Multifunctional brain pericytes: Implications for Brain Disease

https://neurodegenerationresearch.eu/survey/multifunctional-brain-pericytes-implications-for-brain-disease/

Principal Investigators

Gesine Paul-Visse

Institution

Lund University

Contact information of lead PI
Country

Sweden

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Multifunctional brain pericytes: Implications for Brain Disease

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Research Abstract
We aim to further develop and implement regenerative therapies for Parkinson’s disease (PD) and stroke, and specific therapies against malignant brain tumors. Despite multiple efforts, therapeutic options for these diseases are still symptomatic rather than restorative or curative. In many brain disorders, neuronal damage is paralleled by vascular dysfunction and neuroinflammation. This program aims to identify mechanism of pericyte activation and their cell signaling as new targets for anti-inflammatory and restorative therapies, and /or more specific anti-tumor therapies. At the same time, this project is innovative, and could challenge current “neurocentric” dogmas of neurodegeneration. Pericytes are perivascular cells that control many of the key neurovascular functions. Their strategic position and multiple functions indicate a

crucial role, both in the pathogenesis of certain brain disorders and possibly also in reparative processes in the brain. Bridging basic and clinical research, we investigate the functional implications of brain pericytes in three different pathological conditions. In the first subproject, we will clarify the impact of pericyte dysfunction in stroke. Our data demonstrated that pericytes adopt a microglial phenotype in stroke. This work identified the vasculature as a novel, previously unknown source of inflammatory cells that may either contribute to stroke damage or have a protective function. We clarify, if pericytes adopt a pro- or anti-inflammatory microglial subtype in stroke, which molecules or extracellular vesicles they release and we dissect the molecular mechanisms regulating their function. In the second subproject, we investigate the neurorestorative properties of pericytes. We have recently concluded a phase I/IIa clinical study using platelet-derived growth factor (PDGF-BB) in PD. This trial is based on animal studies that demonstrate the restorative effect of PDGF-BB. Surprisingly, the mechanism behind this compelling effect is not known, but is likely mediated by pericytes which highly express PDGF receptors. We identify possible pro-regenerative molecules or microvesicles/exosomes released by pericytes in response to PDGF-BB and determine the molecular pathways underlying the neurorestorative effect. In the third subproject, we investigate the mechanism and impact of the widespread endogenous pericyte activation and recruitment to malign brain tumors that we have recently observed and we identify signaling molecules in the tumor-pericyte interplay that may contribute to this activation. The functional impact of pericytes will be studied in vivo comparing loss of function models to controls in models of stroke, PD and glioblastoma multiforme (GBM) using different genetically modified mice. We corroborate findings using a cell culture system. In addition, the PD subproject comprises the analysis of cerebrospinal fluid (CSF) and blood samples from a unique cohort of Parkinson patients treated with PDGF-BB within an ongoing clinical trial. In the GBM project, findings are verified in human GBM brain sections. We will morphologically analyze different cell types of the neurovascular niche using 2-photon- in vivo imaging, immunohistochemistry and confocal analysis. To identify target molecules and relevant pathways, we examine changes in gene and protein expression under different conditions utilizing microarrays, bioinformatics, qPCR and Western blotting. We identify novel released molecules and extracellular vesicles analyzing CSF, cell culture medium and blood by Multiplex Elisa techniques, FACS and qPCR. For decades, pericytes have been underestimated regarding their role in the pathogenesis of brain disorders and they now emerge as one of the key cells to target for brain repair therapies. Therapies targeting pericytes may stabilize the BBB, control neuroinflammation, enhance neuroregeneration and reduce pericyte recruitment to tumors. Their unique cell signaling may provide molecules that can be developed as novel therapeutics.

Further information available at:

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