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RESEARCH AREA

Homeostasis and proper functioning of the central nervous system are largely determined by the coordinated action of cells of the neurovascular unit. Formed by microvascular endothelial cells, pericytes, glial cells and neurons, the neurovascular unit controls the traffic of solutes and cells between the circulation and the brain (blood-brain barrier function) and regulates cerebral blood flow in response to local neural activity (neurovascular coupling). The neurovascular unit is involved in several pathologies of the brain, including cerebral metastases and small vessel ischemic disease. Recently, we have shown that a poorly characterized cell type, namely cerebral pericytes possess significant pro-metastatic features, especially in triple negative breast cancer. In addition, we observed constriction of capillaries in the vicinity of metastatic cells and also cerebral microinfarcts, which seems to be mediated by pericytes. Therefore, on the one hand, we aim to evaluate the role of capillary pericytes in the regulation of blood supply, which is a highly debated scientific question. On the other hand, we focus on the effects of cancer cells on pericytes and other cells of the brain, to understand the mechanisms of tumour cell-induced shaping of the metastatic niche.

TECHNIQUES AVAILABLE IN THE LAB

classical biochemistry and molecular biology techniques (real-time PCR, western-blot), isolation of primary cells, culture of cerebral and tumour cells, construction of complex in vitro models, gene silencing, impedance measurements, measurement of transendothelial electrical resistance and permeability, exosome isolation, transgenic animal models, injection of tumour cells into the carotid artery, preparation of cranial window, immunofluorescence and confocal microscopy, advanced microscopy (two-photon, superresolution).

ONGOING PROJECTS

Role of brain pericytes in the formation of central nervous system metastases (NKFIH FK-124114; 2017-2021)

In the framework of this project, we have shown that pericytes enhance significantly adhesion and proliferation of metastatic cells in the cerebral environment. These processes are largely mediated by extracellular matrix proteins and the IGF2 growth factor, secreted by brain pericytes.

Tumour cell-induced pericyte responses during brain metastasis development (NKFIH K-135475; 2020-2024)

Main aims of the project starting in December 2020:

1. To understand tumour cell-induced nanotube-mediated communication of brain pericytes.
2. To identify brain pericytes as targets of tumour cell-derived exosomes.
3. To identify brain pericytes as targets of tumour cell-derived miRNAs."

SELECTED PUBLICATIONS

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. **Mol Oncol 14:** 2040-2057.

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Wilhelm, I., Fazakas, C., Molnár, K., Végh, A.G., Haskó, J., Krizbai, I.A. (2018) Foe or friend? Janus-faces of the neurovascular unit in the formation of brain metastases. **J Cereb Blood Flow Metab 38:** 563-587.

Molnár, J., Fazakas, C., Haskó, J., Sipos, O., Nagy, K., Nyúl-Tóth, Á., Farkas, A.E., Végh, A.G., Váró, G., Galajda, P., Krizbai, I.A., **Wilhelm, I.** (2016) Transmigration characteristics of breast cancer and melanoma cells through the brain endothelium: role of Rac and PI3K. **Cell Adh Migr 10:** 269-81.