PROJECT PROPOSAL
for applicants for ITC fellowships (2016/17)

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project title: MOLECULAR BASIS OF THE BLOOD-BRAIN BARRIER FUNCTION UNDER INFLAMMATORY CONDITIONS

PROJECT SUMMARY
By forming a single cell layer lining the blood vessels of the brain, cerebral endothelial cells (CECs) constitute the principal component of the blood-brain barrier (BBB). Tight junctions and adherens junctions play a key role in the maintenance of the barrier function. Despite considerable experimental efforts, regulation of cerebral interendothelial junctions in pathological conditions is less well understood. Using an in vitro model of the BBB and molecular, biochemical and immunofluorescence techniques, changes in the expression, localization, interaction and posttranslational modifications of the junctional proteins will be investigated in CECs in response to inflammatory stimuli. We will also investigate the role of pericytes – important cellular components of the BBB – in the regulation of inflammatory processes of the brain.

BACKGROUND
CECs fulfill several important functions in the central nervous system (CNS). By forming a single-cell layer lining the blood vessels of the brain they constitute the principal component of the blood-brain barrier (BBB).

They form an active interface between blood and neural tissue and play a key role in the maintenance of the homeostasis of central nervous system (CNS). Pathological conditions of the brain, including cerebral ischemia, brain tumors, trauma or neurodegenerative disorders, can often lead to an increased BBB permeability which may severely influence the outcome of the disease. Inflammatory processes are often associated to the above mentioned CNS disorders and these can significantly contribute to the increase in BBB permeability, which could further disturb the homeostasis of the CNS with severe consequences. The innate immune system plays an important role in inflammatory processes, because activation of pattern recognition receptors (PRRs) leads to the production of inflammatory mediators. Sensing of infectious agents or different other – potentially dangerous – molecular structures by the innate immunity relies on a limited number of germline encoded receptors, known as PRRs, that are mainly expressed on macrophages, neutrophils, dendritic cells and other innate immune cells. However, there is increasing evidence that these receptors are expressed in non-immune cells as well,
including epithelial cells, endothelial cells and pericytes.

CURRENT RESEARCH

CECs are in the front of the defense line of the CNS. We have recently revealed that CECs are able to express a large number of pattern recognition receptors – including Toll-like and NOD-like receptors – which are key components of the innate immune system. Furthermore, we have shown that activation of TLR2/6 leads to an increased permeability of the BBB which is accompanied by a downregulation of occludin and claudin-5 expression and disappearance of these tight junction proteins from the cell membrane. Changes in occludin expression and localization could be inhibited by the ERK1/2 inhibitor U0126. Our results suggest a significant role of the cerebral endothelium in mediation of the neural effects of different inflammatory processes. Currently we are investigating the role of NOD-like receptors and inflammasomes expressed in cells of the BBB in inflammatory processes of the brain.

SPECIFIC AIMS

Our investigations will be focused on the regulation of NOD-like receptors in cells of the BBB in response to inflammatory stimuli and oxidative stress, on the elucidation of the effect of NOD-like receptor activation on the barrier functions of the BBB, and signaling pathways leading to possible junctional damage and permeability increase will be investigated as well.

METHODS TO BE LEARNED / APPLIED

• in vitro BBB models
• transendothelial electrical resistance and impedance measurements
• in vivo two-photon microscopy
• molecular biology and biochemistry techniques

SUGGESTED READINGS


SNAPSHOTS FROM THE HOST LABORATORY

Significant publications

Representative recent research grants
“Role of brain endothelial cells and pericytes in the inflammatory responses of the neurovascular unit” (NKFIH-OTKA, 2016-2019)

Some of the latest students in the laboratory
Fazakas C, Ph.D., 2008-2014, "Role of the BBB in brain metastasis formation"
Haskó J, Ph.D., 2010-present, “Role of CB2 receptors in cellular adhesion and transmigration through the BBB”
Nyúl-Tóth A, Ph.D., 2011-present, “Role of NOD-like receptors in the regulation of the BBB”
Molnár J, Ph.D., 2011-present, “Signaling pathways involved in the transmigration of metastatic cells through the BBB”
Molnár K, M.Sc., 2015-present, “Transmigration mechanisms of melanoma and breast cancer cells through the blood-brain barrier”

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