Neurovascular Unit Research Group

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János HASKÓ	Research Scientist	publications	CV
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Research

The neurovascular unit (NVU) plays a key role in the maintenance of the homeostasis of the central nervous system (CNS). Its most important cellular components are cerebral endothelial cells (interconnected by a continuous line of tight and adherens junctions), pericytes and astrocytes.
The main role of the NVU is the formation of a functionally active interface between the circulation and the CNS called the blood-brain barrier (BBB) and the regulation of blood supply according to neuronal demand (neurovascular coupling).
Due to its complex functions the NVU plays an important role in clinical practice. First, the NVU is involved in the mechanism of a large number of CNS diseases like stroke, brain trauma and tumors as well as neurodegenerative disorders and is crucially

involved in age related processes. Second, due to the relative impermeability of the barrier, many drugs are unable to reach the CNS in therapeutically relevant concentration, making the BBB one of the major impediments in the treatment of CNS disorders.
Our research is focused on the elucidation of molecular mechanisms regulating NVU function under physiological and pathological conditions. By using different in vitro models of the BBB and in vivo systems, presently we are investigating the role of the NVU in age related processes and and brain metastasis formation.

Model systems

In vitro models

In order to directly investigate molecular mechanisms regulating NVU function, we use an in vitro model based on the culture of cerebral endothelial cells and other cells (pericytes, astrocytes). The model can be used for basic research and applied research for the study of the interaction of drugs with the BBB and the transport of different drugs through the BBB. Our methods of investigation include different biochemical, molecular biological techniques, immunofluorescence and functional tests of barrier properties.

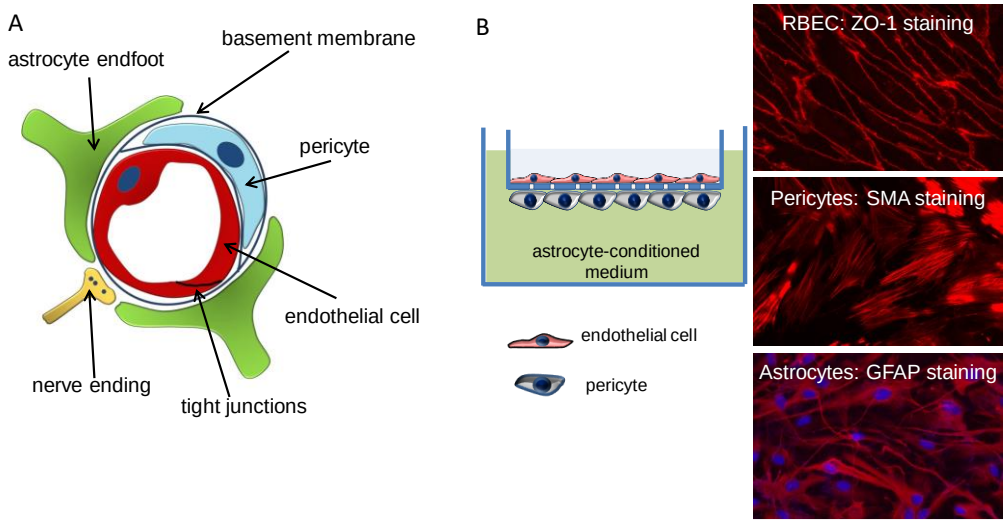

Figure 1. A: Cellular structure of the NVU. B: In vitro model of the NVU.

In vivo models and advanced microscopic techniques

In our in vivo studies we use two-photon microscopy and transgenic animals to reveal morphological and functional changes of the NVU under physiological and pathological circumstances. Besides, superresolution microscopy (STED) is also available to monitor changes at the submicroscopical level.

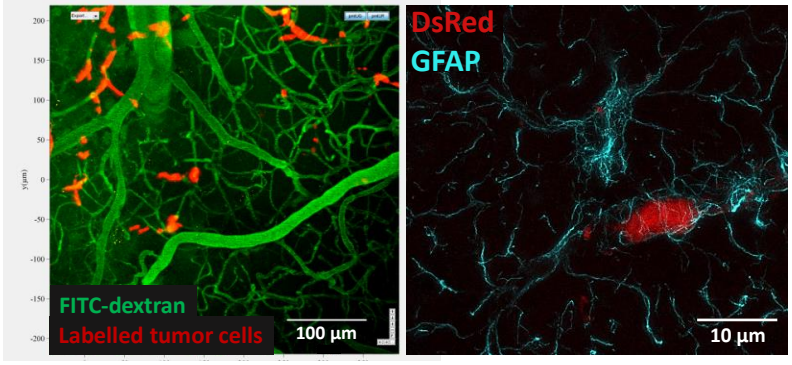

Figure 2. A:Two-photon image of the brain of a living animal. B: STED image of astrocytes and pericytes

Research topics

Role of the NVU in inflammatory and age-related processes

Inflammatory processes are associated with a large number of physiological and pathological conditions of the CNS including stroke, brain trauma and tumors, neurodegenerative disorders as well as aging. Our focus is on the investigation of pattern recognition receptors and inflammasome activation. A key role in inflammatory and age related processes of the NVU may play pericytes. Our investigations include in vitro and in vivo monitoring of brain pericyte functions and contractility during aging-related processes.

Aging especially affects brain capillaries and the regenerative capacity of the endothelium is extremely limited. Therefore, a special focus of our investigations is to explore the therapeutic potential of endothelial precursor cells to alleviate age-induced capillary and consequently cerebral dysfunctions.

Interaction of metastatic cells with the NVU

Despite the potential obstacle represented by the BBB for extravasating malignant cells, metastases – originating primarily from lung cancer, breast cancer and melanoma – are more frequent than primary tumours in the CNS. The brain environment may be very hostile to metastatic cells; however, tumour cells which can adapt to the specific requirements can exploit several advantages, including dense vascularization, supporting factors and shielding against the immune system and drugs.

In the framework of the project, we are studying mechanisms related to endothelial cells, pericytes and glial cells during two specific steps of brain metastasis formation, transmigration of the tumour cells through cerebral capillaries and survival in the brain environment. We are dedicated to understanding the complex cross-talk between tumour cells and host cells in the brain, which is essential for the identification of new therapeutic targets in this devastating disease.

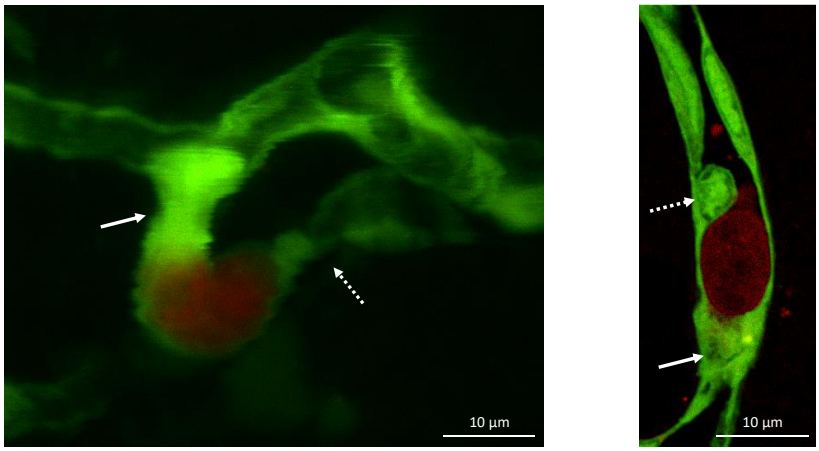

Figure 3. Metastatic cells (red) in the initial stage of the transmigration process (green: endothelial cells). Arrows indicate capillary constriction (left panel) and endothelial plugs (right panel).

Selected recent publications

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