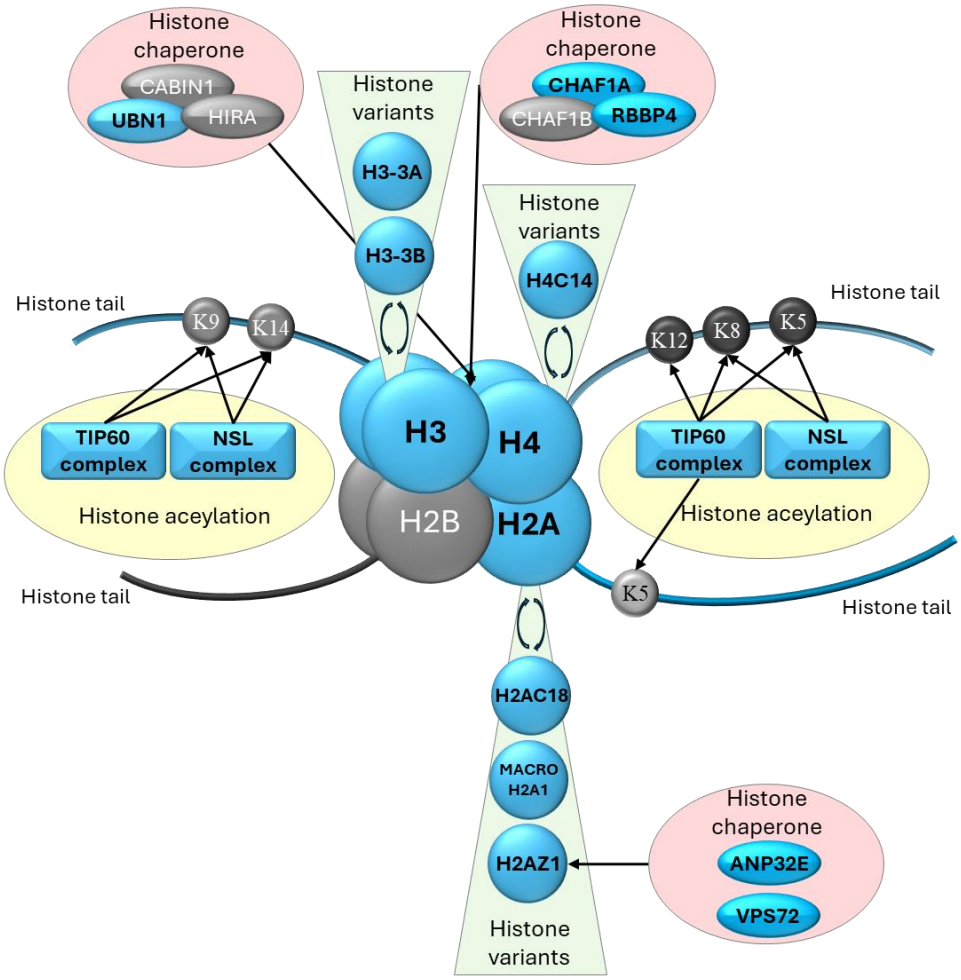


Figure 16. All three layers of histone-related epigenetic modifications are affected by altered expression in non-lesional skin (blue) of psoriatic patients.

4.2.1. Altered expression of histone chaperones in non-lesional skin and their role in cell proliferation and immune system-related processes

The first layer of histone-related epigenetic regulation, mediated by histone chaperones includes the transport, assembly, deposition, removal, and exchange of histones[76]. Histone chaperones play an active role in the assembly of chromatin, which begins with the deposition of H3-H4 tetramers/dimers onto DNA, followed by the addition of H2A and H2B histones[143]. H3-H4 histone deposition is facilitated by the CAF1 histone-chaperone complex in a replication-dependent manner, whereas the HIRA histone-chaperone complex functions in a replication-independent manner[144]. Therefore, we screened for histone chaperones with altered expression in

non-lesional skin. The list of histone chaperones and chaperone complexes applied for our screening is shown in **Figure 17.**

CAF1 histone chaperone complex	FACT histone chaperone complex	H3.3-H4 histone chaperone complex	HIRA histone chaperone complex	Other histone chaperones
CHAF1A	SUPT16H	ATRX	CABIN1	ANP32E
CHAF1B	SSRP1	DAXX	HIRA	HJURP
RBBP4			UBN1	NAP1L1
				NAP1L4
				NCL
				NPM1
				SET
				RSF1
				VPS72

Figure 17. Classification of known human histone chaperones and chaperone complexes applied for our analysis.

As a result of our analysis, we found that CHAF1A and RBBP4, part of the CAF1 complex, and UBN1, part of the HIRA complex, show altered expression in non-lesion skin **(Figure 15.)**. Our literature-based analysis for functions of these chaperones revealed that the replication-dependent histone chaperones of the CAF1 complex including CHAF1A and RBBP4, determine the proliferation–differentiation switch[145]. CHAF1A is known to modulate T cell-associated functions by maintaining the silencing of the Cd4 locus in cytotoxic T cells[146] **(Figure 18.)**. By repressing proliferation-promoting genes, UBN1 regulates cellular senescence[147] **(Figure 18.)**. We also observed differential expression of the histone chaperones NPM1 and SET in non-lesional skin **(Figure 15.)**. NPM1, as a chaperone of the H3-H4 histone[148], contributes to the maintenance of the integrity of the repressed chromatin domain during DNA replication[149] and regulates TLR-mediated signaling[150] **(Figure 18.)**. While SET, protects the H4 histone from premature acetylation modifications[151] and regulates the activity of cyclin B-CDK1 and thus the G2/M phase transition during the cell cycle[152], as well as p53-mediated cellular responses[153,154] **(Figure 18.)**. We also detected differential expression of ANP32E and VPS72 in non-lesional skin **(Figure 15.)**. VPS72 is responsible for the deposition of the replication-independent histone H2AZ1 during mitosis[135], while ANP32E mediates the nucleosomal removal of H2AZ1[155] **(Figure 16.)**. Therefore, the dysregulation of these chaperones may further exacerbate the dysfunction associated with H2AZ1 (see below and **Figure 19.**). Moreover, ANP32E regulates β-catenin/cyclin D1 signaling[156] and together with VPS72 immune cell infiltration[157,158] **(Figure 18.)**.

Members of the FACT and H3.3-H4 chaperone complexes **(Figure 17.)** are expressed normally in non-lesional skin. The heatmap of all differentially expressed chaperone transcripts in non-lesional skin is shown in **Figure 15**.

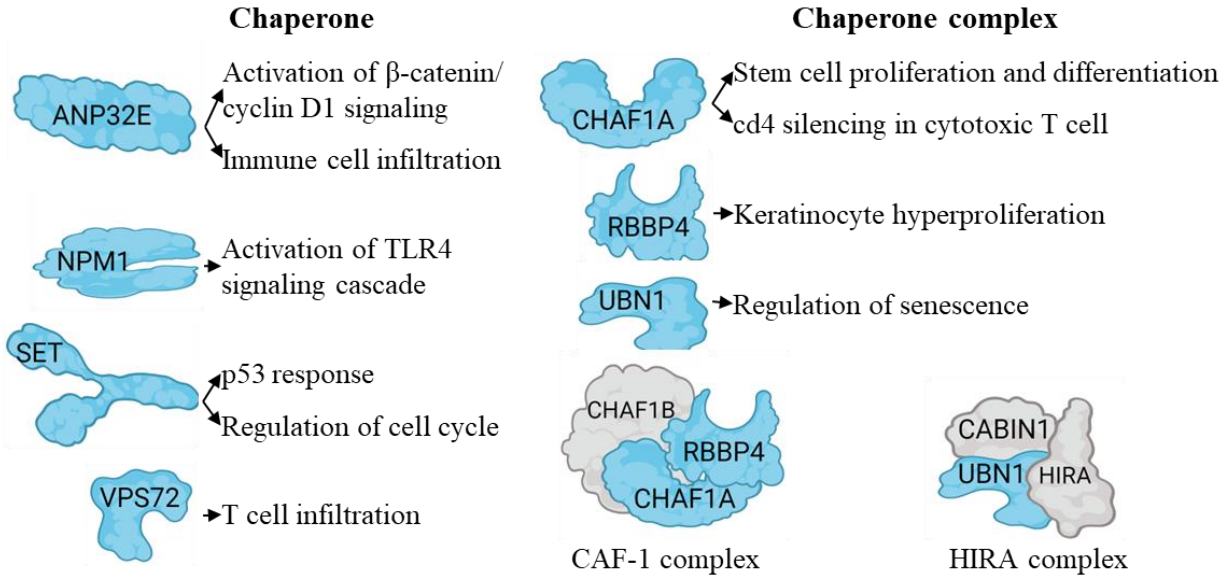


Figure 18. Effects on cell proliferation and immune system-related processes of histone chaperones with altered transcription in non-lesional skin (depicted in blue).

4.2.2. Histones with altered expression in psoriatic non-lesional skin and their effects on cell proliferation and immune system-related processes.

Histones required during DNA replication are called replication-dependent histones that are expressed in a cell cycle-dependent manner[159]. Accordingly, histones can be divided into replication-dependent and replication-independent categories[75] **(Figure 4. and 16.)**.

Based on our analysis, replication-dependent histones H2AC18 and H4C14, (associated with the H2A and H4 histone, respectively) show abnormal expression at the transcription level in non-lesional skin **(Figure 15. and Table 6.)**.

Gene	Transcript	log2fc_LvsH	FDR_LvsH	log2fc_NLvsH	FDR_NLvsH
H2AC18	ENST00000369159.2|HIST2H2AA3-201|549|	0.995	0.370	2.912	0.0093331
H4C14	ENST00000578186.2||HIST2H4A-201|583|	0.043	0.939	1.568	0.0006152

Table 6. Replication-dependent histones with altered expression in non-lesional skin.

Our literature-based analysis of their functions revealed, that apart from DNA replication during proliferation, in non-dividing cells H2AC18 participates in the terminal differentiation program[160]. While the function of H4C14 is largely unknown, however, it is commonly used as a marker for DNA replication[161,162] **(Figure 19.)**.

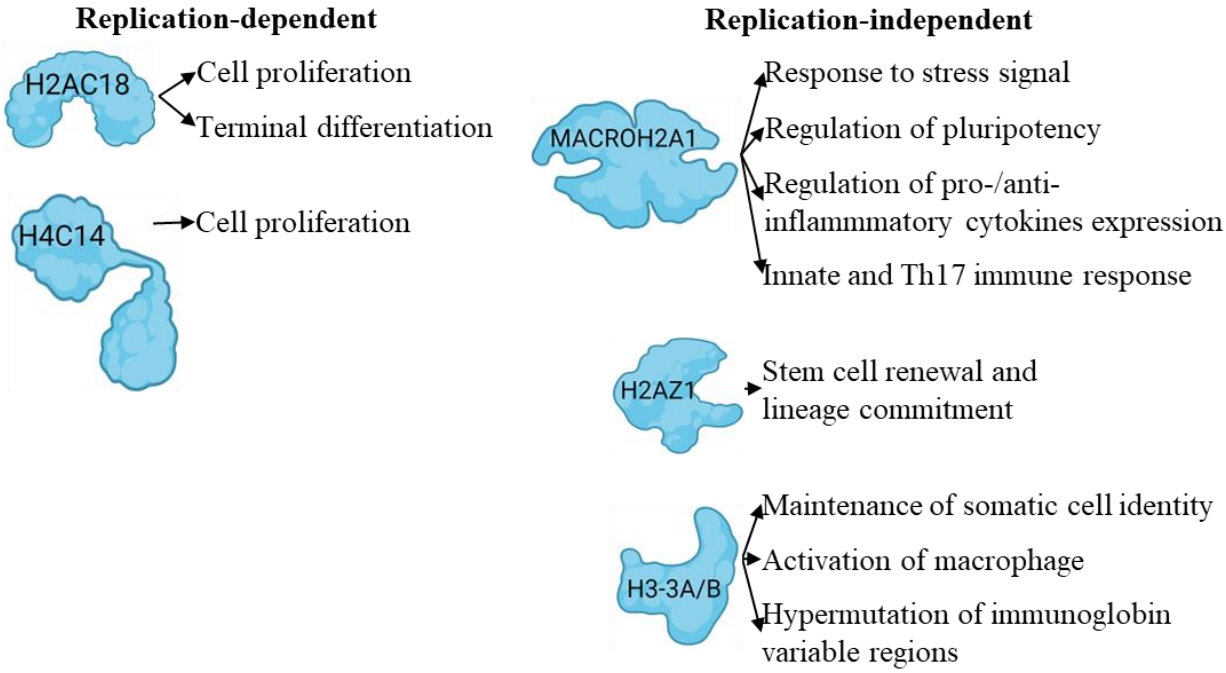


Figure 19. Replication-dependent (left column) and -independent (right column) histones with altered expression in non-lesional psoriatic skin and their known effects on cell proliferation and immune system-related processes.

In contrast to replication-dependent histones, replication-independent histones are expressed throughout the cell cycle[163], they are locus-specific, conferring unique characteristics to chromatin[81]. Replication-independent histones play a specialized role in lineage commitment in general[81]. Our analysis revealed altered transcriptional expression of H2A and H3 histone-associated, replication-independent MACROH2A1; H2AZ1; and H3-3A/B (also known as H3.3 histone**) (Figures 15. and 16.)**.

Our literature-based functional analysis suggests that the MACROH2A1-PARP1 axis plays a multifunctional role in cellular stress responses[164]. MACROH2A1 is known to regulate the transcriptional activity of several key cytokines like IL-1β, IL-6, and IL-8[165] associated with proliferation[166] as well as Th17-mediated inflammatory responses[167]**(Figure 19.).** H2AZ1 is known

to modulate the expression of the proliferation gene Ki-67[168] and influences stem cell renewal[169] and lineage commitment[170] **(Figure 19.)**.

H3.3 histone is involved in the activation of inflammatory macrophages[171], and in the maintenance of somatic cell identity[172,173]. Together with its chaperone (HIRA complex, discussed above and **Figure 18.**), H3.3 histone affects the somatic hypermutation of immunoglobulin variable regions[174] (**Figure 19.)**.

4.2.3. Altered transcription of histone acetyltransferases and complex components and their effects on cell proliferation and immune responses in non-lesional skin

There are two major types of HATs, A-type HATs that acetylate chromatin-incorporated histones, whereas B-type HATs acetylate newly synthesized histones[92]. In addition, several other HATs are not considered to be a part of the two types mentioned above **(Figure 20. A)**. The large majority of HATs function in histone acetyltransferase complexes that exert specific or universal effects[175] **(Figure 20. B)**.

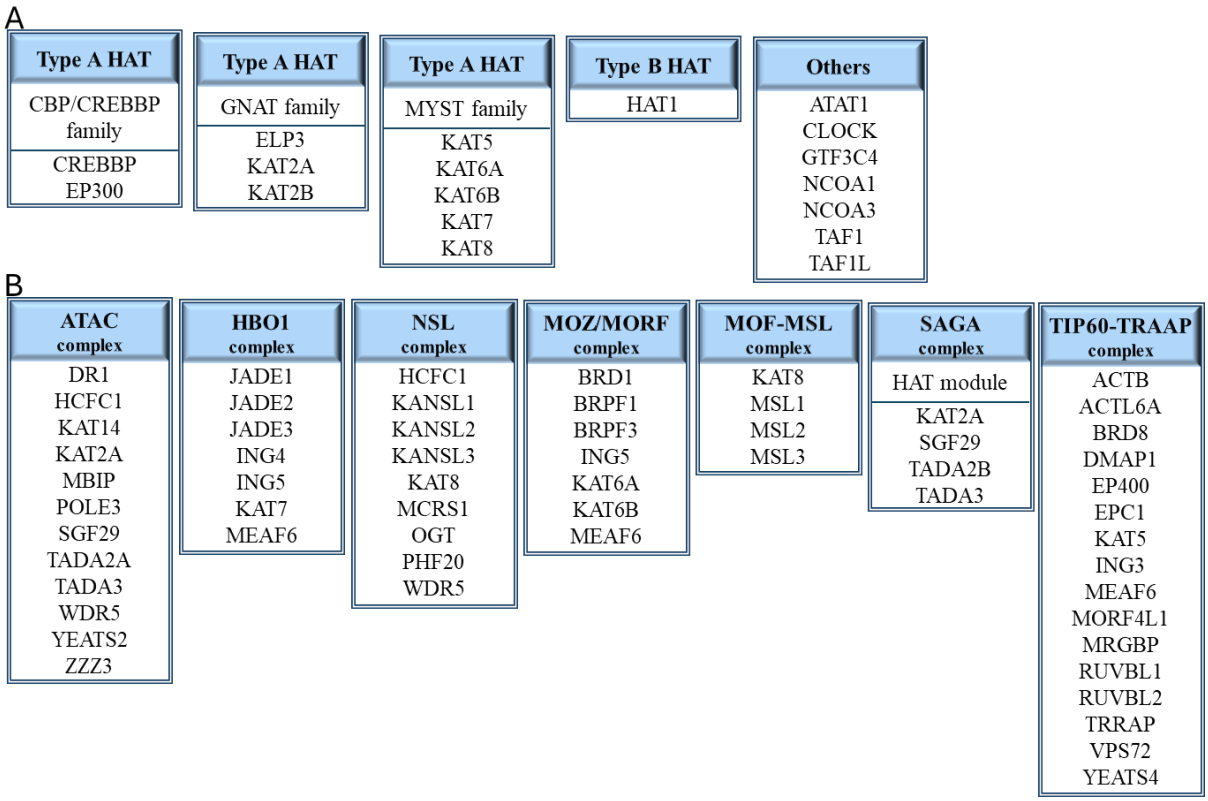


Figure 20. Classification of human histone acetyltransferases (A) and their complexes (B) used in our analysis.

We found that only type A HATs **(Table 7.)** or their modulators show abnormal expression in non-lesional psoriatic skin. In the CBP/CREBBP family, only modulators show abnormal transcription levels, while among members of the GNAT and MYST families, both acetyltransferases and their complexes are affected, including GNAT family associated ATAC and SAGA (HAT module), and the MYST family associated NSL and TIP60 complexes **(Figure 15.)**. Below we present these alterations according to affected HAT families and associated complexes.

Family	Gene ID	Alternative name	Target histone acetylation site	Assay
CBP/ CREBBP	CREBBP	KAT3A	H3K18	Genetic deletion, mouse cells
			H3K27	Cell-free HAT assay; Genetic deletion, mouse cells
			H3K56	siRNA in cells
	EP300	KAT3B	H3K18	Genetic deletion, mouse cells
			H3K27	Genetic deletion, mouse cells
			H3K56	siRNA in cells
GNAT	**ELP3**	KAT9	?	?
	KAT2A	GCN5	H3K9	Cell-free HAT assay; Genetic deletion, mouse cells; shRNA in cell
			H3K14	Cell-free assay; shRNA in cell
	KAT2B	PCAF	H3K9	Genetic deletion, mouse cells
MYST	**KAT5**	TIP60	H2AK5	Cell-free assay
			H2AK15	
			H3K14	
			H4K5	
			H4K8	
			H4K12	
			H4K16	
	KAT6A	MOZ	H3K9	Genetic deletion, mouse embryos; In cells, shRNA KD
			H3K14	In cells, shRNA KD
			H3K23	
	KAT6B	MOZ2	H3K23	In cells, shRNA KD
	KAT7	HBO1	H3K9	In cells, shRNA KD
			H3K14	Constitutive KAT7; Genetic deletion mouse cells; In cells, shRNA, siRNA; Constitutive KAT7
			H4K5	In cells, shRNA , siRNA;
			H4K8	In cells, shRNA KD
			H4K12	In cells, shRNA ,siRNA;
	KAT8	MOF	H4K16	In cells, siRNA; Genetic deletion mouse embryo

Table 7. Type A histone acetyltransferases and their known targets used for our analysis (Based on Voss AK, Thomas T. 2018[176]).

4.2.3.1. CBP/CREBBP histone acetyltransferase-related alternations in non-lesional skin

Members of the CBP/CREBBP family, responsible for the acetylation of the core histones[177], did not show transcriptional differences in non-lesional psoriatic skin. However, abnormal expression of modulators of the CBP/CREBBP family member EP300, such as the EP300 corepressor CTBP1[178], was observed in non-lesional samples (**Figure 15.)**.

4.2.3.2. Histone acetyltransferase-related alternations of the GNAT family in non-lesional skin

Members of the GNAT histone acetyltransferase family are primarily responsible for the acetylation of the lysine residues of histone H2B; H3 and H4[179]. We observed abnormal expression of the GNAT family member ELP3 in non-lesional skin **(Figure 15.)**. ELP3 is known to inhibit M1 and stimulate M2 macrophage polarization[180].

The GNAT family component KAT2A does not show transcriptional level alterations in non-lesional skin. However, KAT2A expresses its enzymatic activity at full capacity only when integrated into one of the two macromolecular complexes ATAC or SAGA[181] (**Figure 20.**). Therefore, the transcription profile of these complex components was also analyzed. In the SAGA multiprotein complex KAT2A serves as the catalytic unit of the HAT module[181]. As part of the HAT module, only TADA2B shows transcriptional abnormalities in non-lesional skin **(Figure 15.)**. Our literature-based functional analysis of TADA2B suggests that TADA2B is involved in the UV-induced p53-dependent response[182] **(Figure 21.)**.

The HAT module of the SAGA complex shares several components with the large acetyltransferase ATAC complex[181], one of the major regulators of mitosis through the acetylation of histone H3 and H4[183]. Among ATAC complex components, MBIP shows altered expression in non-lesioned skin **(Figure 15.)**.

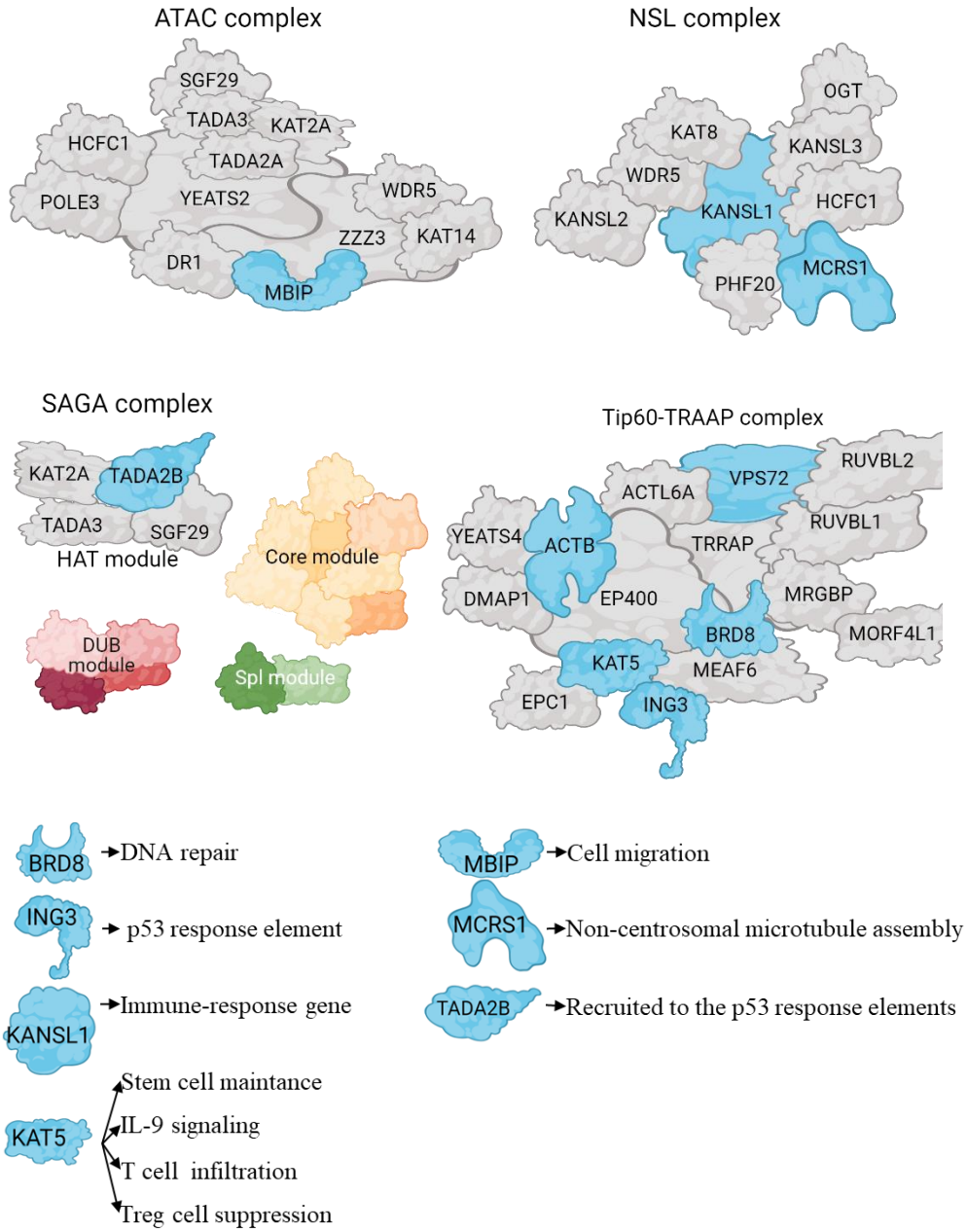


Figure 21. Altered transcription of histone acetyltransferase complex components in non-lesional skin (depicted in blue) affects cell proliferation and immune system-related processes.

4.2.3.3. MYST family histone acetyltransferase-related alternations in non-lesional skin

The MYST family of histone acetyltransferases predominantly acetylates lysine residues on histones H2A, H3, and H4[179].

We found that the MYST family member KAT5 has altered expression in non-lesional skin **(Figure 15.).** KAT5 modulates the differentiation and tissue infiltration of Th17 and Treg cells via FOXP3[184]. KAT5 regulates IL-9 signaling[185] and hematopoietic stem cell maintenance[186] **(Figure**

21.). KAT5 is also a catalytic subunit of the Tip60 histone acetyltransferase complex. Among the members of the Tip60 complex members, we identified abnormal expression of ACTB, BRD8, and ING3, in non-lesional psoriatic skin **(Figure 15.)**. The TIP60 complex coactivators BRD8 and ING3 regulate p53-dependent gene suppression and cell cycle[187,188] **(Figure 21.).**

KAT8, which is also part of the MYST family, does not show differences at the transcriptional level in non-lesional skin. The catalytic activity of KAT8 modulates the acetylation of H4 histone in a complex-dependent manner[189]. According to our analysis, we have identified only differential transcriptional expression of two members of the KAT8-associated NSL complex KANSL1 and MCRS1 in non-lesional skin compared to healthy ones **(Figures 15. and 20.)**. Based on literature mining, the NSL complex regulates the acetylation of H4K5 and H4K8 in general[189]. In particular, KANSL1 is a master regulator of immune gene expression[190]**,** while MCRS1 protects chromosome-associated microtubules from depolymerization during mitosis[191] **(Figure 21).**

4.2.4. Histone deacetylases and complex components: transcriptional alterations in non-lesional skin and their role in cell proliferation and immune responses

Histone deacetylases (HDACs) are enzymes that play a crucial role in regulating gene expression by removing acetyl groups from histone proteins[90], leading to chromatin condensation and transcriptional repression[96]. In humans, HDACs are involved in various biological processes, including cell cycle regulation[192], differentiation[193,194], and immune responses, and are implicated in inflammatory conditions[195]. Therefore, we included these molecules as well in our study. A comprehensive list of the histone deacetylases and their complexes applied in our screening are shown in **Figure 22**. Although most HDACs exert their effects globally on histones, some HDAC enzymes exhibit preferential targeting of histone acetyl chains (**Table 8.**). Our analysis suggests that all four Histone deacetylase (HDAC) families (I-IV), and some members of the HDAC I. family-related complexes are affected in non-lesional skin, which we discuss below according to their families.

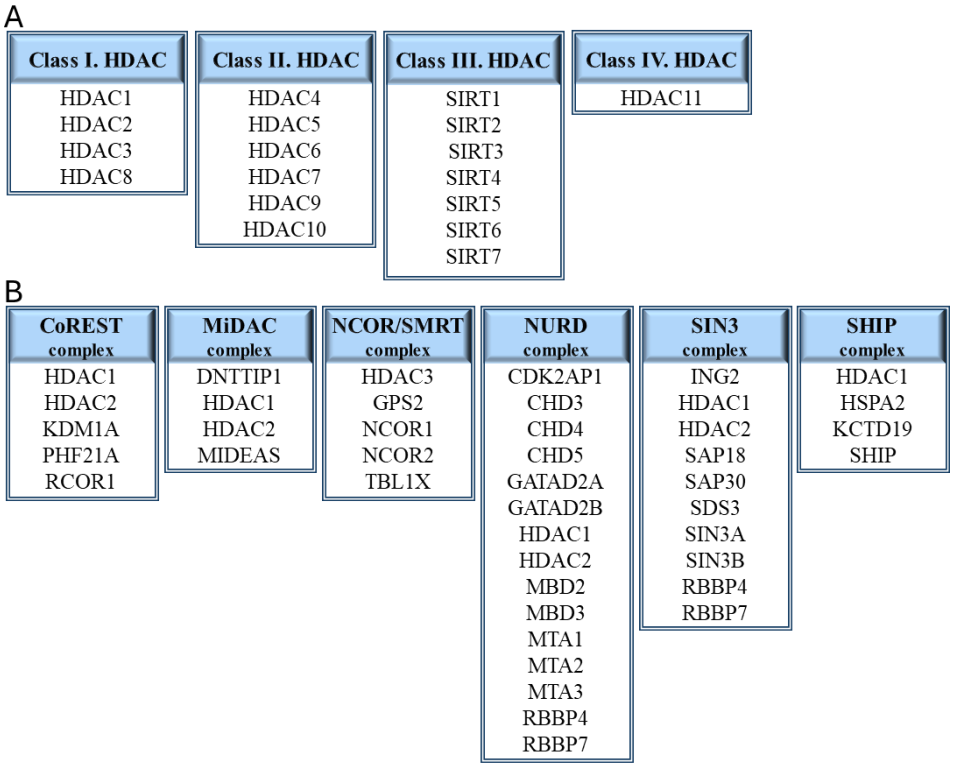


Figure 22. Classification of histone deacetylases (A) and histone deacetylase complexes (B) applied for screening.

Family	Cofactor	Gene ID	Alternative name	Target histone acetylation site
Class I.	Zn2+- dependent	HDAC1	RPD3L1	H2A; H2AB; H3; H4
		HDAC2	-	
		HDAC3	-	?
		HDAC8	HDACL1	H3; H4
Class II.		**HDAC4**	BDMR	H2A; H2B;H3; H4
		HDAC5	-	
		HDAC6	-	H3K9; H3K56
		HDAC7	HDAC7A	?
		HDAC9	-	
		HDAC10	-	
Class III.	NAD+ dependent	SIRT1	-	H3K9; H4K16
		SIRT2	-	H3K56; H4K16
		SIRT3	-	H3K16
		SIRT4	-	?
		SIRT5	-	?
		SIRT6	-	H3K9; H3K56
		SIRT7	-	H3K18
Class IV.	Zn2+- dependent	**HDAC11**	-	H3K9; H3K14

Table 8. HDACs and their targets utilized for our study. (Based on Manou et. al., 2023[196])

4.2.4.1. Differentially expressed HDAC I. family members and complexes in non-lesional skin: their role in proliferation, differentiation, and immune regulation.

Class I. histone deacetylases are responsible for the removal of lysine acetyl groups of histones[197]. Out of four classes of histone deacetylases (HDAC I.-HDAC IV.), members of HDAC Class I. exhibit the strongest histone deacetylase activity[198]. Most of the members of this class including HDAC1; HDAC2 and HDAC3, require multiprotein complexes to achieve maximal enzymatic activity[199].

Among the members of the HDAC I. histone deacetylase family, HDAC3 and HDAC8 showed altered expression in non-lesional skin **(Figure 15.)**. HDAC3 is part of the NCOR/SMRT complex, which is responsible for nuclear receptor-mediated transcriptional repression[200,201] **(Figure 22)**. From the NCOR/SMRT complex, we observed the abnormal expression of the GPS2 and TBL1X genes **(Figure 15.)**. Our literature-based screening for known functions of HDAC3 revealed that by regulating the water channel AQP3, HDAC3 modulates osmotic stress responses to maintain skin moisture and avoid skin dryness[202]. The proper function of HDAC3 is also essential for LPS-induced inflammatory gene expression in macrophages[203] (**Figure 23.**). By interacting with TBL1X, HDAC3 modulates Wnt/β-catenin and NF-κB -regulated transcription[204] **(Figure 24.)**.

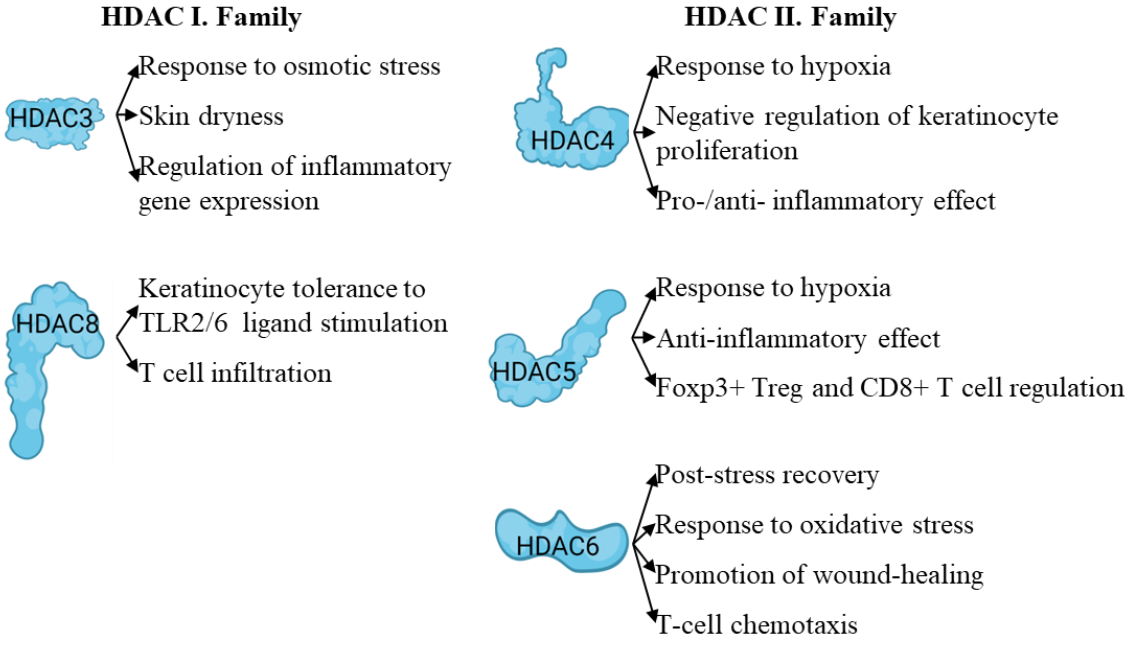


Figure 23. The impact of differentially expressed HDACI and HDACII on proliferation, differentiation, and immune regulation in non-lesional skin.

HDAC8 in keratinocytes regulates skin inflammation and impacts T cell responses by preserving immune tolerance[205] **(Figure 23.)**.

We found that HDAC I. family members HDAC1 and HDAC2 are normally expressed in non-lesional skin, but the expression of their repressor SPHK2 is altered **(Figure 15.)**. SPHK2 by inhibiting HDAC1/2 activity[206], modulates T cell differentiation[207].

In addition, we observed altered expression levels of several members of the HDAC1/2 protein complexes **(Figure 22.)**, which affect the function of the NURD, SHIP, and SIN3 complexes **(Figure 15.).**

The NURD complex is a multi-functional complex that plays a role in chromatin remodeling; regulation of histone deacetylase activities; and control of T cell development[208], their cell cycle progression, and progenitor cell maintenance[209]. Our analysis reveals that NuRD complex members CHD4, GATAD2A, MTA1, and RBBP4 exhibit altered expression in non-lesional skin (**Figure 15.).**

Our literature-based screening revealed that CHD4 plays an important role in the early development of the basal epidermal layer and regulates the induction and development of hair follicles by destabilizing the interactions between DNA and histones[210]. In keratinocytes, CHD4 can increase stress tolerance by limiting the expression of stress response genes[211]. CHD4 also regulates Th2 cell differentiation[212], CD8+ T-cell infiltration[213](**Figure 24.**). Since MTA1 is sensitive to a variety of stress conditions[214], it is often referred to as a "stress-response" protein and also plays a role in the regulation of NF- κB signaling in macrophages[215] **(Figure 24.**).

Among members of the SHIP complex, we identified altered expression of HSPA2 in non-lesional skin (**Figure 15.**). HSPA2 contributes to early keratinocyte differentiation[216] and acts as an important factor in the establishment and maintenance of the properly stratified epidermis[217] **(Figure 24.)**.

The SIN3 multiprotein complex influences protein stability, transcriptional activity, aging and heterochromatinization events, cell proliferation/cell cycle progression, cell survival[218], and maintenance of pluripotency[219]. Among the SIN3 complex components, SIN3A and RBBP4 showed abnormal expression in non-lesional skin **(Figure 15.)**. Sin3A regulated T cell development[220], in particular Th17 cell differentiation, and the establishment of their inflammatory potential[221]. While in the skin, Sin3A is known to regulate terminal differentiation and the maintenance of epidermal homeostasis[222] **(Figure 24.)**.

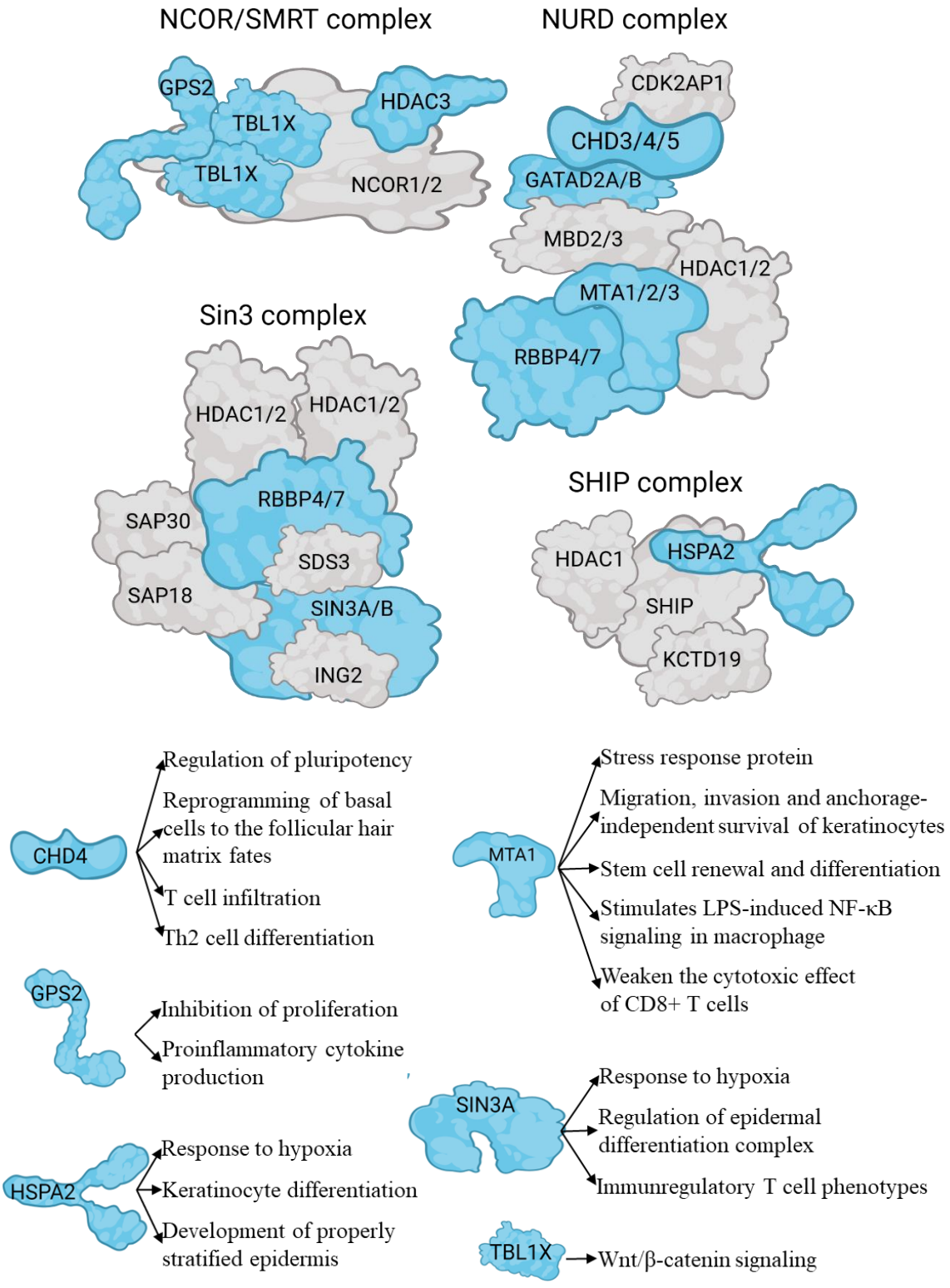


Figure 24. The impact of differentially expressed HDAC complex components (depicted in blue) on proliferation, differentiation, and immune regulation in non-lesional skin.

4.2.4.2. The influence of HDAC II family proteins with differential expression on cellular proliferation, differentiation, and immune regulation in non-lesional skin.

Members of class II. histone deacetylases have relatively weak enzymatic activity compared to other classes[223,224]. Among members of the HDACII family, HDAC4, HDAC5, and HDAC6 show altered expression in non-lesional skin (**Figure 15.**).

The histone deacetylase HDAC4 may exhibit both pro- and anti-inflammatory effects depending on the target gene. While HDAC4-induced NF-κB gene expression inhibition results in the decreased production of proinflammatory cytokines[225], when inflammatory processes are initiated, it can also increase inflammation by indirectly activating Foxo3a[226](**Figure 23.)**.

HDAC5 regulates the transformation of CD4+ T cells into Tregs and the cytokine production of CD8+ T cells[227]. Moreover, fluid shear stress stimulates the phosphorylation and nuclear export of HDAC5, which plays an important role in the establishment and maintenance of flow-regulated anti-inflammatory processes[228] (**Figure 23.)**.

Another HDACII family member, HDAC6, promotes cell motility[229] during wound healing[230] and chemotaxis of T lymphocytes[231], and it regulates the organization of immune synapses[232] (**Figure 23.)**.

4.2.4.3. The contribution of differentially expressed HDAC III family members to cell proliferation, differentiation, and immune regulation in non-lesional skin

Among the HDACIII family members, SIRT5 and SIRT6 showed abnormal expression in non-lesional skin **(Figure 15.)**. SIRT5 has weak histone deacetylase activity[233], while SIRT6 has significant histone deacetylase activity, particularly targeting H3 histones[234 -236]. SIRT5 negatively regulates keratinocyte proliferation and inflammation (IL-17A induction) and improves epidermal barrier dysfunction[237] **(Figure 25.)**.

SIRT6-mediated histone H3 deacetylation at the N-terminal tail (H3K9ac)[234] and during the cell cycle at the globular core (H3K56ac) regulates telomeric chromatin structure[235], which is necessary to maintain genomic stability and proper lifespan[236]. It regulates the balance between the M1 and M2 macrophages, influences wound healing[238], inhibits skin inflammation[239], and plays a role in classical dendritic cell differentiation and function[240] **(Figure 25.)**.

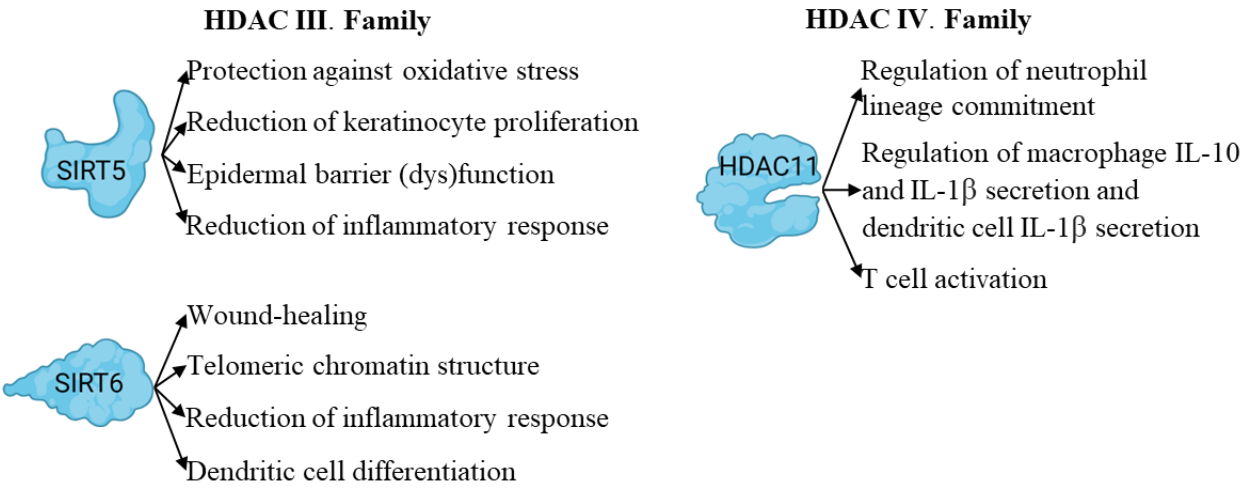


Figure 25. The role of differentially expressed HDAC III. and IV. family in the processes of proliferation, differentiation, and immune regulation in non-lesional skin.

4.2.4.4. The effect of HDAC IV family enzymes with variable expression on the regulation of cellular proliferation, differentiation, and immune functions in non-lesional skin.

Among members of the HDACIV family, only HDAC11 was identified in our analysis with differential expression in non-lesional skin (**Figure 15.**). The biological function of this family is largely unknown. However, HDAC11 plays an important role in immune regulation, neutrophil lineage commitment[241], and inflammatory responses, including the regulation of macrophage IL-10[242] and IL-1β secretion[243], dendritic cell IL-1β secretion[243], and T cell activation[244,245] (**Figure 25.**).

5. DISCUSSION

Psoriasis is a chronic inflammatory skin disease in which interleukin (IL)-17 is one of the main drivers of altered inflammatory responses[246]. Studies, including the imiquimod-induced psoriasis-like skin inflammation models in mice[247], suggest that the peripheral nervous system may play a role in initiating and maintaining the inflammatory and hyperproliferative responses through the release of neuropeptides[43,48]. Neuropeptides of cutaneous nerve projections can activate IL-23 production of dermal dendritic cells, which triggers IL-17 expression of T cells[247]. In line with the central role of this sequence of events, drugs targeting IL-17 and IL-23 are some of the most effective ones available for the treatment of psoriasis[248,249]. Therefore, further knowledge of peripheral nervous system-related abnormalities may contribute to a better understanding of the pathomechanism of psoriasis.

During our transcriptome analysis, we found that neuritogenesis is likely to be disturbed in psoriatic patients. Newly identified transcriptional abnormalities affect the semaphorin-plexin signaling cascades that regulate several features of neuronal projection formation-related processes[250]. Semaphorins were originally identified as neuronal and axon growth guidance molecules. The superfamily of semaphorins includes more than 20 members of soluble extracellular and cell surface transmembrane signaling proteins. Semaphorins can modulate the development and function of several organs, including the cardiovascular[251], immune[252,253], and nervous system[254], among others[255,256]. Despite their massive role in innate immune responses and inflammation[257], only a limited amount of data is available on the involvement of semaphorins' in the pathogenesis of psoriasis pathogenesis[258-260]. Moreover, there is no information on axon formation-related processes in the context of this disease. Since neuritogenesis is known to be affected[57] in psoriasis, it is not surprising that DETs of semaphorins were identified in our study, given their clear role in axon guidance. Most of the molecules, such as SemaB and SemaF, have been implicated in both axon attraction and repulsion[261]. These antagonistic functions may be due to the differences in their local concentrations, and/or the receptor repertoire on the interacting cells. Sema3E can stimulate axon growth of PLXND1 and NRP1 expressing neurons, but when PlexinD1 is expressed without NRP1, Sema3E has an opposite effect[262]. In addition, Sema3E interaction with its co-receptor VEGFR2 can also stimulate axon extension[263]. Although VEGFR2 was not affected in our analyzed dataset, the expression of other Sema receptors, including NRP1, NRP2, PLXNA3, PLXNB1, PLXNB3, PLXND1, as well as L1CAM, and ERBB2 were

differentially expressed in psoriatic samples. The decrease in Sema3D could negatively influence both the numbers and the branching of peripheral axons[264]. Interestingly, the expression of this molecule was affected in lesions, which may be one of the reasons why the number of neurites and axonal branching is reduced in psoriatic patients[57]. In line with our axon growth-related results, NRP1 has been implicated in the pathomechanism of psoriasis by several studies concerning keratinocyte proliferation and differentiation, angiogenesis, and lymphangiogenesis among others (reviewed by Sunhyo Ryu and colleagues[260]).

Class IV semaphorins are thought to be transmembrane proteins[257]. Sema4D presented on the cell surface influences axon regeneration, and its overexpression can inhibit neuronal myelination[142]. Sema4D is also expressed by various immune cells, including T cells, and could modulate dendritic cell functions[265]. In psoriasis, T cells infiltrate not only the dermis, where they may interact with dermal dendritic cells but also the epidermis to contact with Langerhans cells. Sema4D has also been suggested to induce keratinocyte-mediated inflammatory responses in psoriasis[259]. Moreover, myelination of neurites is the least pronounced in the epidermis, where Sema4D(+) T cells may disrupt the myelination processes, and thereby negatively influence axon regeneration. Consistent with this concept, we found several major myelin-associated proteins[266], including MBP, MPZ, PMP22, and RTN4 with altered expression in psoriatic lesions. RTN4 (also known as NOGOA) is a myelin-associated inhibitor of axon growth and regeneration following nerve injury[267] and may contribute to the reduction of neurites[57] in lesions.

We also found differential expression of SLIT2 and its receptor ROBO1 in lesional skin, which are known to be expressed by both axons and Schwann cells, and ROBO2, which is predominantly expressed by axons at least in mice[268]. We also found Schwann cell-expressed NTN1 to be affected in psoriatic lesions, which is not only involved in axon regeneration following nerve injury[269], but can also influence neutrophil, macrophage, and T-cell infiltration[270]. In addition, dendritic cell-derived Sema4A was suggested to play a role in the activation of both Th1 and Th17 cells in the neuroinflammatory demyelinating autoimmune disease, multiple sclerosis[271,272]. This molecule is also affected by DETs in psoriatic patients.

In the nervous system, Sema4B plays a role in synapse formation and maintenance and may influence postsynaptic density[273]. We found altered expression of this molecule only in non-lesional skin. In addition, Sema4B could inhibit basophil-mediated Th2 skewing[274] and contribute to the developing Th1/Th2 imbalance in psoriasis[275]. Apart from this, circular SEMA4B RNA may reduce

the effect of IL-1β through Wnt signaling[276]. This pathway may also influence axon growth/repulsion via WNT5A (and its receptors FZD3 and FZD5) that we found to be affected in psoriatic lesions, consistent with previous observation[277]. It may also act as a suppressor of axonal regeneration[278], and at the same time, facilitate CXCL12-CXCR4-mediated T-cell infiltration[279], with the latter being known to be important in chronic inflammatory skin diseases[280].

Therefore, we propose that dysregulation in 12 different semaphorins and some of their main receptors and co-receptors may contribute to the abnormal neuron projection formation described earlier in psoriasis[57]. Semaphorin signaling may also strongly influence other major hallmarks of psoriasis, including innate immune and inflammatory processes[257]. Therefore, our study can highlight an additional angle of the crosstalk between the neuro-immune system, which may be another important factor in the pathomechanism of psoriasis, in addition to the neurogenic pro-inflammatory mediators.

It is important to note that the vast majority of semaphorin signaling cascades, as well as SLIT-ROBO and NTN-DCC signaling, exert their effect through the small GTPase RAC1[267]. This molecule not only connects the cutaneous nervous system and the immune cells but also keratinocytes, where it can influence proliferation, differentiation, and innate immune processes[281]. Based on these features, RAC1 is likely to be an important molecule in psoriasis. RAC1 is also known as a Ras-related C3 botulinum toxin substrate 1, as it is the primary target of botulinum toxin.

The large number of differentially expressed transcripts found in non-lesional skin suggests a more global transcriptional abnormality that can also influence the neuronal function of the skin. We hypothesized that epigenetic dysregulation can result in such global transcriptional regulatory abnormality. Several epigenetic regulators like histone acetyltransferases and deacetylases impact the development and myelination of the peripheral nervous system[282,283], and thereby affect axon regeneration[284,285] and Schwann cell development[286,287]. Evidence supports the significance of epigenetic modifications in neuronal biology, as indicated by the therapeutic benefits observed with several inhibitors of histone acetyltransferases and histone deacetylases in treating neuronal disorders[288-290]. Trichostatin A and Vorniostat, histone deacetylase inhibitors, have been proven to be potential therapeutic agents in neurodegenerative diseases[288,290]. Trichostatin A inhibits axon degeneration and Schwann cell proliferation/differentiation[288]; whereas Vorniostat promotes neuronal outgrowth and axon regeneration[290]. Therefore, it is not surprising that both Trichostatin

A[291] and Vorniostatin have been established to be potential therapeutic agents in psoriasis[292]. Current literature suggests that Trichostatin A has an advantageous impact on Treg/Th17 cell balance[291], while Vorinostat has a beneficial effect on keratinocyte hyperproliferation in the treatment of psoriasis[292]. These findings propose that a deeper understanding of the molecular mechanisms involved in histone-related epigenetic regulation may be crucial for a better understanding of psoriasis pathogenesis. Histone chaperones, histone variants, and post-translational modifications of histones, including histone acetylation and deacetylation, are located at the apex of epigenetic regulation. Since the molecular mechanisms associated with non-lesional skin are less well understood in psoriasis, our study focuses on the characterization of epigenetic dysregulation of these skin areas.

Histone chaperones by regulating the assembly, deposition, removal, exchange, and transport of histones[76], modulate proliferation rate, and inflammatory responses. Histone chaperones of the CAF1 complex members CHAF1A and RBBP4 found with altered expression in non-lesional skin determine proliferation–differentiation switch[145], and modulate T cell-functions[146] that are known to be abnormally regulated in psoriasis[293 -295]. In line with our results, RBBP4 levels are known to be upregulated in psoriasis by skin-derived mesenchymal stem cells, contributing to epidermal hyperplasia[296]. The histone chaperone UBN1 regulates tissue aging-associated cellular senescence[147]. Consistent with our results, middle and upper epidermal keratinocytes of psoriatic plaques are characterized by a "special state of aging", characterized by cell cycle arrest, as well as the altered release of inflammatory effectors and other molecules characteristic of aging[297]**.** Abnormal expression of chaperone NPM1 and SET in non-lesional skin may further exacerbate H4 histone-related abnormalities. Moreover, NPM1 expression is known to be increased in proliferating keratinocytes of psoriatic lesions influencing CDKs[298] and can activate inflammatory responses when released into the extracellular space[299]. These changes, characteristic of non-lesional skin, may be important in the development of the disease, as previous studies have shown increased activity of CDK1 and CDK2 in the psoriatic epidermis[300,301]. Moreover, chaperone ANP32E together with VPS72 may potentially affect immune cell infiltration in psoriasis[157,158]. ANP32E also regulates β-catenin/cyclin D1 signaling and thereby proliferation[156]. In line with our results, the expression of β-catenin is inversely proportional to keratinocyte hyperproliferation, with a slight decrease in non-lesional skin and an intense decrease in β-catenin expression in lesional skin compared to healthy controls[302].

In summary regarding histone chaperone-related non-lesional skin-associated abnormalities, we found expressional alterations affecting members of the H4 histone-associated CAF-1 and HIRA chaperone complexes and the NPM1 and SET chaperones. Additionally, our analysis also revealed differential expression profiles of two replication-independent H2A histone-related chaperones in non-lesional skin compared to healthy samples. Based on their regulatory functions and their altered expression these histone chaperones may modulate proliferation[145,156,298] and inflammatory process[157,158,299] in non-lesional skin.

Based on their role in DNA replication, replication-dependent, and replication-independent histone variants can be distinguished[75], which substitute each other according to the cellular state[74]. In humans 95 genes code for different histone variants[75], which vary in their structure as well as in the number and position of post-transcription modification sites[303], allowing them to carry out distinct and specialized roles that regulate tissue- and cell type-specific functions.

Our study demonstrated that there are two abnormally expressed replication-dependent histones in non-lesion skin: H2AC18 and H4C14. For rapid and uniform protein production, replication-dependent histone genes lack introns and therefore do not go under splicing[304]. Consequently, replication-dependent histones have only one transcript that is translated into protein. Having only a single transcript, differential expression of H2AC18 and H4C14 in non-lesional skin is likely to have great importance clearly indicating that proliferation[161,162] and/or differentiation[160] is already affected in non-lesional skin of psoriatic patients. Determining the direction and difference in expression level is also relevant in the case of a single protein-coding transcript. Allowing us to conclude that in non-lesional skin the total transcriptional expression of H2AC18 is 7.528-fold increased (FDR=0.0093), whereas the expressional level of H4C14 is 2.966-fold increased (FDR=0.0006) compared to healthy, based on a high and therefore reliable number of samples. Moreover, the expression of these two histones in lesional skin is similar to those of healthy controls. However, further studies are required to establish whether they contribute to proliferation and differentiation-related alterations in psoriasis or play a role in the maintenance of the non-lesional state.

In addition, we detected the involvement of H2A and H3 histone-associated replication-independent histone variants MACROH2A1, H2AZ1, and H3-3A/B at the transcriptional level in non-lesional skin. Replication-independent histones regulate lineage commitment and somatic cell reprogramming[81], therefore their abnormal expression has a potential role in the epithelial-

mesenchymal transition, which is known to take place in psoriatic lesional skin[305]. Altered transcriptional expression of MACROH2A1 and H2AZ1 histones may further exacerbate expression and functional abnormalities associated with replication-dependent H2AC18 in non-lesional skin. MACROH2A1 also regulates cellular stress responses[164], alternative transcriptional expression, and may contribute to the Koebner phonemon[306] characteristic for non-lesional skin. MACROH2A1 also regulates the expression of IL-1β, IL-6, and IL-8[165]. However, these cytokines show altered expression only in psoriatic lesions and have been associated with keratinocyte hyperproliferation[166,307] as well as Th17-mediated (IL-1β)[167,308] immune responses[307]. Similarly, H2AZ1 modulates Ki-67[168] which shows an increased expression only in psoriatic lesions[309]. H3.3 is known to regulate macrophage activation[171], somatic hypermutation of immunoglobins[174], and cell line commitment[172,173], whose abnormalities are characteristic of skin lesions in psoriasis[305,310,311].

The exact consequence of the altered expression of MACROH2A1, H2AZ1, and H3.3 in non-lesional skin is largely unknown. However, in contrast to replication-dependent histones, replication-independent histones have multiple transcript variants (resulting from splicing)[312], coding for different protein isoforms. These different isoforms although being less well characterized, often have modified or even opposing biological functions[120] that may have a yet unrealized relevance in the development of the disease.

Taken together altered expression of histones regulates proliferation[161,162,168], differentiation[160], as well as innate and adaptive immune cell-mediated pro- and anti-inflammatory responses[165,171], suggesting that these processes are already affected in non-lesional skin.

Histone acetylation is carried out by histone acetyltransferases (HATs)[90]. There are two major types of histone acetyltransferases, type A and B[92], among which, only two type A HATs and two of their modulators show abnormal expression in non-lesional psoriatic skin. There are 18 different histone acetyltransferases in humans, which form several regulatory complexes with over 80 additional components and their variants, many of which can be exchanged, resulting in an extremely large combination of complexes. This high variability allows nearly a gene-specific fine-tuning upstream of transcription factor-mediated regulation of gene expression.

In non-lesional psoriatic skin, CBP/CREBBP family members, responsible for H3 histone acetylation, are expressed normally. However, altered expression of the modulator of the CBP/CREBBP family member EP300 namely CTBP1 was observed in non-lesional skin that may

affect type A HAT-mediated histone acetylation. In agreement with our results, elevated levels of CTBP1 have been demonstrated in psoriatic plaques[313]. Moreover, mice overexpressing CTBP1 in keratinocytes show severe skin inflammation with increased expression of Th1 and Th17 cytokines[313].

Members of the GNAT histone acetyltransferase family acetylate histones H2B, H3, and H4[179]. We show that GNAT family member ELP3 is being abnormally expressed in non-lesional skin, potentially influencing the M1/M2 macrophage ratio[180] known to be affected in psoriasis[107]. KAT2A, another GNAT family member, does not show transcriptional changes in non-lesional skin but requires integration into the SAGA or ATAC complexes for proper functioning[181]. Within the SAGA complex, TADA2B exhibits transcriptional abnormalities in non-lesional skin and is linked to UV-induced p53-dependent responses[182]. The ATAC histone acetylation complex, a key regulator of mitosis through, also shows altered expression of the component MBIP in non-lesional skin, with splice variations known to be linked to psoriasis[314]. These findings suggest that changes in specific GNAT family components and their associated complexes may not only contribute to the pathogenesis of psoriasis[314,315] in lesions but are already affected in non-lesional skin.

The MYST HAT family member KAT5, a cofactor of STAT3[185], shows altered expression in non-lesional psoriatic skin and may influence Th17 and Treg cell differentiation[184], IL-9 signaling[185], and hematopoietic stem cell maintenance[186]. All these processes are known to be implicated in the disease[316-318]. Similarly, abnormal expression affects several members of the Tip60 complex, where KAT5 functions as a catalytic subunit[319], which may affect p53 signaling[187] and the cell cycle regulation[188] in non-lesional skin. In line with our result, KAT5 was implicated in psoriasis to influence the IL-9 signaling pathway, angiogenesis, and Th17 responses[316].

KAT8, another MYST family member, does not show transcriptional changes, but its associated NSL complex components, KANSL1 and MCRS1, are differentially expressed in non-lesional skin. These alterations may have a further impact on immune gene expression[190] and mitosis[191]. These findings highlight the potential role of KAT5, KAT8, and their complexes in the immune response and cell cycle regulation in non-lesional skin.

Taken together, histone acetyltransferase-related expressional abnormalities of non-lesional skin, may influence stem cell maintenance[186], proliferation, and inflammatory responses including macrophage polarization[180], regulatory T cell-mediated suppression[184], and cytokine expression of Th1 and Th17 cells[313] already in non-lesional skin.

In contrast to histone acetylation, histone deacetylation performed by histone deacetylases[90] results in transcriptional repression[96]. Similar to histone acetyltransferases there are 18 histone deacetylases, which can be classified into 4 families (HDACI-IV)[198]. In the course of our analysis, we identified the aberrant expression of 8 histone deacetylases in non-lesional skin. Class I HDACs (except for HDAC8) are recruited to large multiprotein complexes to facilitate their function[199,320]. During our analysis, we identified 8 members of the histone deacetylase complex that exhibited differential transcriptional expression, thereby further amplifying the abnormalities associated with histone deacetylation. Since deacetylation is the opposite regulatory process to acetylation[90], the same mechanisms that are described for acetyltransferases are involved.

Class I HDACs have the strongest histone deacetylation activity[198], among which HDAC3 and HDAC8 showed altered expression in non-lesional skin. HDAC3 inhibition is known to result in reduced expression of AQP3[202], which may contribute to psoriatic skin dryness[321] and decreased LPS-induced inflammatory gene expression in macrophages[203]. Despite that HDAC1/2 expression was found to be normal, their function is likely to be affected in non-lesional skin due to abnormal expression of associated complex members (NURD, SHIP, and SIN3 complex). Disturbed HDAC1/2 function via SPHK2 may affect the differentiation of Th17 cells in psoriasis[206,207]. Similarly, the altered expression of the "stress-response" protein MTA1[214], could potentially contribute to disrupted stress-response in non-lesional skin[306]. Ship complex member HSPA2 by regulating keratinocyte differentiation[216] may contribute to the development of hyperkeratosis in psoriasis[322]. In addition, SIN3A may potentially participate in the dysregulated epidermal proliferation[222] and Th17 cell-mediated immune response[221] in psoriasis[323,324]. HDAC8 in keratinocytes serves a critical function in reducing skin inflammation in the IMQ-induced mouse model. HDAC8 inhibition causes upregulation of cytokine expression, enhanced dendritic cell responses, and increased T cell accumulation, emphasizing its function in mitigating psoriasis-like inflammation[205].

Class II HDACs have a weaker deacetylase activity compared to HDACI[325]. Among HDACII members, the expression of HDAC4, HDAC5, and HDAC6 is affected in non-lesional skin. These HDAC are known to modulate inflammatory cytokines, NF-kB[225], Foxo3a signaling[226], Treg differentiation T-cell motility[227], anti-inflammatory processes[228], chemotaxis[231], and immune synapse organization[232]. Therefore, their altered function is likely to have a significant role in psoriasis in general. In particular, the aberrant expression of HDAC5 is likely to influence

Treg/Th17 imbalance in psoriasis[317]. While the modulated expression of HDAC6 may contribute to enhanced wound healing rate[230] in both lesional and non-lesional skin[326].

Class III HDACs (Sirtuins)-related expressional alterations of SIRT5 and SIRT6 are likely to modulate IL17-A-induced inflammation[237] as well as genomic stability[236], wound healing, macrophage balance[238]. While Class IV HDAC member HDAC11-related abnormal expression may influence immune regulation, neutrophil lineage commitment[241], IL-10/IL-1β secretion[242,243], T-cell activation[244,245], that are known to be altered in psoriasis[167,295,327-329].

Taken together, our studies reveal potential mechanisms behind morphological changes in the peripheral nervous system within the skin of psoriasis patients, highlighting semaphorin-related abnormalities that affect not only axon growth but also immune responses. These findings enhance our understanding of neuro-immune interactions in psoriasis and may provide novel therapeutic targets that affect both the immune and nervous systems. Peripheral nerve endings closely interact with skin cells, and abnormal functioning of these cells can affect the structure and function of peripheral nerve endings. Therefore, understanding regulatory mechanisms related to non-lesional skin is critical for comprehending these changes. Our research identified significant differences in epigenetic regulation in non-lesional skin compared to healthy skin that could influence not only immune responses and keratinocyte function but also directly or indirectly neuronal function and projection formation. These results provide a strong base for future research and bring into focus new potential targets for future therapeutic options of the disease.

6. SUMMARY

In summary, our study of complete RNA sequence analysis of more than 300 individuals identifies potential mechanisms that may underlie the morphological changes in the peripheral nervous system within the skin of psoriasis patients. Among these mechanisms, the abnormalities associated with semaphorins, which regulate axon growth and branching while also influencing immune responses, are particularly noteworthy. These findings enhance our understanding of neuro-immune interactions in psoriasis and may open new research options for therapeutic interventions targeting both the immune and nervous system components of the condition.

The axons of the peripheral nervous system closely interact with various skin cells, with the most intimate interactions occurring in the epidermis, where the axons are predominantly demyelinated, allowing direct contact with keratinocytes. Consequently, disturbances in skin cells can affect the functioning and morphology of peripheral nerve axons. Therefore, it is crucial to gain a deeper understanding of the primary regulatory mechanisms behind the abnormalities present in non-lesional skin. Considering the complex abnormalities present in non-lesional skin, we proposed that epigenetic dysregulation may play a role. Our results confirmed several known abnormalities related to epigenetic regulation and revealed new factors that could contribute to already established non-lesional abnormalities. We found that non-lesional skin exhibits differences in expression across all levels of histone-related epigenetic regulation compared to healthy skin, impacting histones themselves, histone chaperones, and histone acetylation processes.

In conclusion, we described several novel alterations related to axon guidance and epigenetic regulation in psoriasis that can influence the formation of immune responses and the functioning of keratinocytes, including their proliferation, which are likely to affect nerve functions before any visible skin changes manifest. However, further studies are required to determine which of these newly described alterations manifest at the protein level and influence their function, as well as to identify the processes that help to maintain the non-lesional state and those that contribute to the disease's progression. Clarifying these questions may provide new targets for future therapeutic options for psoriasis.

.

7. ACKNOWLEDGEMENT

I want to convey my heartfelt gratitude to my supervisor, Dr. Gergely Groma, whose guidance has been instrumental in shaping both my scientific curiosity and personal development throughout the years. His expertise in imparting knowledge, coupled with encouraging words, consistently made me feel acknowledged and valued in my work. Last but not least, I would like to say thanks for the programming and coding that served as the background for the analysis performed during my work.

I extend my thanks to Prof. Dr. Lajos Kemény and Prof. Dr. Rolland Gyulai for granting me the opportunity to conduct my research at the Department of Dermatology and Allergology, Albert Szent-Györgyi Clinical Center, University of Szeged. Their constructive advice consistently propelled my work forward.

I appreciate Dr. Kornélia Szabó for her invaluable support, especially during the preparation of the manuscripts.

A special note of gratitude goes to Dr. Endre Sebestyén for creating the psoriasis transcriptome database, a pivotal element in my research.

I express my thanks to the team at the Molecular Biology- and Cell Biology Laboratories, with special acknowledgment to Ágnes Bessenyei for her assistance during my research. I want to express my sincere thanks to all the staff of the Department of Dermatology and Allergology who assisted me.

Last, but certainly not least, I want to express my gratitude to my family and friends for their unwavering and unconditional support, without which this journey would have been insurmountable.

REFERENCES

1. Vičić M, Kaštelan M, Brajac I, et al. Current Concepts of Psoriasis Immunopathogenesis. Int J Mol Sci 2021;22(21):11574; doi: 10.3390/ijms222111574.

2. Sewerin P, Brinks R, Schneider M, et al. Prevalence and incidence of psoriasis and psoriatic arthritis. Ann Rheum Dis 2019;78(2):286–287; doi: 10.1136/annrheumdis-2018-214065.

3. Zhou X, Chen Y, Cui L, et al. Advances in the pathogenesis of psoriasis: from keratinocyte perspective. Cell Death Dis 2022;13(1):1–13; doi: 10.1038/s41419-022-04523-3.

4. Dhabale A, Nagpure S. Types of Psoriasis and Their Effects on the Immune System. Cureus 2022; doi: 10.7759/cureus.29536.

5. Lande R, Gregorio J, Facchinetti V, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature 2007;449(7162):564–569; doi: 10.1038/nature06116.

6. Nestle FO, Conrad C, Tun-Kyi A, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-α production. J Exp Med 2005;202(1):135–143; doi: 10.1084/jem.20050500.

7. Kim J, Krueger JG. The immunopathogenesis of psoriasis. Dermatol Clin 2015;33(1):13–23; doi: 10.1016/j.det.2014.09.002.

8. Hawkes JE, Yan BY, Chan TC, et al. Discovery of the IL-23/IL-17 Signaling Pathway and the Treatment of Psoriasis. J Immunol 2018;201(6):1605–1613; doi: 10.4049/jimmunol.1800013.

9. Puig L. Guselkumab for the treatment of adults with moderate to severe plaque psoriasis. Expert Review of Clinical Immunology 2019;15(6):589–597; doi: 10.1080/1744666X.2019.1601014.

10. Furue M, Furue K, Tsuji G, et al. Interleukin-17A and Keratinocytes in Psoriasis. International Journal of Molecular Sciences 2020;21(4):1275; doi: 10.3390/ijms21041275.

11. Kurpet K, Chwatko G. S100 Proteins as Novel Therapeutic Targets in Psoriasis and Other Autoimmune Diseases. Molecules 2022;27(19):6640; doi: 10.3390/molecules27196640.

12. Kelemen E, Bozó R, Groma G, et al. The Psoriatic Nonlesional Skin: A Battlefield between Susceptibility and Protective Factors. J Invest Dermatol 2021;141(12):2785–2790; doi: 10.1016/j.jid.2021.05.020.

13. Gudjonsson JE, Ding J, Li X, et al. Global Gene Expression Analysis Reveals Evidence for Decreased Lipid Biosynthesis and Increased Innate Immunity in Uninvolved Psoriatic Skin. Journal of Investigative Dermatology 2009;129(12):2795–2804; doi: 10.1038/jid.2009.173.

14. Ye L, Lv C, Man G, et al. Abnormal Epidermal Barrier Recovery in Uninvolved Skin supports the Notion of an Epidermal Pathogenesis of Psoriasis. J Invest Dermatol 2014;134(11):2843–2846; doi: 10.1038/jid.2014.205.

15. Henno A, Blacher S, Lambert C, et al. Altered expression of angiogenesis and lymphangiogenesis markers in the uninvolved skin of plaque-type psoriasis. Br J Dermatol 2009;160(3):581–590; doi: 10.1111/j.1365-2133.2008.08889.x.

16. Fleischmajer R, Kuroda K, Hazan R, et al. Basement membrane alterations in psoriasis are accompanied by epidermal overexpression of MMP-2 and its inhibitor TIMP-2. J Invest Dermatol 2000;115(5):771–777; doi: 10.1046/j.1523-1747.2000.00138.x.

17. Vaccaro M, Magaudda L, Cutroneo G, et al. Changes in the distribution of laminin alpha1 chain in psoriatic skin: immunohistochemical study using confocal laser scanning microscopy. Br J Dermatol 2002;146(3):392–398; doi: 10.1046/j.1365-2133.2002.04637.x.

18. Pellegrini G, De Luca M, Orecchia G, et al. Expression, topography, and function of integrin receptors are severely altered in keratinocytes from involved and uninvolved psoriatic skin. J Clin Invest 1992;89(6):1783–1795; doi: 10.1172/JCI115782.

19. Bozó R, Szél E, Danis J, et al. Cartilage Oligomeric Matrix Protein Negatively Influences Keratinocyte Proliferation via α5β1-Integrin: Potential Relevance of Altered Cartilage Oligomeric Matrix Protein Expression in Psoriasis. Journal of Investigative Dermatology 2020;140(9):1733-1742.e7; doi: 10.1016/j.jid.2019.12.037.

20. Gubán B, Vas K, Balog Z, et al. Abnormal regulation of fibronectin production by fibroblasts in psoriasis. Br J Dermatol 2016;174(3):533–541; doi: 10.1111/bjd.14219.

21. Keermann M, Kõks S, Reimann E, et al. Transcriptional landscape of psoriasis identifies the involvement of IL36 and IL36RN. BMC Genomics 2015;16(1):322; doi: 10.1186/s12864-015-1508-2.

22. Chiricozzi A, Suárez-Fariñas M, Fuentes-Duculan J, et al. Increased expression of interleukin-17 pathway genes in nonlesional skin of moderate-to-severe psoriasis vulgaris. Br J Dermatol 2016;174(1):136–145; doi: 10.1111/bjd.14034.

23. Zhou X, Krueger JG, Kao M-CJ, et al. Novel mechanisms of T-cell and dendritic cell activation revealed by profiling of psoriasis on the 63,100-element oligonucleotide array. Physiological Genomics 2003;13(1):69–78; doi: 10.1152/physiolgenomics.00157.2002.

24. Göblös A, Danis J, Vas K, et al. Keratinocytes express functional CARD18, a negative regulator of inflammasome activation, and its altered expression in psoriasis may contribute to disease pathogenesis. Molecular Immunology 2016;73:10–18; doi: 10.1016/j.molimm.2016.03.009.

25. Danis J, Göblös A, Bata-Csörgő Z, et al. PRINS Non-Coding RNA Regulates Nucleic Acid-Induced Innate Immune Responses of Human Keratinocytes. Front Immunol 2017;8:1053; doi: 10.3389/fimmu.2017.01053.

26. Sonkoly E, Bata-Csorgo Z, Pivarcsi A, et al. Identification and Characterization of a Novel, Psoriasis Susceptibility-related Noncoding RNA gene, PRINS *. Journal of Biological Chemistry 2005;280(25):24159–24167; doi: 10.1074/jbc.M501704200.

27. Rácz E, Kurek D, Kant M, et al. GATA3 expression is decreased in psoriasis and during epidermal regeneration; induction by narrow-band UVB and IL-4. PLoS One 2011;6(5):e19806; doi: 10.1371/journal.pone.0019806.

28. Eyre RW, Krueger GG. Response to injury of skin involved and uninvolved with psoriasis, and its relation to disease activity: Koebner and "reverse" Koebner reactions. Br J Dermatol 1982;106(2):153–159; doi: 10.1111/j.1365-2133.1982.tb00924.x.

29. Szabó K, Bata-Csörgő Z, Dallos A, et al. Regulatory networks contributing to psoriasis susceptibility. Acta Derm Venereol 2014;94(4):380–385; doi: 10.2340/00015555-1708.

30. Oh S, Chung H, Chang S, et al. Effect of Mechanical Stretch on the DNCB-induced Proinflammatory Cytokine Secretion in Human Keratinocytes. Scientific Reports 2019;9; doi: 10.1038/s41598-019-41480-y.

31. Baumbauer KM, DeBerry JJ, Adelman PC, et al. Keratinocytes can modulate and directly initiate nociceptive responses. eLife n.d.;4:e09674; doi: 10.7554/eLife.09674.

32. Yosipovitch G, Chan YH, Tay YK, et al. Thermosensory abnormalities and blood flow dysfunction in psoriatic skin. Br J Dermatol 2003;149(3):492–497; doi: 10.1046/j.1365-2133.2003.05585.x.

33. Dewing SB. Remission of psoriasis associated with cutaneous nerve section. Arch Dermatol 1971;104(2):220–221.

34. Zhu TH, Nakamura M, Farahnik B, et al. The Role of the Nervous System in the Pathophysiology of Psoriasis: A Review of Cases of Psoriasis Remission or Improvement Following Denervation Injury. Am J Clin Dermatol 2016;17(3):257–263; doi: 10.1007/s40257-016-0183-7.

35. Farber EM, Lanigan SW, Boer J. The role of cutaneous sensory nerves in the maintenance of psoriasis. Int J Dermatol 1990;29(6):418–420; doi: 10.1111/j.1365-4362.1990.tb03825.x.

36. Qin B, Sun C, Chen L, et al. The nerve injuries attenuate the persistence of psoriatic lesions. J Dermatol Sci 2021;102(2):85–93; doi: 10.1016/j.jdermsci.2021.02.006.

37. Joseph T, Kurian J, Warwick DJ, et al. Unilateral remission of psoriasis following traumatic nerve palsy. Br J Dermatol 2005;152(1):185–186; doi: 10.1111/j.1365-2133.2005.06330.x.

38. González C, Franco M, Londoño A, et al. Breaking paradigms in the treatment of psoriasis: Use of botulinum toxin for the treatment of plaque psoriasis. Dermatol Ther 2020;33(6):e14319; doi: 10.1111/dth.14319.

39. Aschenbeck KA, Hordinsky MK, Kennedy WR, et al. Neuromodulatory treatment of recalcitrant plaque psoriasis with onabotulinumtoxinA. J Am Acad Dermatol 2018;79(6):1156–1159; doi: 10.1016/j.jaad.2018.07.058.

40. Amalia SN, Uchiyama A, Baral H, et al. Suppression of neuropeptide by botulinum toxin improves imiquimod-induced psoriasis-like dermatitis via the regulation of neuroimmune system. J Dermatol Sci 2021;101(1):58–68; doi: 10.1016/j.jdermsci.2020.11.003.

41. Farber EM, Nickoloff BJ, Recht B, et al. Stress, symmetry, and psoriasis: possible role of neuropeptides. J Am Acad Dermatol 1986;14(2 Pt 1):305–311; doi: 10.1016/s0190-9622(86)70034-0.

42. Zhang Y, Zhang H, Jiang B, et al. A promising therapeutic target for psoriasis: Neuropeptides in human skin. International Immunopharmacology 2020;87:106755; doi: 10.1016/j.intimp.2020.106755.

43. Saraceno R, Kleyn C e., Terenghi G, et al. The role of neuropeptides in psoriasis. British Journal of Dermatology 2006;155(5):876–882; doi: 10.1111/j.1365-2133.2006.07518.x.

44. Legat FJ, Griesbacher T, Schicho R, et al. Repeated subinflammatory ultraviolet B irradiation increases substance P and calcitonin gene-related peptide content and augments mustard oil-induced neurogenic inflammation in the skin of rats. Neuroscience Letters 2002;329(3):309–313; doi: 10.1016/S0304-3940(02)00428-7.

45. Dias M, Newton D, McLeod G, et al. Vasoactive properties of calcitonin gene-related peptide in human skin. Int Angiol 2011;30(5):424–428.

46. He Y, Ding G, Wang X, et al. Calcitonin gene-related peptide in Langerhans cells in psoriatic plaque lesions. Chin Med J (Engl) 2000;113(8):747–751.

47. Raychaudhuri SP, Raychaudhuri SK. Role of NGF and neurogenic inflammation in the pathogenesis of psoriasis. Prog Brain Res 2004;146:433–437; doi: 10.1016/S0079-6123(03)46027-5.

48. Glinski W, Brodecka H, Glinska-Ferenz M, et al. Neuropeptides in psoriasis: possible role of beta-endorphin in the pathomechanism of the disease. Int J Dermatol 1994;33(5):356–360; doi: 10.1111/j.1365-4362.1994.tb01068.x.

49. Naukkarinen A, Nickoloff BJ, Farber EM. Quantification of cutaneous sensory nerves and their substance P content in psoriasis. J Invest Dermatol 1989;92(1):126–129; doi: 10.1111/1523-1747.ep13071340.

50. Choi JE, Di Nardo A. Skin neurogenic inflammation. Semin Immunopathol 2018;40(3):249–259; doi: 10.1007/s00281-018-0675-z.

51. Szepietowski JC, Reich A. Itch in Psoriasis Management. Curr Probl Dermatol 2016;50:102–110; doi: 10.1159/000446050.

52. Szepietowski JC, Reich A. Pruritus in psoriasis: An update. Eur J Pain 2016;20(1):41–46; doi: 10.1002/ejp.768.

53. Tsianakas A, Mrowietz U. [Pruritus in psoriasis : Profile and therapy]. Hautarzt 2016;67(8):601–605; doi: 10.1007/s00105-016-3835-x.

54. Arck P, Paus R. From the brain-skin connection: the neuroendocrine-immune misalliance of stress and itch. Neuroimmunomodulation 2006;13(5–6):347–356; doi: 10.1159/000104863.

55. Leon A, Rosen JD, Hashimoto T, et al. Itching for an answer: A review of potential mechanisms of scalp itch in psoriasis. Exp Dermatol 2019;28(12):1397–1404; doi: 10.1111/exd.13947.

56. Dj P, Ka R, Eb L, et al. Psoriasis-associated cutaneous pain: etiology, assessment, impact, and management. The Journal of dermatological treatment 2019;30(5); doi: 10.1080/09546634.2018.1528330.

57. Casper M. 3-Dimensional Imaging of Cutaneous Nerve Endings. J Invest Dermatol 2019;139(5):999–1001; doi: 10.1016/j.jid.2018.12.015.

58. Sahoo PK, Smith DS, Perrone-Bizzozero N, et al. Axonal mRNA transport and translation at a glance. J Cell Sci 2018;131(8):jcs196808; doi: 10.1242/jcs.196808.

59. Dalla Costa I, Buchanan CN, Zdradzinski MD, et al. The functional organization of axonal mRNA transport and translation. Nat Rev Neurosci 2021;22(2):77–91; doi: 10.1038/s41583-020-00407-7.

60. Szél E, Bozó R, Hunyadi-Gulyás É, et al. Comprehensive Proteomic Analysis Reveals Intermediate Stage of Non-Lesional Psoriatic Skin and Points out the Importance of Proteins Outside this Trend. Sci Rep 2019;9(1):11382; doi: 10.1038/s41598-019-47774-5.

61. Chen S-Q, Chen X-Y, Cui Y-Z, et al. Cutaneous nerve fibers participate in the progression of psoriasis by linking epidermal keratinocytes and immunocytes. Cell Mol Life Sci 2022;79(5):267; doi: 10.1007/s00018-022-04299-x.

62. Simpson RT. Structure of the chromatosome, a chromatin particle containing 160 base pairs of DNA and all the histones. Biochemistry 1978;17(25):5524–5531; doi: 10.1021/bi00618a030.

63. Huisinga KL, Brower-Toland B, Elgin SCR. The contradictory definitions of heterochromatin: transcription and silencing. Chromosoma 2006;115(2):110–122; doi: 10.1007/s00412-006-0052-x.

64. Wang J, Lawry ST, Cohen AL, et al. Chromosome boundary elements and regulation of heterochromatin spreading. Cell Mol Life Sci 2014;71(24):4841–4852; doi: 10.1007/s00018-014-1725-x.

65. Moudrianakis EN, Arents G. Structure of the Histone Octamer Core of the Nucleosome and Its Potential Interactions with DNA. Cold Spring Harb Symp Quant Biol 1993;58:273–279; doi: 10.1101/SQB.1993.058.01.032.

66. Luger K, Mäder AW, Richmond RK, et al. Crystal structure of the nucleosome core particle at 2.8 Å resolution. Nature 1997;389(6648):251–260; doi: 10.1038/38444.

67. Jd M, G F. Nucleosome structure. Annual review of biochemistry 1980;49; doi: 10.1146/annurev.bi.49.070180.005343.

68. Geeven G, Zhu Y, Kim BJ, et al. Local compartment changes and regulatory landscape alterations in histone H1-depleted cells. Genome Biol 2015;16:289; doi: 10.1186/s13059-015-0857-0.

69. Widom J. Toward a unified model of chromatin folding. Annu Rev Biophys Biophys Chem 1989;18:365–395; doi: 10.1146/annurev.bb.18.060189.002053.

70. Berger SL, Kouzarides T, Shiekhattar R, et al. An operational definition of epigenetics. Genes Dev 2009;23(7):781–783; doi: 10.1101/gad.1787609.

71. Hamilton JP. Epigenetics: principles and practice. Dig Dis 2011;29(2):130–135; doi: 10.1159/000323874.

72. Miller JL, Grant PA. The Role of DNA Methylation and Histone Modifications in Transcriptional Regulation in Humans. In: Epigenetics: Development and Disease. (Kundu TK. ed) Springer Netherlands: Dordrecht; 2013; pp. 289–317; doi: 10.1007/978-94-007-4525-4_13.

73. Nandy D, M R S, Dutta D. A three layered histone epigenetics in breast cancer metastasis. Cell & Bioscience 2020;10; doi: 10.1186/s13578-020-00415-1.

74. Talbert PB, Henikoff S. Histone variants on the move: substrates for chromatin dynamics. Nat Rev Mol Cell Biol 2017;18(2):115–126; doi: 10.1038/nrm.2016.148.

75. Amatori S, Tavolaro S, Gambardella S, et al. The dark side of histones: genomic organization and role of oncohistones in cancer. Clinical Epigenetics 2021;13(1):71; doi: 10.1186/s13148-021-01057-x.

76. De Koning L, Corpet A, Haber JE, et al. Histone chaperones: an escort network regulating histone traffic. Nat Struct Mol Biol 2007;14(11):997–1007; doi: 10.1038/nsmb1318.

77. Hondele M, Ladurner AG. The chaperone-histone partnership: for the greater good of histone traffic and chromatin plasticity. Curr Opin Struct Biol 2011;21(6):698–708; doi: 10.1016/j.sbi.2011.10.003.

78. Davie JR. Covalent modifications of histones: expression from chromatin templates. Current Opinion in Genetics & Development 1998;8(2):173–178; doi: 10.1016/S0959-437X(98)80138-X.

79. Liu R, Wu J, Guo H, et al. Post-translational modifications of histones: Mechanisms, biological functions, and therapeutic targets. MedComm (2020) 2023;4(3):e292; doi: 10.1002/mco2.292.

80. Kamakaka RT, Biggins S. Histone variants: deviants? Genes Dev 2005;19(3):295–316; doi: 10.1101/gad.1272805.

81. Buschbeck M, Hake SB. Variants of core histones and their roles in cell fate decisions, development and cancer. Nat Rev Mol Cell Biol 2017;18(5):299–314; doi: 10.1038/nrm.2016.166.

82. Millán-Zambrano G, Burton A, Bannister AJ, et al. Histone post-translational modifications - cause and consequence of genome function. Nat Rev Genet 2022;23(9):563–580; doi: 10.1038/s41576-022-00468-7.

83. Loyola A, Almouzni G. Marking histone H3 variants: how, when and why? Trends Biochem Sci 2007;32(9):425–433; doi: 10.1016/j.tibs.2007.08.004.

84. Talbert PB, Henikoff S. Histone variants--ancient wrap artists of the epigenome. Nat Rev Mol Cell Biol 2010;11(4):264–275; doi: 10.1038/nrm2861.

85. Albig W, Doenecke D. The human histone gene cluster at the D6S105 locus. Hum Genet 1997;101(3):284–294; doi: 10.1007/s004390050630.

86. Marzluff WF, Wagner EJ, Duronio RJ. Metabolism and regulation of canonical histone mRNAs: life without a poly(A) tail. Nat Rev Genet 2008;9(11):843–854; doi: 10.1038/nrg2438.

87. Schick S, Fournier D, Thakurela S, et al. Dynamics of chromatin accessibility and epigenetic state in response to UV damage. J Cell Sci 2015;128(23):4380–4394; doi: 10.1242/jcs.173633.

88. Viéitez C, Martínez-Cebrián G, Solé C, et al. A genetic analysis reveals novel histone residues required for transcriptional reprogramming upon stress. Nucleic Acids Research 2020;48(7):3455–3475; doi: 10.1093/nar/gkaa081.

89. Leaver DJ, Cleary B, Nguyen N, et al. Discovery of Benzoylsulfonohydrazides as Potent Inhibitors of the Histone Acetyltransferase KAT6A. J Med Chem 2019;62(15):7146–7159; doi: 10.1021/acs.jmedchem.9b00665.

90. Loidl P. Histone acetylation: facts and questions. Chromosoma 1994;103(7):441–449; doi: 10.1007/BF00337382.

91. Hebbes TR, Thorne AW, Crane-Robinson C. A direct link between core histone acetylation and transcriptionally active chromatin. EMBO J 1988;7(5):1395–1402; doi: 10.1002/j.1460-2075.1988.tb02956.x.

92. Parthun MR. Hat1: the emerging cellular roles of a type B histone acetyltransferase. Oncogene 2007;26(37):5319–5328; doi: 10.1038/sj.onc.1210602.

93. Huang M, Huang J, Zheng Y, et al. Histone acetyltransferase inhibitors: An overview in synthesis, structure-activity relationship and molecular mechanism. European Journal of Medicinal Chemistry 2019;178:259–286; doi: 10.1016/j.ejmech.2019.05.078.

94. Roth SY, Denu JM, Allis CD. Histone Acetyltransferases. Annual Review of Biochemistry 2001;70(Volume 70, 2001):81–120; doi: 10.1146/annurev.biochem.70.1.81.

95. Schemies J, Uciechowska U, Sippl W, et al. NAD+-dependent histone deacetylases (sirtuins) as novel therapeutic targets. Medicinal Research Reviews 2010;30(6):861–889; doi: 10.1002/med.20178.

96. Wade PA. Transcriptional control at regulatory checkpoints by histone deacetylases: molecular connections between cancer and chromatin. Human Molecular Genetics 2001;10(7):693–698; doi: 10.1093/hmg/10.7.693.

97. Wang Y, Sen GL. Enhanc(er)ing Skin Stem Cells. Cell Stem Cell 2016;19(4):415–417; doi: 10.1016/j.stem.2016.09.003.

98. Frye M, Fisher AG, Watt FM. Epidermal Stem Cells Are Defined by Global Histone Modifications that Are Altered by Myc-Induced Differentiation. PLoS One 2007;2(8):e763; doi: 10.1371/journal.pone.0000763.

99. Shue YT, Lee KT, Walters BW, et al. Dynamic shifts in chromatin states differentially mark the proliferative basal cells and terminally differentiated cells of the developing epidermis. Epigenetics n.d.;15(9):932–948; doi: 10.1080/15592294.2020.1738028.

100. Masalha M, Ben-Dov IZ, Ram O, et al. H3K27Ac modification and gene expression in psoriasis. Journal of Dermatological Science 2021;103(2):93–100; doi: 10.1016/j.jdermsci.2021.07.003.

101. Ortiz-Lopez LI, Choudhary V, Bollag WB. Updated Perspectives on Keratinocytes and Psoriasis: Keratinocytes are More Than Innocent Bystanders. Psoriasis: Targets and Therapy 2022;12:73; doi: 10.2147/PTT.S327310.

102. Xia X, Cao G, Sun G, et al. GLS1-mediated glutaminolysis unbridled by MALT1 protease promotes psoriasis pathogenesis. J Clin Invest 2020;130(10):5180–5196; doi: 10.1172/JCI129269.

103. Verhoeckx K, Cotter P, López-Expósito I, et al., (eds). The Impact of Food Bioactives on Health: In Vitro and Ex Vivo Models. Springer: Cham (CH); 2015.

104. Wu M, Dai C, Zeng F. Cellular Mechanisms of Psoriasis Pathogenesis: A Systemic Review. Clinical, Cosmetic and Investigational Dermatology 2023;16:2503–2515; doi: 10.2147/CCID.S420850.

105. Zhang P, Su Y, Zhao M, et al. Abnormal histone modifications in PBMCs from patients with psoriasis vulgaris. Eur J Dermatol 2011;21(4):552–557; doi: 10.1684/ejd.2011.1383.

106. Zhou D, Yang K, Chen L, et al. Promising landscape for regulating macrophage polarization: epigenetic viewpoint. Oncotarget 2017;8(34):57693–57706; doi: 10.18632/oncotarget.17027.

107. Lin S-H, Chuang H-Y, Ho J-C, et al. Treatment with TNF-α inhibitor rectifies M1 macrophage polarization from blood CD14+ monocytes in patients with psoriasis independent of STAT1 and IRF-1 activation. J Dermatol Sci 2018;91(3):276–284; doi: 10.1016/j.jdermsci.2018.05.009.

108. Clamp M, Fry B, Kamal M, et al. Distinguishing protein-coding and noncoding genes in the human genome. Proc Natl Acad Sci U S A 2007;104(49):19428–19433; doi: 10.1073/pnas.0709013104.

109. Poliseno L, Lanza M, Pandolfi PP. Coding, or non-coding, that is the question. Cell Res 2024;34(9):609–629; doi: 10.1038/s41422-024-00975-8.

110. Zhang P, Wu W, Chen Q, et al. Non-Coding RNAs and their Integrated Networks. J Integr Bioinform 2019;16(3):20190027; doi: 10.1515/jib-2019-0027.

111. Keren H, Lev-Maor G, Ast G. Alternative splicing and evolution: diversification, exon definition and function. Nat Rev Genet 2010;11(5):345–355; doi: 10.1038/nrg2776.

112. Zheng J-T, Lin C-X, Fang Z-Y, et al. Intron Retention as a Mode for RNA-Seq Data Analysis. Front Genet 2020;11:586; doi: 10.3389/fgene.2020.00586.

113. Nilsen TW, Graveley BR. Expansion of the eukaryotic proteome by alternative splicing. Nature 2010;463(7280):457–463; doi: 10.1038/nature08909.

114. Wong JJ-L, Au AYM, Ritchie W, et al. Intron retention in mRNA: No longer nonsense. BioEssays 2016;38(1):41–49; doi: 10.1002/bies.201500117.

115. Jacob AG, Smith CWJ. Intron retention as a component of regulated gene expression programs. Hum Genet 2017;136(9):1043–1057; doi: 10.1007/s00439-017-1791-x.

116. Grabski DF, Broseus L, Kumari B, et al. Intron retention and its impact on gene expression and protein diversity: A review and a practical guide. WIREs RNA 2021;12(1):e1631; doi: 10.1002/wrna.1631.

117. Vasudevan S, Peltz SW, Wilusz CJ. Non-stop decay--a new mRNA surveillance pathway. Bioessays 2002;24(9):785–788; doi: 10.1002/bies.10153.

118. Harrow J, Frankish A, Gonzalez JM, et al. GENCODE: The reference human genome annotation for The ENCODE Project. Genome Res 2012;22(9):1760–1774; doi: 10.1101/gr.135350.111.

119. Anonymous. 6 Non-coding RNA characterization. Nature 2019;1–1; doi: 10.1038/nature28175.

120. Guberovic I, Farkas M, Corujo D, et al. Evolution, structure and function of divergent macroH2A1 splice isoforms. Seminars in Cell & Developmental Biology 2023;135:43–49; doi: 10.1016/j.semcdb.2022.03.036.

121. Li B, Tsoi LC, Swindell WR, et al. Transcriptome Analysis of Psoriasis in a Large Case–Control Sample: RNA-Seq Provides Insights into Disease Mechanisms. Journal of Investigative Dermatology 2014;134(7):1828–1838; doi: 10.1038/jid.2014.28.

122. Tsoi LC, Iyer MK, Stuart PE, et al. Analysis of long non-coding RNAs highlights tissue-specific expression patterns and epigenetic profiles in normal and psoriatic skin. Genome Biology 2015;16(1):24; doi: 10.1186/s13059-014-0570-4.

123. Liang Y, Tsoi LC, Xing X, et al. A gene network regulated by the transcription factor VGLL3 as a promoter of sex-biased autoimmune diseases. Nat Immunol 2017;18(2):152–160; doi: 10.1038/ni.3643.

124. Bray NL, Pimentel H, Melsted P, et al. Near-optimal probabilistic RNA-seq quantification. Nat Biotechnol 2016;34(5):525–527; doi: 10.1038/nbt.3519.

125. Soneson C, Love MI, Robinson MD. Differential analyses for RNA-seq: transcript-level estimates improve gene-level inferences. F1000Res 2016;4:1521; doi: 10.12688/f1000research.7563.2.

126. McCarthy DJ, Chen Y, Smyth GK. Differential expression analysis of multifactor RNA-Seq experiments with respect to biological variation. Nucleic Acids Research 2012;40(10):4288–4297; doi: 10.1093/nar/gks042.

127. Schwämmle V, León IR, Jensen ON. Assessment and Improvement of Statistical Tools for Comparative Proteomics Analysis of Sparse Data Sets with Few Experimental Replicates. J Proteome Res 2013;12(9):3874–3883; doi: 10.1021/pr400045u.

128. Ritchie ME, Phipson B, Wu D, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res 2015;43(7):e47; doi: 10.1093/nar/gkv007.

129. Liu R, Holik AZ, Su S, et al. Why weight? Modelling sample and observational level variability improves power in RNA-seq analyses. Nucleic Acids Res 2015;43(15):e97; doi: 10.1093/nar/gkv412.

130. Berchtold W. Comparison of the Kastenbaum-Bowman test and Fisher's exact test. Arch Genet (Zur) 1975;48(2–3):151–157.

131. Eden E, Navon R, Steinfeld I, et al. GOrilla: a tool for discovery and visualization of enriched GO terms in ranked gene lists. BMC Bioinformatics 2009;10:48; doi: 10.1186/1471-2105-10-48.

132. Ferreira JA. The Benjamini-Hochberg method in the case of discrete test statistics. Int J Biostat 2007;3(1):Article 11; doi: 10.2202/1557-4679.1065.

133. Filipescu D, Szenker E, Almouzni G. Developmental roles of histone H3 variants and their chaperones. Trends Genet 2013;29(11):630–640; doi: 10.1016/j.tig.2013.06.002.

134. Lamaa A, Humbert J, Aguirrebengoa M, et al. Integrated analysis of H2A.Z isoforms function reveals a complex interplay in gene regulation. Elife 2020;9:e53375; doi: 10.7554/eLife.53375.

135. Moreno-Andrés D, Yokoyama H, Scheufen A, et al. VPS72/YL1-Mediated H2A.Z Deposition Is Required for Nuclear Reassembly after Mitosis. Cells 2020;9(7):1702; doi: 10.3390/cells9071702.

136. Arede L. Buffering noise: KAT2A modular contributions to stabilization of transcription and cell identity in cancer and development. Experimental Hematology 2020;93; doi: 10.1016/j.exphem.2020.10.003.

137. Di Cerbo V, Schneider R. Cancers with wrong HATs: the impact of acetylation. Brief Funct Genomics 2013;12(3):231–243; doi: 10.1093/bfgp/els065.

138. Fang Z, Wang X, Sun X, et al. The Role of Histone Protein Acetylation in Regulating Endothelial Function. Front Cell Dev Biol 2021;9:672447; doi: 10.3389/fcell.2021.672447.

139. Herbst DA, Esbin MN, Louder RK, et al. Structure of the human SAGA coactivator complex. Nat Struct Mol Biol 2021;28(12):989–996; doi: 10.1038/s41594-021-00682-7.

140. Seo S, Macfarlan T, McNamara P, et al. Regulation of Histone Acetylation and Transcription by Nuclear Protein pp32, a Subunit of the INHAT Complex *. Journal of Biological Chemistry 2002;277(16):14005–14010; doi: 10.1074/jbc.M112455200.

141. Yang Q, Yang Y, Zhou N, et al. Epigenetics in ovarian cancer: premise, properties, and perspectives. Molecular Cancer 2018;17(1):109; doi: 10.1186/s12943-018-0855-4.

142. Zhang H-L, Wang J, Tang L. Sema4D knockdown in oligodendrocytes promotes functional recovery after spinal cord injury. Cell Biochem Biophys 2014;68(3):489–496; doi: 10.1007/s12013-013-9727-0.

143. Worcel A, Han S, Wong ML. Assembly of newly replicated chromatin. Cell 1978;15(3):969–977; doi: 10.1016/0092-8674(78)90280-5.

144. Morrison O, Thakur J. Molecular Complexes at Euchromatin, Heterochromatin and Centromeric Chromatin. International Journal of Molecular Sciences 2021;22(13):6922; doi: 10.3390/ijms22136922.

145. Franklin R, Guo Y, He S, et al. Regulation of chromatin accessibility by the histone chaperone CAF-1 sustains lineage fidelity. Nature Communications 2022;13(1):2350; doi: 10.1038/s41467-022-29730-6.

146. Ng C, Aichinger M, Nguyen T, et al. The histone chaperone CAF-1 cooperates with the DNA methyltransferases to maintain Cd4 silencing in cytotoxic T cells. Genes Dev 2019;33(11–12):669–683; doi: 10.1101/gad.322024.118.

147. Banumathy G, Somaiah N, Zhang R, et al. Human UBN1 Is an Ortholog of Yeast Hpc2p and Has an Essential Role in the HIRA/ASF1a Chromatin-Remodeling Pathway in Senescent Cells. Molecular and Cellular Biology 2009;29(3):758–770; doi: 10.1128/MCB.01047-08.

148. Okuwaki M, Matsumoto K, Tsujimoto M, et al. Function of nucleophosmin/B23, a nucleolar acidic protein, as a histone chaperone. FEBS Letters 2001;506(3):272–276; doi: 10.1016/S0014-5793(01)02939-8.

149. Escobar TM, Yu J-R, Liu S, et al. Inheritance of repressed chromatin domains during S phase requires the histone chaperone NPM1. Sci Adv 2022;8(17):eabm3945; doi: 10.1126/sciadv.abm3945.

150. Nakatomi K, Ueno H, Ishikawa Y, et al. TLR4/MD-2 is a receptor for extracellular nucleophosmin 1. Biomed Rep 2021;14(2):21; doi: 10.3892/br.2020.1397.

151. Saavedra F, Rivera C, Rivas E, et al. PP32 and SET/TAF-Iβ proteins regulate the acetylation of newly synthesized histone H4. Nucleic Acids Res 2017;45(20):11700–11710; doi: 10.1093/nar/gkx775.

152. Canela N, Rodriguez-Vilarrupla A, Estanyol JM, et al. The SET Protein Regulates G2/M Transition by Modulating Cyclin B-Cyclin-dependent Kinase 1 Activity *. Journal of Biological Chemistry 2003;278(2):1158–1164; doi: 10.1074/jbc.M207497200.

153. Yao H, Xu W, Liu Y, et al. The repression of oncoprotein SET by the tumor suppressor p53 reveals a p53-SET-PP2A feedback loop for cancer therapy. Sci China Life Sci 2023;66(1):81–93; doi: 10.1007/s11427-021-2123-8.

154. Wang D, Kon N, Lasso G, et al. Acetylation-regulated interaction between p53 and SET reveals a widespread regulatory mode. Nature 2016;538(7623):118–122; doi: 10.1038/nature19759.

155. Obri A, Ouararhni K, Papin C, et al. ANP32E is a histone chaperone that removes H2A.Z from chromatin. Nature 2014;505(7485):648–653; doi: 10.1038/nature12922.

156. Zhang J, Lan Z, Qiu G, et al. Over-expression of ANP32E is associated with poor prognosis of pancreatic cancer and promotes cell proliferation and migration through regulating β-catenin. BMC Cancer 2020;20(1):1065; doi: 10.1186/s12885-020-07556-z.

157. Liu X, He Y, Wang P, et al. ANP32 Family as Diagnostic, Prognostic, and Therapeutic Biomarker Related to Immune Infiltrates in Hepatocellular Carcinoma. Dis Markers 2022;2022:5791471; doi: 10.1155/2022/5791471.

158. Huang J, Gan J, Wang J, et al. VPS72, a member of VPS protein family, can be used as a new prognostic marker for hepatocellular carcinoma. Immunity, Inflammation and Disease 2023;11(5):e856; doi: 10.1002/iid3.856.

159. Armstrong C, Spencer SL. Replication-dependent histone biosynthesis is coupled to cell-cycle commitment. Proceedings of the National Academy of Sciences 2021;118(31):e2100178118; doi: 10.1073/pnas.2100178118.

160. Lyons SM, Cunningham CH, Welch JD, et al. A subset of replication-dependent histone mRNAs are expressed as polyadenylated RNAs in terminally differentiated tissues. Nucleic Acids Res 2016;44(19):9190–9205; doi: 10.1093/nar/gkw620.

161. Kubrova E, Su M, Galeano-Garces C, et al. Differences in Cytotoxicity of Lidocaine, Ropivacaine, and Bupivacaine on the Viability and Metabolic Activity of Human Adipose-Derived Mesenchymal Stem Cells. Am J Phys Med Rehabil 2021;100(1):82–91; doi: 10.1097/PHM.0000000000001529.

162. Nie H, Kubrova E, Wu T, et al. Effect of Lidocaine on Viability and Gene Expression of Human Adipose-derived Mesenchymal Stem Cells: An in vitro Study. PM R 2019;11(11):1218–1227; doi: 10.1002/pmrj.12141.

163. Oeffinger M, Zenklusen D, (eds). The Biology of mRNA: Structure and Function. Advances in Experimental Medicine and Biology. Springer International Publishing: Cham; 2019.; doi: 10.1007/978-3-030-31434-7.

164. Hurtado-Bagès S, Guberovic I, Buschbeck M. The MacroH2A1.1 - PARP1 Axis at the Intersection Between Stress Response and Metabolism. Front Genet 2018;9:417; doi: 10.3389/fgene.2018.00417.

165. Chen H, Ruiz PD, McKimpson WM, et al. MacroH2A1 and ATM play opposing roles in paracrine senescence and the senescence-associated secretory phenotype. Mol Cell 2015;59(5):719–731; doi: 10.1016/j.molcel.2015.07.011.

166. Grossman RM, Krueger J, Yourish D, et al. Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. Proc Natl Acad Sci U S A 1989;86(16):6367–6371; doi: 10.1073/pnas.86.16.6367.

167. Cai Y, Xue F, Quan C, et al. A Critical Role of the IL-1β-IL-1R Signaling Pathway in Skin Inflammation and Psoriasis Pathogenesis. J Invest Dermatol 2019;139(1):146–156; doi: 10.1016/j.jid.2018.07.025.

168. Sales-Gil R, Kommer DC, de Castro IJ, et al. Non-redundant functions of H2A.Z.1 and H2A.Z.2 in chromosome segregation and cell cycle progression. EMBO reports 2021;22(11):e52061; doi: 10.15252/embr.202052061.

169. Hu G, Cui K, Northrup D, et al. H2A.Z facilitates access of active and repressive complexes to chromatin in embryonic stem cell self-renewal and differentiation. Cell Stem Cell 2013;12(2):180–192; doi: 10.1016/j.stem.2012.11.003.

170. Creyghton MP, Markoulaki S, Levine SS, et al. H2AZ Is Enriched at Polycomb Complex Target Genes in ES Cells and Is Necessary for Lineage Commitment. Cell 2008;135(4):649–661; doi: 10.1016/j.cell.2008.09.056.

171. Armache A, Yang S, Martínez de Paz A, et al. Histone H3.3 phosphorylation amplifies stimulation-induced transcription. Nature 2020;583(7818):852–857; doi: 10.1038/s41586-020-2533-0.

172. Banaszynski LA, Wen D, Dewell S, et al. Hira-dependent histone H3.3 deposition facilitates PRC2 recruitment at developmental loci in ES cells. Cell 2013;155(1):107–120; doi: 10.1016/j.cell.2013.08.061.

173. Fang H-T, EL Farran CA, Xing QR, et al. Global H3.3 dynamic deposition defines its bimodal role in cell fate transition. Nat Commun 2018;9(1):1537; doi: 10.1038/s41467-018-03904-7.

174. Yu G, Zhang Y, Gupta V, et al. The role of HIRA-dependent H3.3 deposition and its modifications in the somatic hypermutation of immunoglobulin variable regions. Proceedings of the National Academy of Sciences 2021;118(50):e2114743118; doi: 10.1073/pnas.2114743118.

175. Yang X-J, Seto E. HATs and HDACs: from structure, function and regulation to novel strategies for therapy and prevention. Oncogene 2007;26(37):5310–5318; doi: 10.1038/sj.onc.1210599.

176. Voss AK, Thomas T. Histone Lysine and Genomic Targets of Histone Acetyltransferases in Mammals. Bioessays 2018;40(10):e1800078; doi: 10.1002/bies.201800078.

177. Weinert BT, Narita T, Satpathy S, et al. Time-Resolved Analysis Reveals Rapid Dynamics and Broad Scope of the CBP/p300 Acetylome. Cell 2018;174(1):231-244.e12; doi: 10.1016/j.cell.2018.04.033.

178. Kim J-H, Cho E-J, Kim S-T, et al. CtBP represses p300-mediated transcriptional activation by direct association with its bromodomain. Nat Struct Mol Biol 2005;12(5):423–428; doi: 10.1038/nsmb924.

179. Burke TL, Grant PA. Chapter 285 - Histone Acetylation Complexes. In: Handbook of Cell Signaling (Second Edition). (Bradshaw RA, Dennis EA. eds) Academic Press: San Diego; 2010; pp. 2369–2378; doi: 10.1016/B978-0-12-374145-5.00285-0.

180. Chen D, Nemazanyy I, Peulen O, et al. Elp3-mediated codon-dependent translation promotes mTORC2 activation and regulates macrophage polarization. The EMBO Journal 2022;41(18):e109353; doi: 10.15252/embj.2021109353.

181. Riss A, Scheer E, Joint M, et al. Subunits of ADA-two-A-containing (ATAC) or Spt-Ada-Gcn5-acetyltrasferase (SAGA) Coactivator Complexes Enhance the Acetyltransferase Activity of GCN5. J Biol Chem 2015;290(48):28997–29009; doi: 10.1074/jbc.M115.668533.

182. Gamper AM, Kim J, Roeder RG. The STAGA Subunit ADA2b Is an Important Regulator of Human GCN5 Catalysis. Mol Cell Biol 2009;29(1):266–280; doi: 10.1128/MCB.00315-08.

183. Orpinell M, Fournier M, Riss A, et al. The ATAC acetyl transferase complex controls mitotic progression by targeting non-histone substrates. EMBO J 2010;29(14):2381–2394; doi: 10.1038/emboj.2010.125.

184. Su Q, Jing J, Li W, et al. Impaired Tip60-mediated Foxp3 acetylation attenuates regulatory T cell development in rheumatoid arthritis. Journal of Autoimmunity 2019;100:27–39; doi: 10.1016/j.jaut.2019.02.007.

185. Sliva D, Zhu YX, Tsai S, et al. Tip60 Interacts with Human Interleukin-9 Receptor α-Chain. Biochemical and Biophysical Research Communications 1999;263(1):149–155; doi: 10.1006/bbrc.1999.1083.

186. Numata A, Kwok HS, Zhou Q-L, et al. Lysine acetyltransferase Tip60 is required for hematopoietic stem cell maintenance. Blood 2020;136(15):1735–1747; doi: 10.1182/blood.2019001279.

187. Lashgari A, Fauteux M, Maréchal A, et al. Cellular Depletion of BRD8 Causes p53-Dependent Apoptosis and Induces a DNA Damage Response in Non-Stressed Cells. Sci Rep 2018;8(1):14089; doi: 10.1038/s41598-018-32323-3.

188. Nagashima M, Shiseki M, Pedeux RM, et al. A novel PHD-finger motif protein, p47ING3, modulates p53-mediated transcription, cell cycle control, and apoptosis. Oncogene 2003;22(3):343–350; doi: 10.1038/sj.onc.1206115.

189. Radzisheuskaya A, Shliaha PV, Grinev VV, et al. Complex-dependent histone acetyltransferase activity of KAT8 determines its role in transcription and cellular homeostasis. Molecular Cell 2021;81(8):1749-1765.e8; doi: 10.1016/j.molcel.2021.02.012.

190. Fejzo MS, Chen H-W, Anderson L, et al. Analysis in epithelial ovarian cancer identifies KANSL1 as a biomarker and target gene for immune response and HDAC inhibition. Gynecologic Oncology 2021;160(2):539–546; doi: 10.1016/j.ygyno.2020.11.008.

191. Meunier S, Vernos I. K-fibre minus ends are stabilized by a RanGTP-dependent mechanism essential for functional spindle assembly. Nat Cell Biol 2011;13(12):1406–1414; doi: 10.1038/ncb2372.

192. Telles E, Seto E. Modulation of cell cycle regulators by HDACs. Front Biosci (Schol Ed) 2012;4(3):831–839; doi: 10.2741/s303.

193. Reichert N, Choukrallah M-A, Matthias P. Multiple roles of class I HDACs in proliferation, differentiation, and development. Cell Mol Life Sci 2012;69(13):2173–2187; doi: 10.1007/s00018-012-0921-9.

194. Clocchiatti A, Florean C, Brancolini C. Class IIa HDACs: from important roles in differentiation to possible implications in tumourigenesis. Journal of Cellular and Molecular Medicine 2011;15(9):1833–1846; doi: 10.1111/j.1582-4934.2011.01321.x.

195. Shakespear MR, Halili MA, Irvine KM, et al. Histone deacetylases as regulators of inflammation and immunity. Trends in Immunology 2011;32(7):335–343; doi: 10.1016/j.it.2011.04.001.

196. Manou M, Kanakoglou DS, Loupis T, et al. Role of Histone Deacetylases in the Pathogenesis of Salivary Gland Tumors and Therapeutic Targeting Options. Int J Mol Sci 2023;24(12):10038; doi: 10.3390/ijms241210038.

197. Seto E, Yoshida M. Erasers of histone acetylation: the histone deacetylase enzymes. Cold Spring Harb Perspect Biol 2014;6(4):a018713; doi: 10.1101/cshperspect.a018713.

198. Park S-Y, Kim J-S. A short guide to histone deacetylases including recent progress on class II enzymes. Exp Mol Med 2020;52(2):204–212; doi: 10.1038/s12276-020-0382-4.

199. Milazzo G, Mercatelli D, Di Muzio G, et al. Histone Deacetylases (HDACs): Evolution, Specificity, Role in Transcriptional Complexes, and Pharmacological Actionability. Genes (Basel) 2020;11(5):556; doi: 10.3390/genes11050556.

200. Hörlein AJ, Näär AM, Heinzel T, et al. Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. Nature 1995;377(6548):397–404; doi: 10.1038/377397a0.

201. Chen JD, Evans RM. A transcriptional co-repressor that interacts with nuclear hormone receptors. Nature 1995;377(6548):454–457; doi: 10.1038/377454a0.

202. Choudhary V, Olala LO, Kagha K, et al. Regulation of the Glycerol Transporter, Aquaporin-3, by Histone Deacetylase-3 and p53 in Keratinocytes. J Invest Dermatol 2017;137(9):1935–1944; doi: 10.1016/j.jid.2017.04.031.

203. Thatikonda S, Pooladanda V, Sigalapalli DK, et al. Piperlongumine regulates epigenetic modulation and alleviates psoriasis-like skin inflammation via inhibition of hyperproliferation and inflammation. Cell Death Dis 2020;11(1):1–17; doi: 10.1038/s41419-019-2212-y.

204. Pray BA, Youssef Y, Alinari L. TBL1X: At the crossroads of transcriptional and posttranscriptional regulation. Experimental Hematology 2022;116:18–25; doi: 10.1016/j.exphem.2022.09.006.

205. Sawada Y, Nakatsuji T, Dokoshi T, et al. Cutaneous innate immune tolerance is mediated by epigenetic control of MAP2K3 by HDAC8/9. Sci Immunol 2021;6(59):eabe1935; doi: 10.1126/sciimmunol.abe1935.

206. Hait NC, Allegood J, Maceyka M, et al. Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. Science 2009;325(5945):1254–1257; doi: 10.1126/science.1176709.

207. Shin S-H, Cho K-A, Hahn S, et al. Inhibiting Sphingosine Kinase 2 Derived-sphingosine-1-phosphate Ameliorates Psoriasis-like Skin Disease via Blocking Th17 Differentiation of Naïve CD4 T Lymphocytes in Mice. Acta Derm Venereol 2019;99(6):594–601; doi: 10.2340/00015555-3160.

208. Dege C, Hagman J. Mi-2/NuRD chromatin remodeling complexes regulate B and T-lymphocyte development and function. Immunological Reviews 2014;261(1):126–140; doi: 10.1111/imr.12209.

209. Basta J, Rauchman M. The nucleosome remodeling and deacetylase complex in development and disease. Translational Research 2015;165(1):36–47; doi: 10.1016/j.trsl.2014.05.003.

210. Kashiwagi M, Morgan BA, Georgopoulos K. The chromatin remodeler Mi-2β is required for establishment of the basal epidermis and normal differentiation of its progeny. Development 2007;134(8):1571–1582; doi: 10.1242/dev.001750.

211. Shibata S, Kashiwagi M, Morgan BA, et al. Functional interactions between Mi-2β and AP1 complexes control response and recovery from skin barrier disruption. J Exp Med 2019;217(3):jem.20182402; doi: 10.1084/jem.20182402.

212. Hosokawa H, Tanaka T, Suzuki Y, et al. Functionally distinct Gata3/Chd4 complexes coordinately establish T helper 2 (Th2) cell identity. Proceedings of the National Academy of Sciences 2013;110(12):4691–4696; doi: 10.1073/pnas.1220865110.

213. Shao S, Cao H, Wang Z, et al. CHD4/NuRD complex regulates complement gene expression and correlates with CD8 T cell infiltration in human hepatocellular carcinoma. Clinical Epigenetics 2020;12(1):31; doi: 10.1186/s13148-020-00827-3.

214. Wang R-A. MTA1--a stress response protein: a master regulator of gene expression and cancer cell behavior. Cancer Metastasis Rev 2014;33(4):1001–1009; doi: 10.1007/s10555-014-9525-1.

215. Pakala SB, Reddy SDN, Bui-Nguyen TM, et al. MTA1 Coregulator Regulates LPS Response via MyD88-dependent Signaling *. Journal of Biological Chemistry 2010;285(43):32787–32792; doi: 10.1074/jbc.M110.151340.

216. Scieglinska D, Krawczyk Z, Sojka DR, et al. Heat shock proteins in the physiology and pathophysiology of epidermal keratinocytes. Cell Stress and Chaperones 2019;24(6):1027–1044; doi: 10.1007/s12192-019-01044-5.

217. Gogler-Pigłowska A, Klarzyńska K, Sojka DR, et al. Novel role for the testis-enriched HSPA2 protein in regulating epidermal keratinocyte differentiation. Journal of Cellular Physiology 2018;233(3):2629–2644; doi: 10.1002/jcp.26142.

218. Kadamb R, Mittal S, Bansal N, et al. Sin3: Insight into its transcription regulatory functions. European Journal of Cell Biology 2013;92(8):237–246; doi: 10.1016/j.ejcb.2013.09.001.

219. Saunders A, Huang X, Fidalgo M, et al. The SIN3A/HDAC Corepressor Complex Functionally Cooperates with NANOG to Promote Pluripotency. Cell Reports 2017;18(7):1713–1726; doi: 10.1016/j.celrep.2017.01.055.

220. Cowley SM, Iritani BM, Mendrysa SM, et al. The mSin3A Chromatin-Modifying Complex Is Essential for Embryogenesis and T-Cell Development. Mol Cell Biol 2005;25(16):6990–7004; doi: 10.1128/MCB.25.16.6990-7004.2005.

221. Perucho L, Icardi L, Simone ED, et al. The Transcriptional Regulator Sin3A Balances IL-17A and Foxp3 Expression in Primary CD4 T Cells. 2022;2022.04.19.488789; doi: 10.1101/2022.04.19.488789.

222. Nascimento EM, Cox CL, MacArthur S, et al. The opposing transcriptional functions of Sin3a and c-Myc are required to maintain tissue homeostasis. Nat Cell Biol 2011;13(12):1395–1405; doi: 10.1038/ncb2385.

223. Grozinger CM, Hassig CA, Schreiber SL. Three proteins define a class of human histone deacetylases related to yeast Hda1p. Proc Natl Acad Sci U S A 1999;96(9):4868–4873; doi: 10.1073/pnas.96.9.4868.

224. Schuetz A, Min J, Allali-Hassani A, et al. Human HDAC7 Harbors a Class IIa Histone Deacetylase-specific Zinc Binding Motif and Cryptic Deacetylase Activity *. Journal of Biological Chemistry 2008;283(17):11355–11363; doi: 10.1074/jbc.M707362200.

225. Luan B, Goodarzi MO, Phillips NG, et al. Leptin-Mediated Increases in Catecholamine Signaling Reduce Adipose Tissue Inflammation via Activation of Macrophage HDAC4. Cell Metabolism 2014;19(6):1058–1065; doi: 10.1016/j.cmet.2014.03.024.

226. Yang D, Xiao C, Long F, et al. HDAC4 regulates vascular inflammation via activation of autophagy. Cardiovascular Research 2018;114(7):1016–1028; doi: 10.1093/cvr/cvy051.

227. Xiao H, Jiao J, Wang L, et al. HDAC5 controls the functions of Foxp3+ T-regulatory and CD8+ T cells. International Journal of Cancer 2016;138(10):2477–2486; doi: 10.1002/ijc.29979.

228. Wang W, Ha CH, Jhun BS, et al. Fluid shear stress stimulates phosphorylation-dependent nuclear export of HDAC5 and mediates expression of KLF2 and eNOS. Blood 2010;115(14):2971–2979; doi: 10.1182/blood-2009-05-224824.

229. Gao Y, Hubbert CC, Lu J, et al. Histone deacetylase 6 regulates growth factor-induced actin remodeling and endocytosis. Mol Cell Biol 2007;27(24):8637–8647; doi: 10.1128/MCB.00393-07.

230. Qin Y-M, Li P, Mu X-P, et al. Histone deacetylase 6 promotes skin wound healing by regulating fibroblast migration and differentiation in aged mice. Sheng Li Xue Bao 2022;74(6):979–992.

231. Cabrero JR, Serrador JM, Barreiro O, et al. Lymphocyte chemotaxis is regulated by histone deacetylase 6, independently of its deacetylase activity. Mol Biol Cell 2006;17(8):3435–3445; doi: 10.1091/mbc.e06-01-0008.

232. Serrador JM, Cabrero JR, Sancho D, et al. HDAC6 deacetylase activity links the tubulin cytoskeleton with immune synapse organization. Immunity 2004;20(4):417–428; doi: 10.1016/s1074-7613(04)00078-0.

233. Du J, Zhou Y, Su X, et al. Sirt5 Is an NAD-Dependent Protein Lysine Demalonylase and Desuccinylase. Science 2011;334(6057):806–809; doi: 10.1126/science.1207861.

234. Michishita E, McCord RA, Berber E, et al. SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin. Nature 2008;452(7186):492–496; doi: 10.1038/nature06736.

235. Michishita E, McCord RA, Boxer LD, et al. Cell cycle-dependent deacetylation of telomeric histone H3 lysine K56 by human SIRT6. Cell Cycle 2009;8(16):2664–2666; doi: 10.4161/cc.8.16.9367.

236. Yang B, Zwaans BMM, Eckersdorff M, et al. The sirtuin SIRT6 deacetylates H3 K56Ac in vivo to promote genomic stability. Cell Cycle 2009;8(16):2662–2663; doi: 10.4161/cc.8.16.9329.

237. Wang C, He D, Shi C. SIRT5 reduces the inflammatory response and barrier dysfunction in IL-17A-induced epidermal keratinocytes. Allergologia et Immunopathologia 2023;51(1):30–36; doi: 10.15586/aei.v51i1.675.

238. Koo J-H, Jang H-Y, Lee Y, et al. Myeloid cell-specific sirtuin 6 deficiency delays wound healing in mice by modulating inflammation and macrophage phenotypes. Exp Mol Med 2019;51(4):1–10; doi: 10.1038/s12276-019-0248-9.

239. Zhang R, Li H, Guo Q, et al. Sirtuin6 inhibits c-triggered inflammation through TLR4 abrogation regulated by ROS and TRPV1/CGRP. Journal of Cellular Biochemistry 2018;119(11):9141–9153; doi: 10.1002/jcb.27176.

240. Lasigliè D, Boero S, Bauer I, et al. Sirt6 regulates dendritic cell differentiation, maturation, and function. Aging (Albany NY) 2016;8(1):34–49; doi: 10.18632/aging.100870.

241. Sahakian E, Powers J, Chen J, et al. A Novel Role For Histone Deacetylase 11 (HDAC11) As a Regulator Of Neutrophil Function and Differentiation In Normal and Malignant Hematopoesis. Blood 2013;122(21):2267; doi: 10.1182/blood.V122.21.2267.2267.

242. Cheng F, Lienlaf M, Perez-Villarroel P, et al. ,DIVERGENT ROLES OF HISTONE DEACETYLASE 6 (HDAC6) AND HISTONE DEACETYLASE 11 (HDAC11) ON THE

TRANSCRIPTIONAL REGULATION OF IL10 IN ANTIGEN PRESENTING CELLS. Mol Immunol 2014;60(1):44–53; doi: 10.1016/j.molimm.2014.02.019.

243. Stammler D, Eigenbrod T, Menz S, et al. Inhibition of Histone Deacetylases Permits Lipopolysaccharide-Mediated Secretion of Bioactive IL-1β via a Caspase-1–Independent Mechanism. The Journal of Immunology 2015;195(11):5421–5431; doi: 10.4049/jimmunol.1501195.

244. Woods DM, Woan KV, Cheng F, et al. T cells lacking HDAC11 have increased effector functions and mediate enhanced alloreactivity in a murine model. Blood 2017;130(2):146–155; doi: 10.1182/blood-2016-08-731505.

245. Yanginlar C, Logie C. HDAC11 is a regulator of diverse immune functions. Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms 2018;1861(1):54–59; doi: 10.1016/j.bbagrm.2017.12.002.

246. Furue K, Ito T, Tsuji G, et al. Psoriasis and the TNF/IL23/IL17 axis. G Ital Dermatol Venereol 2019;154(4):418–424; doi: 10.23736/S0392-0488.18.06202-8.

247. Riol-Blanco L, Ordovas-Montanes J, Perro M, et al. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. Nature 2014;510(7503):157–161; doi: 10.1038/nature13199.

248. Dattola A, Silvestri M, Tamburi F, et al. Emerging role of anti-IL23 in the treatment of psoriasis: When humanized is very promising. Dermatol Ther 2020;33(6):e14504; doi: 10.1111/dth.14504.

249. Amoruso GF, Nisticò SP, Iannone L, et al. Ixekizumab May Improve Renal Function in Psoriasis. Healthcare (Basel) 2021;9(5):543; doi: 10.3390/healthcare9050543.

250. Worzfeld T, Offermanns S. Semaphorins and plexins as therapeutic targets. Nat Rev Drug Discov 2014;13(8):603–621; doi: 10.1038/nrd4337.

251. Adams RH, Eichmann A. Axon guidance molecules in vascular patterning. Cold Spring Harb Perspect Biol 2010;2(5):a001875; doi: 10.1101/cshperspect.a001875.

252. Suzuki K, Kumanogoh A, Kikutani H. Semaphorins and their receptors in immune cell interactions. Nat Immunol 2008;9(1):17–23; doi: 10.1038/ni1553.

253. Kumanogoh A, Kikutani H. Immunological functions of the neuropilins and plexins as receptors for semaphorins. Nat Rev Immunol 2013;13(11):802–814; doi: 10.1038/nri3545.

254. Yoshida Y. Semaphorin signaling in vertebrate neural circuit assembly. Front Mol Neurosci 2012;5:71; doi: 10.3389/fnmol.2012.00071.

255. Messina A, Ferraris N, Wray S, et al. Dysregulation of Semaphorin7A/β1-integrin signaling leads to defective GnRH-1 cell migration, abnormal gonadal development and altered fertility. Human Molecular Genetics 2011;20(24):4759–4774; doi: 10.1093/hmg/ddr403.

256. Giacobini P, Prevot V. Semaphorins in the development, homeostasis and disease of hormone systems. Semin Cell Dev Biol 2013;24(3):190–198; doi: 10.1016/j.semcdb.2012.11.005.

257. Kanth SM, Gairhe S, Torabi-Parizi P. The Role of Semaphorins and Their Receptors in Innate Immune Responses and Clinical Diseases of Acute Inflammation. Front Immunol 2021;12:672441; doi: 10.3389/fimmu.2021.672441.

258. Sabag AD, Dias-Polak D, Bejar J, et al. Altered expression of regulatory molecules in the skin of psoriasis. Immunol Res 2018;66(6):649–654; doi: 10.1007/s12026-018-9057-9.

259. Zhang C, Xiao C, Dang E, et al. CD100-Plexin-B2 Promotes the Inflammation in Psoriasis by Activating NF-κB and the Inflammasome in Keratinocytes. J Invest Dermatol 2018;138(2):375–383; doi: 10.1016/j.jid.2017.09.005.

260. Ryu S, Broussard L, Youn C, et al. Therapeutic Effects of Synthetic Antimicrobial Peptides, TRAIL and NRP1 Blocking Peptides in Psoriatic Keratinocytes. Chonnam Med J 2019;55(2):75–85; doi: 10.4068/cmj.2019.55.2.75.

261. Julien F, Bechara A, Fiore R, et al. Dual Functional Activity of Semaphorin 3B Is Required for Positioning the Anterior Commissure. Neuron 2005;48(1):63–75; doi: 10.1016/j.neuron.2005.08.033.

262. Chauvet S, Cohen S, Yoshida Y, et al. Gating of Sema3E/PlexinD1 Signaling by Neuropilin-1 Switches Axonal Repulsion to Attraction during Brain Development. Neuron 2007;56(5):807–822; doi: 10.1016/j.neuron.2007.10.019.

263. Bellon A, Luchino J, Haigh K, et al. VEGFR2 (KDR/Flk1) signaling mediates axon growth in response to semaphorin 3E in the developing brain. Neuron 2010;66(2):205–219; doi: 10.1016/j.neuron.2010.04.006.

264. Liu Y, Halloran MC. Central and Peripheral Axon Branches from One Neuron Are Guided Differentially by Semaphorin3D and Transient Axonal Glycoprotein-1. J Neurosci 2005;25(45):10556–10563; doi: 10.1523/JNEUROSCI.2710-05.2005.

265. Moretti S, Procopio A, Boemi M, et al. Neuronal semaphorins regulate a primary immune response. Curr Neurovasc Res 2006;3(4):295–305; doi: 10.2174/156720206778792939.

266. Siems SB, Jahn O, Eichel MA, et al. Proteome profile of peripheral myelin in healthy mice and in a neuropathy model. Elife 2020;9:e51406; doi: 10.7554/eLife.51406.

267. Kalpachidou T, Spiecker L, Kress M, et al. Rho GTPases in the Physiology and Pathophysiology of Peripheral Sensory Neurons. Cells 2019;8(6):591; doi: 10.3390/cells8060591.

268. Carr L, Parkinson DB, Dun X. Expression patterns of Slit and Robo family members in adult mouse spinal cord and peripheral nervous system. PLoS One 2017;12(2):e0172736; doi: 10.1371/journal.pone.0172736.

269. Dun X-P, Parkinson DB. Role of Netrin-1 Signaling in Nerve Regeneration. Int J Mol Sci 2017;18(3):491; doi: 10.3390/ijms18030491.

270. Boneschansker L, Nakayama H, Eisenga M, et al. Netrin-1 Augments Chemokinesis in CD4+ T Cells In Vitro and Elicits a Proinflammatory Response In Vivo. J Immunol 2016;197(4):1389–1398; doi: 10.4049/jimmunol.1502432.

271. Nakatsuji Y, Okuno T, Moriya M, et al. Elevation of Sema4A implicates Th cell skewing and the efficacy of IFN-β therapy in multiple sclerosis. JIMMUNOL 2012;188(10):4858–4865; doi: 10.4049/jimmunol.1102023.

272. Koda T, Namba A, Kinoshita M, et al. Sema4A is implicated in the acceleration of Th17 cell-mediated neuroinflammation in the effector phase. J Neuroinflammation 2020;17(1):82; doi: 10.1186/s12974-020-01757-w.

273. Burkhardt C, Müller M, Badde A, et al. Semaphorin 4B interacts with the post-synaptic density protein PSD-95/SAP90 and is recruited to synapses through a C-terminal PDZ-binding motif. FEBS Letters 2005;579(17):3821–3828; doi: 10.1016/j.febslet.2005.05.079.

274. Nakagawa Y, Takamatsu H, Okuno T, et al. Identification of semaphorin 4B as a negative regulator of basophil-mediated immune responses. J Immunol 2011;186(5):2881–2888; doi: 10.4049/jimmunol.1003485.

275. Zhu K, Ye J, Wu M, et al. Expression of Th1 and Th2 cytokine-associated transcription factors, T-bet and GATA-3, in peripheral blood mononuclear cells and skin lesions of patients with psoriasis vulgaris. Arch Dermatol Res 2010;302(7):517–523; doi: 10.1007/s00403-010-1048-1.

276. Wang X, Wang B, Zou M, et al. CircSEMA4B targets miR-431 modulating IL-1β-induced degradative changes in nucleus pulposus cells in intervertebral disc degeneration via Wnt pathway. Biochim Biophys Acta Mol Basis Dis 2018;1864(11):3754–3768; doi: 10.1016/j.bbadis.2018.08.033.

277. Romanowska M, Evans A, Kellock D, et al. Wnt5a Exhibits Layer-Specific Expression in Adult Skin, Is Upregulated in Psoriasis, and Synergizes with Type 1 Interferon. Didier E. ed. PLoS ONE 2009;4(4):e5354; doi: 10.1371/journal.pone.0005354.

278. Clark CEJ, Liu Y, Cooper HM. The Yin and Yang of Wnt/Ryk axon guidance in development and regeneration. Sci China Life Sci 2014;57(4):366–371; doi: 10.1007/s11427-014-4640-3.

279. Ghosh MC, Collins GD, Vandanmagsar B, et al. Activation of Wnt5A signaling is required for CXC chemokine ligand 12-mediated T-cell migration. Blood 2009;114(7):1366–1373; doi: 10.1182/blood-2008-08-175869.

280. Zgraggen S, Huggenberger R, Kerl K, et al. An Important Role of the SDF-1/CXCR4 Axis in Chronic Skin Inflammation. PLoS One 2014;9(4):e93665; doi: 10.1371/journal.pone.0093665.

281. Winge MCG, Ohyama B, Dey CN, et al. RAC1 activation drives pathologic interactions between the epidermis and immune cells. J Clin Invest n.d.;126(7):2661–2677; doi: 10.1172/JCI85738.

282. Schoof M, Launspach M, Holdhof D, et al. The transcriptional coactivator and histone acetyltransferase CBP regulates neural precursor cell development and migration. Acta Neuropathologica Communications 2019;7(1):199; doi: 10.1186/s40478-019-0849-5.

283. He X, Zhang L, Queme LF, et al. A histone deacetylase 3-dependent pathway delimits peripheral myelin growth and functional regeneration. Nat Med 2018;24(3):338–351; doi: 10.1038/nm.4483.

284. Cho Y, Cavalli V. HDAC signaling in neuronal development and axon regeneration. Curr Opin Neurobiol 2014;27:118–126; doi: 10.1016/j.conb.2014.03.008.

285. Puttagunta R, Tedeschi A, Sória MG, et al. PCAF-dependent epigenetic changes promote axonal regeneration in the central nervous system. Nat Commun 2014;5(1):3527; doi: 10.1038/ncomms4527.

286. Gomez-Sanchez JA, Patel N, Martirena F, et al. Emerging Role of HDACs in Regeneration and Ageing in the Peripheral Nervous System: Repair Schwann Cells as Pivotal Targets. Int J Mol Sci 2022;23(6):2996; doi: 10.3390/ijms23062996.

287. Chen Y, Wang H, Yoon SO, et al. HDAC-mediated deacetylation of NF-κB is critical for Schwann cell myelination. Nat Neurosci 2011;14(4):437–441; doi: 10.1038/nn.2780.

288. Kim M, Park C, Jung J, et al. The histone deacetylase class I, II inhibitor trichostatin A delays peripheral neurodegeneration. J Mol Hist 2019;50(2):167–178; doi: 10.1007/s10735-019-09815-1.

289. Deb S, Phukan BC, Mazumder MK, et al. Garcinol, a multifaceted sword for the treatment of Parkinson's disease. Neurochem Int 2019;128:50–57; doi: 10.1016/j.neuint.2019.04.004.

290. Shukla S, Shariat-Madar Z, Walker LA, et al. Mechanism for neurotropic action of vorinostat, a pan histone deacetylase inhibitor. Molecular and Cellular Neuroscience 2016;77:11–20; doi: 10.1016/j.mcn.2016.09.003.

291. Bovenschen HJ, van de Kerkhof PC, van Erp PE, et al. Foxp3+ regulatory T cells of psoriasis patients easily differentiate into IL-17A-producing cells and are found in lesional skin. J Invest Dermatol 2011;131(9):1853–1860; doi: 10.1038/jid.2011.139.

292. Samuelov L, Bochner R, Magal L, et al. Vorinostat, a histone deacetylase inhibitor, as a potential novel treatment for psoriasis. Experimental Dermatology 2022;31(4):567–576; doi: 10.1111/exd.14502.

293. Leuner K, Kraus M, Woelfle U, et al. Reduced TRPC channel expression in psoriatic keratinocytes is associated with impaired differentiation and enhanced proliferation. PLoS One 2011;6(2):e14716; doi: 10.1371/journal.pone.0014716.

294. Buerger C, Shirsath N, Lang V, et al. Inflammation dependent mTORC1 signaling interferes with the switch from keratinocyte proliferation to differentiation. PLoS ONE 2017;12(7); doi: 10.1371/journal.pone.0180853.

295. Zhang P, Su Y, Li S, et al. The roles of T cells in psoriasis. Front Immunol 2023;14:1081256; doi: 10.3389/fimmu.2023.1081256.

296. Li J, Xing J, Lu F, et al. Psoriatic Dermal-derived Mesenchymal Stem Cells Reduce Keratinocyte Junctions, and Increase Glycolysis. Acta Dermato-Venereologica 2020;100(8):1–7; doi: 10.2340/00015555-3480.

297. Nickoloff BJ. Creation of psoriatic plaques: the ultimate tumor suppressor pathway. Journal of Cutaneous Pathology 2001;28(2):57–64; doi: 10.1034/j.1600-0560.2001.280201.x.

298. Szegedi K, Göblös A, Bacsa S, et al. Expression and Functional Studies on the Noncoding RNA, PRINS. International Journal of Molecular Sciences 2013;14(1):205–225; doi: 10.3390/ijms14010205.

299. D'Agostino M, Beji S, Sileno S, et al. Extracellular Nucleophosmin Is Increased in Psoriasis and Correlates With the Determinants of Cardiovascular Diseases. Front Cardiovasc Med 2022;9:867813; doi: 10.3389/fcvm.2022.867813.

300. Melero JL, Andrades S, Arola L, et al. Deciphering psoriasis. A bioinformatic approach. Journal of Dermatological Science 2018;89(2):120–126; doi: 10.1016/j.jdermsci.2017.11.010.

301. Henri P, Prevel C, Pellerano M, et al. Psoriatic epidermis is associated with upregulation of CDK2 and inhibition of CDK4 activity. British Journal of Dermatology 2020;182(3):678–689; doi: 10.1111/bjd.18178.

302. El-wahed Gaber MA, El-Halim Kandil MA, El-Farargy SM, et al. Beta-catenin expression in psoriasis. Indian Dermatol Online J 2015;6(1):13–16; doi: 10.4103/2229-5178.148923.

303. Joseph FM, Young NL. Histone Variant-Specific Post-Translational Modifications. Semin Cell Dev Biol 2023;135:73–84; doi: 10.1016/j.semcdb.2022.02.012.

304. Jaeger S, Barends S, Giegé R, et al. Expression of metazoan replication-dependent histone genes. Biochimie 2005;87(9):827–834; doi: 10.1016/j.biochi.2005.03.012.

305. Man X-Y, Chen X-B, Li W, et al. Analysis of epithelial–mesenchymal transition markers in psoriatic epidermal keratinocytes. Open Biology 2015;5(8):150032; doi: 10.1098/rsob.150032.

306. Stankler L. An Experimental Investigation on the Site of Skin Damage Inducing the Koebner Reaction in Psoriasis. British Journal of Dermatology 1969;81(7):534–535; doi: 10.1111/j.1365-2133.1969.tb16029.x.

307. Schulz BS, Michel G, Wagner S, et al. Increased expression of epidermal IL-8 receptor in psoriasis. Down-regulation by FK-506 in vitro. J Immunol 1993;151(8):4399–4406.

308. Axtell RC, Raman C, Steinman L. Interferon-β exacerbates Th17-mediated inflammatory disease. Trends Immunol 2011;32(6):272–277; doi: 10.1016/j.it.2011.03.008.

309. Doger FK, Dikicioglu E, Ergin F, et al. Nature of cell kinetics in psoriatic epidermis. Journal of Cutaneous Pathology 2007;34(3):257–263; doi: 10.1111/j.1600-0560.2006.00719.x.

310. Shi L, Liu C, Xiong H, et al. Elevation of IgE in patients with psoriasis: Is it a paradoxical phenomenon? Frontiers in Medicine 2022;9; doi: 10.3389/fmed.2022.1007892.

311. Yang S, Zhao M, Jia S. Macrophage: Key player in the pathogenesis of autoimmune diseases. Front Immunol 2023;14:1080310; doi: 10.3389/fimmu.2023.1080310.

312. Martire S, Banaszynski LA. The roles of histone variants in fine-tuning chromatin organization and function. Nat Rev Mol Cell Biol 2020;21(9):522–541; doi: 10.1038/s41580-020-0262-8.

313. Li H, Zhang C, Bian L, et al. Inhibition of CtBP-Regulated Proinflammatory Gene Transcription Attenuates Psoriatic Skin Inflammation. J Invest Dermatol 2022;142(2):390–401; doi: 10.1016/j.jid.2021.06.029.

314. Aggarwal S, Nayek A, Pradhan D, et al. dbGAPs: A comprehensive database of genes and genetic markers associated with psoriasis and its subtypes. Genomics 2018;110(4):240–247; doi: 10.1016/j.ygeno.2017.10.003.

315. Qin J-Z, Chaturvedi V, Denning MF, et al. Regulation of apoptosis by p53 in UV-irradiated human epidermis, psoriatic plaques and senescent keratinocytes. Oncogene 2002;21(19):2991–3002; doi: 10.1038/sj.onc.1205404.

316. Midde HS, Priyadarssini M, Rajappa M, et al. Interleukin-9 serves as a key link between systemic inflammation and angiogenesis in psoriasis. Clinical and Experimental Dermatology 2021;46(1):50–57; doi: 10.1111/ced.14335.

317. Zhang L, Yang X-Q, Cheng J, et al. Increased Th17 cells are accompanied by FoxP3+ Treg cell accumulation and correlated with psoriasis disease severity. Clinical Immunology 2010;135(1):108–117; doi: 10.1016/j.clim.2009.11.008.

318. Zhang L, Li Y, Yang X, et al. Characterization of Th17 and FoxP3(+) Treg Cells in Paediatric Psoriasis Patients. Scand J Immunol 2016;83(3):174–180; doi: 10.1111/sji.12404.

319. Carrozza MJ, Utley RT, Workman JL, et al. The diverse functions of histone acetyltransferase complexes. Trends in Genetics 2003;19(6):321–329; doi: 10.1016/S0168-9525(03)00115-X.

320. Hayakawa T, Nakayama J. Physiological Roles of Class I HDAC Complex and Histone Demethylase. J Biomed Biotechnol 2011;2011:129383; doi: 10.1155/2011/129383.

321. Lee Y, Je Y-J, Lee S-S, et al. Changes in Transepidermal Water Loss and Skin Hydration according to Expression of Aquaporin-3 in Psoriasis. Annals of Dermatology 2012;24(2):168–174; doi: 10.5021/ad.2012.24.2.168.

322. Ayala F. CLINICAL PRESENTATION OF PSORIASIS. Reumatismo 2007;59(s1):40–45; doi: 10.4081/reumatismo.2007.1s.40.

323. Weinstein GD, Frost P. Abnormal cell proliferation in psoriasis. J Invest Dermatol 1968;50(3):254–259.

324. Li B, Huang L, Lv P, et al. The role of Th17 cells in psoriasis. Immunol Res 2020;68(5):296–309; doi: 10.1007/s12026-020-09149-1.

325. Lahm A, Paolini C, Pallaoro M, et al. Unraveling the hidden catalytic activity of vertebrate class IIa histone deacetylases. Proc Natl Acad Sci U S A 2007;104(44):17335–17340; doi: 10.1073/pnas.0706487104.

326. Morhenn VB, Nelson TE, Gruol DL. The rate of wound healing is increased in psoriasis. J Dermatol Sci 2013;72(2):87–92; doi: 10.1016/j.jdermsci.2013.06.001.

327. Mussi A, Bonifati C, Carducci M, et al. IL-10 levels are decreased in psoriatic lesional skin as compared to the psoriatic lesion-free and normal skin suction blister fluids. J Biol Regul Homeost Agents 1994;8(4):117–120.

328. Asadullah K, Sterry W, Stephanek K, et al. IL-10 is a key cytokine in psoriasis. Proof of principle by IL-10 therapy: a new therapeutic approach. J Clin Invest 1998;101(4):783–794; doi: 10.1172/JCI1476.

329. Wang W-M, Jin H-Z. Role of Neutrophils in Psoriasis. J Immunol Res 2020;2020:3709749; doi: 10.1155/2020/3709749.