University of Szeged
Albert Szent-Györgyi Medical School
Doctoral School of Theoretical Medicine

HUN-REN Biological Research Centre
Institute of Biophysics
Neurovascular Unit Research Group

Ageing-related microinfarct-induced alterations in contractile protein expression in brain pericytes

Ph.D. thesis

Fanni Győri

Supervisor:
Imola Wilhelm M.D., Ph.D.

Szeged
2025

Introduction

The neurovascular unit (NVU) represents a close structural and functional relationship between cerebral microvascular cells (endothelial cells and pericytes) and neural cells (neurons and glia) having two main functions, regulation of cerebral blood flow (CBF) and the blood–brain barrier (BBB). Among cells of the NVU, pericytes are the least well-defined and most controversial cells. They are mural cells located in the duplication of the basement membrane of microvessels, coming in close contact with cerebral endothelial and glial cells. Although discovered almost 150 years ago, pericytes remain largely uncharacterized cells, heterogenic in their morphology and function, only defined by their perivascular localization (1).

Pericytes are multipotent cells, which form a phenotypic and probably functional continuum with vascular smooth muscle cells (VSMCs) to regulate key functions of the NVU (2). Based on morphology, α-SMA expression, calcium signalling, and dye uptake, mural cells on microvessels are categorized as ensheathing, mesh, and thin-strand pericytes (3–5). Ensheathing pericytes are short cells in their length, having a protruding cell body, exhibiting a high vessel coverage and expressing detectable amounts of α-SMA. They have been also called transitional pericytes or pre-capillary VSMCs (6). These cells usually cover the first four branches ramifying from the penetrating arteriole. On the other hand, mesh and thin-strand pericytes, together called capillary pericytes, have low levels of α-SMA that are usually detectable using special fixation techniques (7). Mesh pericytes are longer than ensheathing pericytes, endowing microvessels of approximately 6 μm diameter with an intermediate coverage in the mouse brain, while thin-strand pericytes have long processes along the length of the smallest capillaries with small perpendicular processes partly embracing the vessel.

Considering their heterogeneity, it is not surprising that the role of pericytes in the regulation of CBF has been intensively debated and initially thought to be restricted to transitional/ensheathing cells (8–10). Ensheathing pericytes encircling the vessel lumen were shown to control both vasodilation

and vasoconstriction in the brain, first-order vessels dilating even before penetrating arterioles covered by VSMCs (8). However, selective ablation of capillary pericytes led to vasodilation (11), while their optogenetic stimulation decreased lumen diameter (12). These data indicated that capillary pericytes take part in the regulation of the basal vascular tone and the slow modulation of CBF.

Involved in several aspects of neurovascular functions, pericytes are subject to alterations in both normal and pathological ageing. Age-related morphological and functional changes of the NVU, including vessel rarefaction, micro-haemorrhages, increased BBB permeability, as well as diminished CBF and reduced neurovascular coupling are the consequence of cellular and molecular changes, which involve senescence and inflamm-ageing (13,14). Pericyte dysfunction and even pericyte loss are the main components of these alterations (15); local pericyte loss results in focal capillary dilation that leads to increased flow heterogeneity (16). Alterations in cell contractility may also contribute to age-related pericyte dysfunction.

Pericyte dysfunction is even more pronounced in ageing-related pathologies, including neurodegenerative and ischaemic conditions (17,18) or in brain metastasis (19). Ischaemia was shown to induce pericyte contraction that could be followed by pericyte death in rigour, which may irreversibly constrict capillaries (8); while mammary carcinoma cells induced vasoconstriction before transmigration into brain parenchyma (20).

As parts of the cerebral small vessel disease spectrum, microinfarcts are one of the most common ischaemic lesions of the ageing brain, contributing significantly to cognitive decline and dementia (21,22). Microinfarcts affect a large number of vessels globally throughout the brain; thus, the best method to model this condition is injection of microspheres into the circulation (23). However, changes in pericytes, especially in their expression of contractile proteins remain largely unknown in response to microinfarcts.

Aims of the study

In this study, we aimed to understand how ageing, microinfarcts and metastatic cells influence the expression of contractile elements of pericytes, and how these changes potentially cause CBF disturbances. Our research focused on three main questions:

1. First, how does the expression of α-SMA change during ageing in pericytes, and what is the regulator of the α-SMA change?
2. Second, do microinfarcts induce changes in the expression of α-SMA of pericytes in young and old mouse brains?
3. Third, do other contractile proteins, like γ-actin play a role in the contractility of pericytes in the context of ischaemia?
4. Finally, do metastatic tumour cells induce the expression of α-SMA in cerebral pericytes?

Results

1. Age-related changes in the contractile protein expression of brain pericytes

To investigate contractile protein expression in the cerebral microvessels of young and old mice, we first isolated small vessels from the brains of young (2 to 3 months of age) and old (24 months of age) BALB/c mice. Isolated microvessels contained endothelial cells and pericytes (Figure 1 a).

Comparing microvessels of young and old mice, we observed that the amount of CD13 (aminopeptidase N) protein did not change significantly with ageing (Figure 1 b, c). On the other hand, expression of *Acta2*/α-SMA decreased drastically both on the mRNA and protein levels in the microvessels of old mice in comparison to microvessels isolated from the brains of young animals (Figure 2 a-c). Since the decrease in the amount of α-SMA was much more pronounced than that of CD13, this suggests that not

change in pericyte number, but rather that of protein expression is responsible for the observed phenomenon.

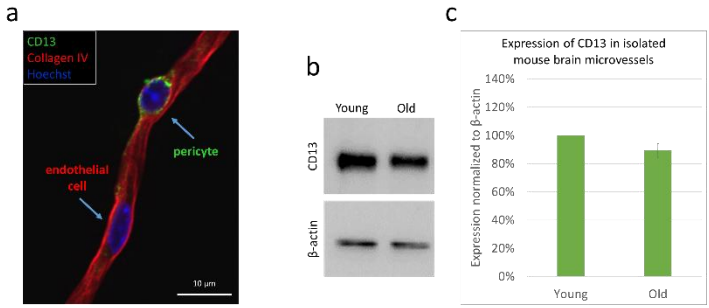

Figure 1. Expression of CD13 in isolated brain microvessels of young and old mice. **a:** Representative immunofluorescence micrograph (maximum intensity projection) showing an isolated brain microvessel. **b**: Representative western blot showing the expression of CD13 in brain microvessels of young and old mice (β-actin was used as a loading control). **c**: Quantitative analysis of CD13 levels compared to β-actin expression, as assessed by western blot. Graphs represent the average ± SEM (N = 2). No significant difference was detected between the two groups (Student's *t*-test).

In both VSMCs and pericytes, one of the main regulators of α-SMA expression is TGF-β1 (24,25). Therefore, we next analysed the expression of *Tgfb1*/TGF-β1 and detected significantly lower gene and protein expression levels in the 2-year-old mice than in the young (Figure 2 d-f). This is in line with the decreased expression of *Acta2*/α-SMA, most probably contributing to this latter.

Similar results were obtained from young (2–3 months) and old (14–21 months) Wistar rats regarding to the contractile protein amount. *Acta2*/α-SMA expression exhibited a significant downregulation at both transcript and protein levels in cerebral microvessels of aged rats, relative to those isolated from young animals.

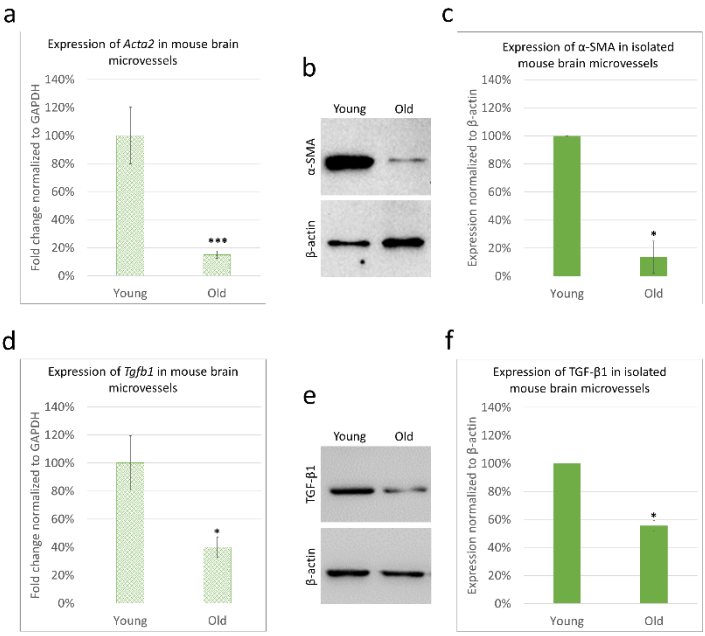

Figure 2. Expression of *Acta2*/α-SMA and *Tgfb1*/TGF-β1 in brain microvessels of young and old mice.

a: Gene expression of *Acta2* in microvessels isolated from the brains of young (2 to 3 months of age) and old (24 months of age) BALB/c mice. Graphs represent the fold change (normalized to GAPDH), average ± SEM (N = 2 independent experiments, each performed in triplicate). *** P≤0.001 (Student's *t*-test). **b**: Representative western blot showing the expression of α-SMA in brain microvessels of young and old mice (β-actin was used as a loading control). **c**: Quantitative analysis of α-SMA levels compared to β-actin expression, as assessed by western blot. Graphs represent the average ± SEM (N = 2). * P≤0.05 (Student's *t*-test). **d**: Gene expression of *Tgfb1* in microvessels isolated from the brains of young (2 to 3 months of age) and old (24 months of age) BALB/c mice. Graphs represent the fold change (normalized to GAPDH), average ± SEM (N = 2 independent experiments, each performed in triplicate). * P≤0.05 (Student's *t*-test). **e**: Representative western blot showing the expression of TGF-β1 in brain microvessels of young and old mice (β-actin was used as a loading control). **f**: Quantitative analysis of TGF-β1 levels compared to β-actin expression, as assessed by western blot. Graphs represent the average ± SEM (N = 2). * P≤0.05 (Student's *t*-test).

2. Changes in α-SMA expression in brain pericytes in response to microsphere-induced lumen obstruction

As cerebral microinfarcts are common in ageing, we next aimed at understanding how contractility of mural cells might influence the outcome of vessel obstruction. We modelled this condition by delivering fluorescent microspheres of 10 μm diameter into the brain vessels of mice via injection into the internal carotid artery. In accordance with previous results (23), we observed the highest number of microspheres blocked in the neocortex (in young mice, 33.43%, while in old mice, 32.47% of the total number), followed by the thalamus (15.01% and 13.90%, respectively) and the hippocampus (8.93% in young and 11.63% in old animals).

Although not significantly higher than at 2 or 24 hours, the number of α-SMA-positive microsphere-containing vessels was the highest 4 hours after injection of the beads, both in young and old animals. Therefore, we performed all the subsequent experiments at this time point and focused on evaluating the cortical areas where the majority of the microspheres became lodged. Using immunofluorescence staining of α-SMA in brain sections, we observed a tendency of vasoconstriction in the vessels encompassing the microspheres, although a substantial narrowing of the lumen of blood vessels was a rare event especially in old animals.

We quantified and compared α-SMA expression intensity in the microbead-containing and control hemispheres of young and old mice. As expected, in both age groups, ensheathing pericytes were richer in α-SMA than mesh pericytes. Decreased levels of α-SMA were detected in both ensheathing and mesh pericytes, respectively, in old animals in comparison to their young counterparts (Figure 3). In young mice, expression of α-SMA increased significantly in both ensheathing and mesh pericytes in response to the presence of the microspheres (Figure 3). In ensheathing pericytes of old animals there was only a tendency of higher α-SMA expression in microbead-containing vessels versus control vessels (Figure 3), while in mesh pericytes of 24-month-old animals, α-SMA increased significantly surrounding

microbead-containing vessels, approximately reaching the level of that measured in young control vessels (Figure 3). Increased α-SMA expression was predominantly observed on one side of the microsphere; however, due to the thin sections used, we were unable to determine whether this occurred in the upstream or downstream direction. Changes in thin-strand pericytes are not shown since expression of α-SMA was very low in these cells and only detectable in young animals. Microspheres usually stalled in lower order vessels and were very rarely observed in capillaries covered by thin-strand pericytes.

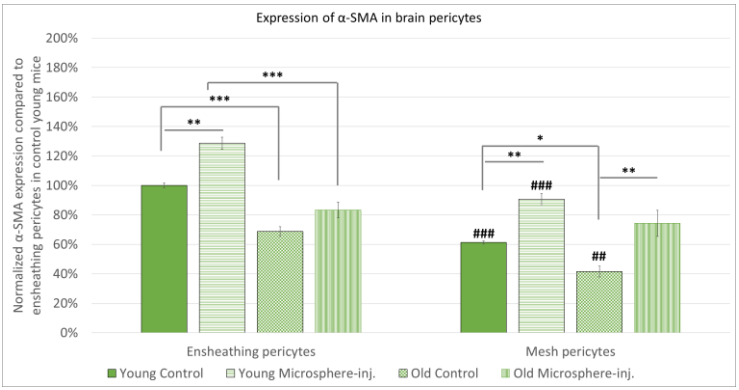

Figure 3. Expression of α-SMA in brain pericytes at 4 hours after injection of microspheres in young and old mice.
Expression of α-SMA in ensheathing and mesh pericytes, measured by immunofluorescence intensity in brain sections of young (2 to 3 months of age) and old (24 months of age) BALB/c mice at 4 hours after injection of the microspheres. Graph represents the average ± SEM (n = 5-10 cells per animal, N = 2 animals per group). * P≤0.05, ** P≤0.01, *** P≤0.001; ## P≤0.01, ### P≤0.001 compared to ensheathing pericytes of the same group (ANOVA and Tukey's multiple comparisons test). Microsphere-inj. = microsphere-injected.

3. Changes in γ-actin expression in brain microvessels following microsphere-induced lumen obstruction

Contractility of pericytes and their involvement in the regulation of CBF has long been debated mainly due to the difficulties in the detection of α-SMA in thin-strand pericytes (26). Contribution of other actin isoforms has

been suggested, like γ-actin; however recently, expression of γ-actin was detected only in pericytes of lower order vessels (7). We wanted to acquire a more nuanced understanding of γ-actin expression in brain capillaries and to appreciate whether it shows similar changes as α-SMA in response to lumen obstruction. The same 10 μm-size microbeads were injected unilaterally, but in higher numbers to ensure the majority of microvessels are affected. As detected by western blot, α-SMA increased significantly. On the contrary, expression of γ-actin decreased in microvessels isolated from the microsphere-containing hemispheres (Figure 4 a, b). Finally, we wanted to determine which vascular cells express γ-actin. By performing immunofluorescence staining in isolated microvessels, γ-actin was clearly detected in von Willebrand factor (vWF)-positive endothelial cells, but was absent in CD13-positive pericytes (Figure 4 c), suggesting a difference between endothelial cells and pericytes in the expression of actin isoforms both in basal and injured conditions.

4. **α-SMA expression in brain pericytes in response to tumour cell-induced lumen obstruction**

It has been previously described in our laboratory that breast cancer cells induce vasoconstriction in the brain after spending 1-2 days in the vessel lumen (20). To elucidate the molecular background of this mechanism, we aimed to investigate the contractile protein expression of pericytes near to the tumour cells. In brain sections of young FVB/Ant:TgCAG-YFP mice, which express Venus yellow fluorescent protein (YFP) in endothelial cells, we observed α-SMA expression around cancer cells lodged in microvessels three days after their injection (Figure 5).

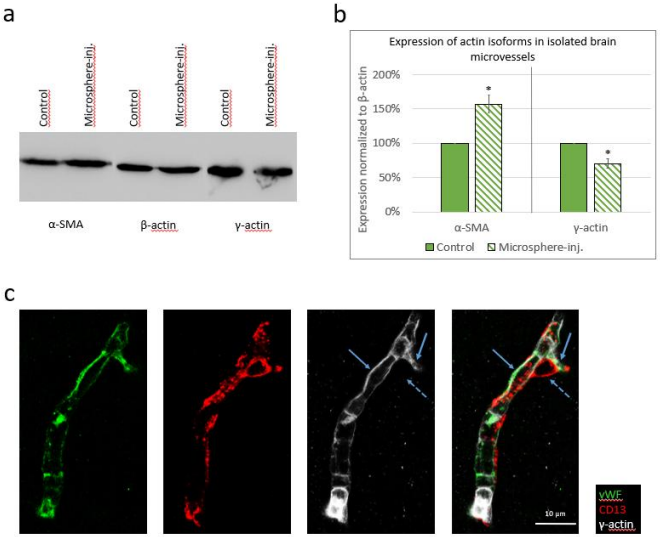

Figure 4. Expression of actin isoforms in brain microvessels.
a: Representative western blot showing the expression of α-SMA, β- and γ-actin in brain microvessels isolated from young mice injected with 10 µm-diameter microspheres. **b**: Quantitative analysis of α-SMA and γ-actin levels compared to β-actin expression, as assessed by western blot. Graphs represent the average ± SEM (N = 2). * P≤0.05 (Student's *t*-test). **c**: Representative immunofluorescence micrographs (maximum intensity projections) showing expression of γ-actin in brain sections of young BALB/c mice. Arrows denote endothelial localization of γ-actin. The dashed arrow indicates absence of γ-actin from pericytes.

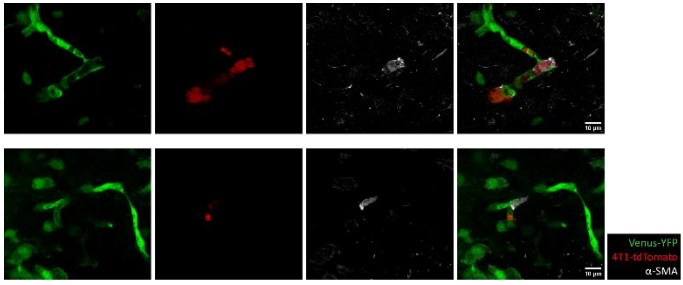

Figure 5. Expression of α-SMA of brain microvessels containing tumour cells.
Representative immunofluorescence micrographs (maximum intensity projections) showing α-SMA expression in brain sections of young (2 to 3 months of age) FVB/Ant:TgCAG-yfp mice 3 days after the injection of 4T1-tdTomato cells.

Summary

Brain pericytes are mural cells embedded in the basement membrane of microvessels, intimately associated with endothelial and glial cells. Due to their heterogeneity, they are organized as ensheathing, mesh and thin-strand types. These latter two, together called capillary pericytes, have low levels of α-SMA, regulating basal vascular tone and applying a slow influence on CBF, while ensheathing pericytes possess more contractile protein, allowing them to robustly regulate vasoconstriction and vasodilation.

Pericytes are subject to alterations in ageing which may be even more pronounced in age-related pathologies, including microinfarcts, which usually affect a large number of vessels in the ageing brain. We modelled this condition by injecting 10 µm-size microspheres into the circulation of mice resulting in the occlusion of capillaries covered by ensheathing and mesh pericytes. We observed that α-SMA and *Acta2*, the gene encoding it, as well as TGF-β1/*Tgfb1*, the major regulator of α-SMA, decreased during ageing in cerebral microvessels. In the vicinity of the microspheres stalled in the capillaries, expression of α-SMA increased significantly in both ensheathing and especially in mesh pericytes, both in young (2 to 3 months of age) and old (24 months of age) mice. On the other hand, γ-actin was detected in endothelial cells, but not in pericytes, and decreased in microvessels of microsphere-containing hemispheres. Furthermore, while investigating the vascular changes in brain metastasis, we found high α-SMA expression in cerebral capillaries containing tumour cells.

Altogether, our data show that obstruction of cerebral microvessels increases α-SMA expression in pericytes in both age groups, but this does not compensate for the lower expression of the contractile protein in old animals. Increased α-SMA expression may lead to constriction of the obstructed vessels probably aggravating flow heterogeneity in the aged brain or in the context of brain metastasis. In conclusion, brain pericytes are key players in regulating ageing-associated ischaemic responses, therefore targeting pericytes may offer new therapeutic opportunities for ischaemic stroke.

List of publications

1. List of publications related to the dissertation

Győri, F., Mészáros, Á., Krecsmarik, M., Molnár, K., Balta, C., Hermenean, A., Farkas, A. E., Krizbai, I. A., & Wilhelm, I. (2025). Expression of alpha smooth muscle actin decreases with ageing and increases upon lumen obstruction in mouse brain pericytes. *GeroScience*, 47(2), 2525–2540. https://doi.org/10.1007/s11357-024-01429-0

D1, IF: 5.4 (2024)

Wilhelm, I., **Győri, F.**, Dudás, T., Nagy, V., Shreeya, T., Krecsmarik, M., Farkas, A. E., Fazakas, C., Krizbai, I. A. (2025). Eppur si muove: The dynamic brain pericyte (manuscript has been accepted for publication in *Fluids and Barriers of the CNS*)

2. Other publications

Sere, P., Zsigri, N., Raffai, T., Furdan, S., **Győri, F.**, Crunelli, V., & Lőrincz, M. L. (2021). Activity of the lateral hypothalamus during genetically determined absence seizures. *International journal of molecular sciences*, *22*(17), 9466. https://doi.org/10.3390/ijms22179466

D1, IF: 6.208

Molnár, K., Mészáros, Á., Fazakas, C., Kozma, M., **Győri, F.**, Reisz, Z., Tiszlavicz, L., Farkas, A. E., Nyúl-Tóth, Á., Haskó, J., Krizbai, I. A., & Wilhelm, I. (2020). Pericyte-secreted IGF2 promotes breast cancer brain metastasis formation. *Molecular oncology*, *14*(9), 2040–2057. https://doi.org/10.1002/1878-0261.12752

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Haskó, J., Fazakas, C., Molnár, K., Mészáros, Á., Patai, R., Szabó, G., Erdélyi, F., Nyúl-Tóth, Á., **Győri, F.**, Kozma, M., Farkas, A. E., Krizbai, I. A., & Wilhelm, I. (2019). Response of the neurovascular unit to brain metastatic breast cancer cells. *Acta neuropathologica communications*, *7*(1), 133. https://doi.org/10.1186/s40478-019-0788-1

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Nyúl-Tóth, Á., Mészáros, Á., **Győri, F.**, Wilhelm, I., & Krizbai, I. A. (2018). A vér-agy gát területi heterogenitásainak vizsgálata emberben és egérben [Analysis of regional heterogeneities of the blood-brain barrier in humans and mice]. *Bulletin of medical sciences / Orvostudományi értesítő*, *91*(1), 26–36. http://doi.org/10.2478/orvtudert-2018-0005

Acknowledgements

First and foremost, I would like to express my deepest gratitude to my supervisor, Imola Wilhelm, for her guidance, support, and encouragement throughout my research. I am also sincerely grateful to István Krizbai, head of the Neurovascular Unit Research Group for providing me with the opportunity to carry out my research in his laboratory, and for his support.

I would like to express my heartfelt thanks to all my colleagues in the Neurovascular Unit Research Group for their help, the useful discussions, and the good atmosphere that made this journey more enjoyable. In particular, I am deeply grateful to Ádám Mészáros for his invaluable help in my work, which contributed greatly to the completion of this research. I would also like to thank Attila Farkas, Csilla Fazakas and Mónika Krecsmarik for their contribution and help during my work. I would like to express my special thanks to Tamás Dudás and Valentina Nagy for their encouragement, and emotional support, which helped me through the more difficult periods of my studies. I am also grateful to my present and former colleagues, Tejal Shreeya, Lam Tri Duc, Kinga Mészáros-Molnár, János Haskó, Ádám Nyúl-Tóth, Maryam Naeem, Lebogang Duba Ledile, and Rabiya Bano for creating a friendly and supportive work environment throughout these years.

I would like to thank Anca Hermenean's research group at the Vasile Goldiș Western University of Arad for generously providing the experimental animals and allowing us to carry out part of the study in their laboratory. I am especially grateful to Cornel Balta, Hildegard Herman, and Bianca Maria Mladin for their kind support and assistance during the experimental work.

Last but not least, I would like to thank my family and friends for continuous support throughout this period. Their patience and help have been invaluable to me during these years.

My work was supported by a research scholarship from the New National Excellence Program of the Ministry of Human Capacities (ÚNKP-23-3 - SZTE-287), for which I am truly grateful.

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