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Ph.D. Thesis Summary

Ubiquitylation-mediated RNAPII eviction and Transcription Regulation in response to DNA Double-Strand Breaks

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II. Khanam, T., Muñoz, I., Weiland, F., Carroll, T., Morgan, M., Borsos, B.N., **Pantazi, V**., Slean, M., Novak, M., Toth, R., Appleton P., Pankotai, T., Zhou, H., Rouse, J et al. CDKL5 kinase controls transcription-coupled responses to DNA damage. The EMBO Journal e108271 (2021) doi:10.15252/EMBJ.2021108271., MTMT: 32289388
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II. Borsos, N.B., **Pantazi, V**., Pahi, Z.G., Majoros, H., Ujfaludi, Z., Berzsenyi, I., Pankotai, T., The role of p53 in the DNA damage-related ubiquitylation of S2P RNAPII. PLOS ONE, (2022), doi:10.1371/journal.pone.026761, MTMT: 32808068
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III. Berzsenyi, I*., **Pantazi, V***., Borsos, B. N. & Pankotai, T. Systematic overview on the most widespread techniques for inducing and visualizing the DNA double-strand breaks. Mutation Research/Reviews in Mutation Research 788, 108397 (2021)., MTMT: 32480150
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IV. **Pantazi, V**., Berzsenyi, I., Borsos, B. N. & Pankotai, T., Visualizing and Quantifying Endonuclease-Based Site-Specific DNA Damage. JoVE (Journal of Visualized Experiments), 174, 8, (2021) doi: 10.3791/62175, MTMT: 32165045
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V. Páhi, Z. G., Borsos, B. N., **Pantazi, V.,** Ujfaludi, Z. & Pankotai, T., PARylation During Transcription: Insights into the Fine-Tuning Mechanism and Regulation. Cancers (Basel). 12, 183 (2020), MTMT: 31130671
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1. Introduction

The DNA sequence holds vital genetic information necessary for biological processes, requiring high fidelity during cell division. Genome integrity is constantly challenged by genotoxic stresses, leading to various DNA lesions, contributing to diseases like cancer and aging. Humans experience around 10^3 to 10^7 DNA lesions per cell daily. Paradoxically, cells use these mechanisms intentionally, such as in meiosis and immune response, to disrupt genomic integrity strategically. Studies highlight programmed DNA double-strand breaks (DSBs) during meiosis and V(D)J recombination, facilitating genetic diversity and immune function. Deficiencies in DNA repair mechanisms are linked to aging, cancer, and neurodegenerative disorders. Understanding the sources of DNA damage and the DNA damage response (DDR) is crucial, as proper repair mechanisms are essential for maintaining genome integrity and preventing disease.

Among those, the DNA double-strand breaks (DSBs), induced by various agents, are linked to numerous human disorders and cancers. Their repair is managed primarily by homologous recombination (HR) and non-homologous end joining (NHEJ), with additional pathways like alt-NHEJ and MMEJ. Recognition of DSBs begins with chromatin modification, involving ATM and DNAPK activation and recruitment of repair proteins. NHEJ, error-prone, involves Ku heterodimer binding to DSBs, recruiting DNA-PKcs, XRCC4, and LIG4, and processing DNA ends, leading to ligation by LIG4. HR, high-fidelity, operates mainly in S/G2 phase, utilizing the MRN complex, ATM, TIP60, BRCA1, and RAD51 to facilitate DNA strand invasion and repair synthesis.

In the eukaryotic nucleus, transcription, DNA replication, and DNA repair occur simultaneously, necessitating mechanisms to prevent conflicts between these processes to maintain genomic integrity. DNA replication, a major source of endogenous double-strand breaks (DSBs), can lead to two types of DSBs: "two-ended" in G1/G2 phases and "single-ended" (seDSBs) during S phase. seDSBs arise from replication fork stalling and are primarily repaired by homologous recombination (HR). Camptothecin (CPT) induces seDSBs by trapping TOP1 on DNA, with repairs involving proteasome pathways, TDP1, or the XPF-ERCC1 complex. HR repair of seDSBs begins with Ku70/80 binding inhibition, followed by DNA-PKcs-dependent removal, aided by CtIP, which also promotes MRE11

endonuclease activity. Subsequent resection is carried out by EXO1, DNA2-BLM, and the MRN complex, preparing the DNA for RAD51-mediated HR repair

With a primary focus on transcription, its regulation is crucial for gene expression and cellular balance, with each stage—initiation, elongation, and termination—being precisely controlled. The initiation and elongation phases are especially vulnerable to DSBs or replication machinery collisions, posing risks to genome integrity. Complex mechanisms have evolved to mitigate these threats, although they remain poorly understood.

When DSBs occur near transcribed genes, transcription is halted to facilitate DDR processes. DNA-PK, ATM, and PARP1 play significant roles in this transcriptional arrest. DNA-PKcs directly regulates RNA polymerase II (RNAPII) through mediating its post-translational modifications. On the other hand, ATM halts RNAPII elongation by modifying the chromatin environment, involving ubiquitination marks and the recruitment of repressive complexes while PARP1 induces poly(ADP-ribosylation) on RNAPII and chromatin proteins, pausing transcription and recruiting factors, among which is CDKL5, for chromatin modification and transcription arrest.

After UV-induced DNA damage, prolonged transcription arrest leads to the ubiquitination and degradation of RNA polymerase II (RNAPII). Initial studies showed that UV and cisplatin induce RNAPII ubiquitination, which shows to be a conserved event. In yeast, RNAPII ubiquitination serves as a last resort mechanism to clear stalled molecules, while in humans, it directly aids transcription-coupled nucleotide excision repair (TC-NER). The ubiquitination of RNAPII involves multiple E3 ligases, such as BRCA1/BARD1 in humans and Rsp5 in yeast, with differing roles and mechanisms. Furthermore, the Elongin/Cullin complex and Def1 in yeast mediate RNAPII degradation, while in humans, NEDD4 and the Elongin A/B/C-Cullin 5 complex, along with VCP unfoldase, facilitate this process. Recent studies also identified ARMC5 as a novel E3 ligase component affecting RNAPII ubiquitination and degradation, with implications for diseases like primary bilateral macronodular adrenal hyperplasia (PBMAH). Lastly, WWP2 has been also shown to play a role in RNAPII degradation and DSB repair, highlighting the complexity and clinical relevance of these pathways.

2. Aims

- Clarify the indispensable role of ubiquitylation during DNA repair.
- Identify E3 ligases involved during elongating RNAPII-ubiquitylation and transcription misregulation
- Explore the impact of ubiquitylation dysregulation on gene expression, potentially linking it to genomic instability.
- Characterize the ubiquitin code written on transcirbing RNAPII upon encountering a DSB.
- Investigate the functional roles the E3 ligases have during DNA DSB repair

3. Results

I. The HECT ligases WWP2 and NEDD4 as well CRL3 complexes interact with and differentially ubiquitylate RNAPII in response to Double-Strand Breaks

Recent research identified that in physiological conditions depleting eukaryotic SPT5 causes the accumulation of the E3 ligase Cullin 3 and unfoldase VCP/p97 on chromatin, initiating RPB1 degradation, which is conserved from yeast to humans. Unlike this and the well-studied UV response, few studies have explored RPB1 ubiquitylation during DNA double-strand breaks (DSBs). To investigate Cullin 3 (CUL3)'s role in DSB repair, a U2OS-based shCUL3 knock-down cell line was created. LC-MS/MS after ionising radiation (IR) treatment revealed changes in interactions between CUL3 and the three RNA polymerase enzymes subunits. Stronger CUL3-RNAPII subunit interactions were noted during DNA damage, prompting further exploration of CUL3-mediated RNAPII regulation. Furthermore, the mass spectrometry could capture the E3 ligases WWP2 and NEDD4 with no significant enrichment potentially due to their interaction with RNAPII during DSB repair. Immunoprecipitation confirmed WWP2's immediate and NEDD4's and CUL3’s delayed interaction with RNAPII during DSB response while further Tandem Ubiquitin Binding Entities (TUBE) pull down assay revealed WWP2's early and NEDD4/CUL3's later impact on S2P-RNAPII ubiquitylation during DSBs. These findings indicate that WWP2 acts as the initial responder, while CUL3 and NEDD4 act as late responders during prolonged damage that interact with and ubiquitylate elongating RNAPII.

II. The E3 ligases WWP2, NEDD4 and CRL3 complexes repress transcription in response to DNA Double-Strand Breaks

To examine how ligases involved in the ubiquitylation of transcribing RNAPII during DNA breaks affect gene expression, we created a doxycycline (DOX)-inducible cell line for the expression and cytoplasmic sequestration of the restriction endonuclease AsiSI. AsiSI, fused with the estrogen receptor (ER) ligand-binding domain, translocates to the nucleus and induces sequence-specific genomic DSBs upon 4-hydroxitamoxifen (4-OHT) addition, as shown by γH2AX foci elevation post-treatment. From previous studies, we identified AsiSI target sites (KREBZF, PSMD3, CRNKL1) and generated DOX-inducible E3 ligase knock-down derivatives (LentiVAsiSI-shWWP2, LentiVAsiSI-shCUL3, LentiVAsiSI-shNEDD4) to measure PSMD3 and KREBZF expression after AsiSI induction and ligase knock-down. Results indicated that gene transcription fails to be repressed during DSBs when ligases are knocked-down.

We further used a U2OS-based cell line, pEP15-I-PpoI, employing the I-PpoI endonuclease to target DAB1, RYR, and INTS4. Ligase silencing followed by I-PpoI system activation and qRT-PCR confirmed that CUL3 and NEDD4 ligases facilitate transcriptional repression during DSBs, aligning with previous findings on WWP2.

Nevertheless, to connect global genomic DSB induction with transcription repression, we measured nascent RNA using 5-ethynyl uridine (EU) staining after ligase siRNA-mediated knockdown and 4-hour NCS treatment. Once again, transcription was not suppressed when ligases were silenced, as indicated by elevated EU foci, suggesting this mechanism is crucial for proper transcription shutdown during DSB repair possibly through mediating elongating RNAPII's ubiquitylation.

III. K63- linked ubiquitin chains are assembled on elongating RNAPII during DSB induction and primarily mediated by NEDD4

In the ubiquitin-proteasome system, the fate of proteins is intricately linked to the type of ubiquitin chain they bear. For instance, K48- and K11-linked chains are known to target proteins for proteasomal degradation, whereas K63-linked chains are typically involved in non-

degradative signaling processes, often acting as scaffolds for protein complex assembly. However, recent research has started to connect K63 chains with degradative outcomes for specific substrates. Upon confirming that agents inducing double-strand breaks (DSBs) such as ionizing radiation (IR), neocarzinostatin (NCS), and phleomycin (Phl) robustly induce ubiquitylation of the elongating form of RNA polymerase II (RNAPII) in a proteasome-dependent manner, we were interested to unravel the the specific types of ubiquitin linkages involved and their roles in driving RNAPII degradation. We employed recombinant deubiquitylase enzymes (OTUB1, AMSH and USP2/USP21), which selectively cleave K48, K63 or pan-ubiquitin chains, respectively. Using these enzymes in ubiquitin restriction digestion reactions (UbiCRest), we found that AMSH treatment post-DSB induction (1-2 hours) allowed digestion of ubiquitin specifically linked to RNAPII via K63, indicating that during transcription elongation, RNAPII becomes marked with K63-linked ubiquitin chains. Interestingly, we observed a significant reduction in total ubiquitin intensity after 2 hours of DSB induction compared to 1 hour. This decrease suggested that most RNAPII molecules might have been degraded by the proteasome within this timeframe. Blocking proteasome activity with MG132 unexpectedly reinforced our finding that RNAPII is primarily targeted with K63-linked ubiquitin chains, marking S2P-RNAPII (phosphorylated at serine 2 of its C-terminal domain) for proteasomal degradation. Further experiments using sequential combinations of OTUB1 and AMSH treatments underscored AMSH's role in providing access for subsequent OTUB1 cleavage, indicating a hierarchical assembly of ubiquitin chains on RNAPII during DSB response. This process likely involves the formation of complex, heterogeneous branched ubiquitin chains where K48-linked chains scaffold K63-linked ones, suggesting a dynamic and time-dependent mechanism in DSB repair signaling and RNAPII regulation.

To identify the specific E3 ligase responsible for generating the S2P-RNAPII ubiquitin code during DSB response, we employed siRNA-mediated knockdown of WWP2, CUL3, and NEDD4. We also overexpressed lysine-specific ubiquitin molecules (pcDNA3.1-HA-Ub-WT, -K0, -K48, -K63) and performed S2P-RNAPII immunoprecipitation before and after DSB induction. Our findings implicated NEDD4 as crucial for utilizing K63 ubiquitin linkages in response to damage, while CUL3 depletion affected both K48 and K63 linkages under physiological conditions. WWP2 primarily generated K48-linked chains, particularly in non-damaged states, and to a lesser extent during DSB response.

Interestingly, inhibiting the proteasome with MG132 highlighted NEDD4's indispensable role in proper ubiquitylation events on transcribing RNAPII, whereas CUL3 depletion primarily inhibited S2P-RNAPII mono-ubiquitylation, particularly during extended DNA damage. Overall, the findings suggest a model where WWP2 forms K48-linked ubiquitin chains that are extended with K63 chains by NEDD4, while CUL3 plays a supportive role in monoubiquitylation during later stages of DSB response. These insights deepen our understanding of how ubiquitin linkages orchestrate RNAPII regulation in the context of DNA damage repair pathways.

IV. K63-linked ubiquitin chains provide the scaffolding for K48-linked chains on the RNAPII holoenzyme

We additionally sought to investigate whether the same ubiquitin linkage types target the holoenzyme of RNAPII, without focusing directly on RNAPII's gene localization and phosphorylation status (such as promoter-bound initiating form, elongating, or terminating RNAPII molecules). We theorize that the K63-linked ubiquitin chains, which selectively modify the elongating RNAPII as we reported previously, are crucial for those RNAPII molecules that directly encounter DNA breaks, facilitating the signalling of repair factors and efficient DSB repair. To explore this, we induced random genome breaks using ionizing radiation (IR), blocked the proteasome to capture all the ubiquitylated RNNAPII molecules and performed immunoprecipitation of the RNAPII C-terminal domain (CTD) or TUBE experiments to pull down all ubiquitylated proteins, subsequently targeting RNAPII ubiquitylation via Western Blot. These experiments were followed by UbiCRest digestion reactions as previously described.
Notably, after normalising the intensity of the ubiquitin blot to each No DUB treatment/ condition as well as to the IP (RNAPII CTD) we detected that K63 chains are secondary to K48 chains in the case of total RNAPII molecules (Figure 4A-B). During immediate or prolonged DNA damage, RNAPII molecules throughout a transcribing gene predominantly exhibit K48-linked ubiquitin chains, with K63-linked chains being less prominent. Interestingly, the sequential combination of OTUB1 and AMSH, with OTUB1 acting first, resulted in an almost complete reduction of ubiquitin chains. This finding highlights the presence of both types of ubiquitin linkages on RNAPII and underscores the complexity of its regulation. The sequential targeting of RNAPII with K63 and then K48 ubiquitin chains highlights a dynamic regulatory

process. Initially, K63 chains modify the transcriptional machinery for repair or signalling purposes, and subsequently, K48 chains mark it for degradation to maintain cellular homeostasis.

V. The E3 ligases exhibit interdependence with DNA-PK to mediate proficient NHEJ

We investigated the temporal dynamics of elongating RNAPII interactions following DNA breaks using LC-MS/MS in U2OS cells treated with NCS. Specific proteins were detected exclusively at 30 minutes or 2 hours post-treatment, but not under physiological conditions. These proteins were analyzed for biological pathway enrichment via Gene Ontology. Immediately after break induction, proteins involved in proteasome-mediated ubiquitin-dependent protein catabolic processes were enriched, while prolonged damage enriched DDR protein interactions with S2P-RNAPII. We did not detect WWP2, NEDD4, or CUL3 interacting with transcribing RNAPII, suggesting their transient role in RNAPII ubiquitylation. Instead, we found CUL4A and CUL1, previously reported to ubiquitylate RNAPII in response to UV radiation. Proteasome subunits PSMC3 and PSME3 increased interaction with RNAPII immediately after break induction. We propose that ubiquitylation of RNAPII is crucial for initiating DDR signaling. In addition, depleting WWP2, NEDD4, or CUL3 exhibited lethal effects on cells post-DSB induction, significantly impacting cell viability and our subcellular fractionation showed that these ligases' knockdown altered chromatin binding of key NHEJ proteins. Investigating even more the invovlement of DNA-PK, we demonstrate that by Inhibiting it prevented RNAPII ubiquitylation as was reported as well as transcription repression, but strikingly reduced to the minimum the chromatin binding of CUL3 and NEDD4 exhibiting a DNA-PK dependence. Our findings highlight an interdependence between DNA-PK and these ligases in for mediating proficient DDR and eventually transcription shutdown.

VI. WWP2, NEDD4 and CRL3 are crucial members of transcription repression in response to DSBs

From our subcellular fractionation experiments, we observed that depleting WWP2, CUL3, and NEDD4 significantly affected the chromatin binding of elongating RNAPII. WWP2 depletion caused RNAPII to remain strongly associated with chromatin regardless of DNA breaks,

indicating its role in the disassociation process during the transcription cycle. CUL3 depletion led to a pronounced RNAPII chromatin association only after DNA break induction, peaking two hours post-damage response while NEDD4 depletion resulted in a delayed but robust binding of S2P-RNAPII to chromatin following break induction, deviating from the usual oscillatory pattern seen under physiological conditions. These findings highlight the distinct yet interconnected roles of these ligases in regulating RNAPII's chromatin dynamics during DNA damage response (DDR).

Further, ChIP experiments with qPCR in the LentiVAsiSI cell line post-depletion of WWP2, NEDD4, or CUL3 showed that γH2AX spread across the entire gene after break induction, indicating DDR activation. Significant reduction in γH2AX signal was observed 15-20 kbp from the break site. Transcription repression post-DSB was recapitulated by reduced chromatin-bound S2P-RNAPII molecules across damaged loci. Remarkably, transcription repression failed with ligase depletion. WWP2 knockdown increased S2P-RNAPII chromatin occupancy throughout the DNA damage time-course while CUL3 depletion rescued early transcription. On the other hand, NEDD4 depletion showed delayed S2P-RNAPII association, indicating a time-shifted transcription regulation response. Overall, these results underscore the crucial, interconnected roles of WWP2, CUL3, and NEDD4 in modulating RNAPII dynamics and transcriptional regulation during DDR, essential for maintaining genomic integrity.

4. Conclusions

- CRL3 complexes interact with subunits of RNAPI, RNAPII and RNAPIII upon IR with enriched interaction shown with specific subunits of RNAPII.
- CRL3 LC-MS/MS pulled down E3 ligases, NEDD4 and WWP2, previously characterized to participate in UV-damage induced and DSB-induced transcription control and RPB1 degradation, respectively
- CUL3 and NEDD4 interacted with the holoenzyme as well as with the elongating RNAPII (S2P-RNAPII) late during DSB response whereas WWP2 exhibited immediate profound interaction during DSBs.

- In the same notion, CUL3 and NEDD4 knock-down showed reduced S2P-RNAPII ubiquitylation only during prolonged DNA damage whereas WWP2 knock-down resulted in almost complete loss of S2P-RNAPII ubiquitylation immediately after damage.
- All 3 ubiquitin ligases tested showed to be indispensable for proficient DSB-induced transcription repression either in gene specific loci (tested in LentiVAsiSI or pEP15-I-PpoI cell lines) or in global genomic level.
- K63-linked ubiquitin chains are the main linkage types that target elongating RNAPII during DSB response with K48-linked chains providing the scaffolds for the generation of K63 ones.
- On the other hand, the holoenzyme of RNAPII is targeted predominantly with K48-linked ubiquitin chains with K63 ones providing the scaffolds.
- NEDD4 is the main E3 ligase that marks K63-linkage ubiquitin chains on elongating RNAPII in response to DSB.
- The knock-down of the E3 ubiquitin ligases WWP2, NEDD4 and CRL3 complexes compromised proficient DNA-PK activation and chromatin loading as well as Ku86 but not XRCC4.
- E3 ligase knock-down and DSB induction gave rise to a synthetic defect in colony outgrowth.
- Ubiquitylation mechanisms occur prior to DSB repair, serving as an initial component of the DSB response.
- CUL3 and NEDD4 are recruiting at the site of the damage in a DNA-PK dependent fashion (WWP2 has been reported to do so earlier by members of our lab)
- Ligase knock-down led to significant enrichment in elongating RNAPII occupancy at the break site as opposed to its downregulation in physiological conditions during DSB.

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Declaration:

I declare as the supervisor and the corresponding/co-author of the below listed publications that the contribution of Vasiliki Pantazi was significant in these publications and that the doctoral process is based on these publications. The results reported in the PhD dissertation were not used to acquire any PhD degree in the past and will not be used in the future either.

Pantazi V., Miklós V., Smith P., Ólah-Németh O., Pankotai-Bodó G., Teja Dondapati D., Ayaydin F., D'Angiolella V., Pankotai T. **Prognostic potential of CUL3 ligase with differential roles in Luminal A and basal type breast cancer tumors.** Scientific Reports, 2024 doi: 10.1038/s41598-024-65692-z, MTMT: 35076497
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Khanam, T., Muñoz, I., Weiland, F., Carroll, T., Morgan, M., Borsos, B.N., Pantazi, V., Slean, M., Novak, M., Toth, R., Appleton P., Pankotai, T., Zhou, H., Rouse, J et al. **CDKL5 kinase controls transcription-coupled responses to DNA damage.** The EMBO Journal e108271 (2021) doi:10.15252/EMBJ.2021108271., MTMT: 32289388
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