Nuclear receptor signalling in immune-metabolic functions of cerebrovascular endothelial cells

Summary

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Supervisor:	Prof. Dr. Ute Panzenboeck
Availability:	This position is available.
Offered by:	Medical University of Graz
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Description

Background:

Normal brain function requires high and constant levels of cholesterol. The brain uses a unique mechanism for compensatory elimination that involves CYP46-mediated conversion of cholesterol into 24*(S)*OH-cholesterol, which is readily transported across the BBB. In contrast, 27OH-cholesterol is transported in the opposite direction from blood to brain (reviewed in 1). Oxysterols are endogenous activators of liver-X receptors (LXRs) and promote HDL formation by activating several target genes of reverse cholesterol transport. LXR target genes (ABCA1, ABCG1 and PLTP) are also centrally involved in HDL mediated cholesterol efflux from BCEC (2-4). LXR (and other) agonists also beneficially modulate the production and transport of A# peptides at the BBB in vitro and in vivo. While HDL itself exerts anti-inflammatory actions on endothelial cells, LXRs also regulate immune regulatory functions and can reduce inflammation by sumoylation-dependent and -independent mechanisms (5).

Hypothesis and Objectives:

Upon activation, LXRs can be sumoylated and as a monomer can stabilize repressor complexes present on the promoter sequence of proinflammatory genes such as activator protein 1 (AP-1) and nuclear factor kB (NF-kB), thereby preventing the expression of proinflammatory factors (5). We hypothesize that endogenous and/or pharmacologic activation of LXRs may improve cerebrovascular endothelial function in conditions of AD and insulin resistance/diabetes.

Methodology:

To test this hypothesis, the student will investigate effects of LXR activation by oxysterols or synthetic agonists on expression of inflammatory genes along with altered cellular cholesterol metabolism and APP processing pathways in pBCEC and mBCEC from in vitro and in vivo experiments, respectively. All assays are established in our laboratory (e.g. 6). Techniques applied will include primary cell culture, RTQ-PCR, immunoblotting, immunoprecipitation, sumoylation assay, ELISA, IHC, RNAi, functional assays for ABC transporters, cholesterol efflux and synthesis assays, TLC, and GC-MS.

References:

1. Björkhem I (2006) Crossing the barrier: oxysterols as cholesterol transporters and metabolic modulators in the brain. J Intern Med. 260(6):493-508. Review. doi:10.1111/j.1365-2796.2006.01725.x
2. Panzenboeck U, Balazs Z, Sovic A, Hrzenjak A, Levak-Frank S, Wintersperger A, Malle E, and Sattler W (2002) ABCA1 and scavenger receptor class B, type I, are modulators of reverse sterol transport at an in vitro blood-brain barrier constituted of porcine brain capillary endothelial cells. J Biol Chem 277(45):42781-9
3. Chirackal Manavalan AP, Kober A, Metso J, Lang I, Becker T, Hasslitzer K, Zandl M, Fanaee-Danesh E, Pippal JB, Sachdev V, Kratky D, Stefulj J, Jauhiainen M, Panzenboeck U (2014) Phospholipid transfer protein is expressed in cerebrovascular endothelial cells and involved in high density lipoprotein biogenesis and remodeling at the blood-brain barrier. J Biol Chem. 289(8):4683-98. doi: 10.1074/jbc.M113.499129
4. Kober AC, Manavalan APC, Tam-Amersdorfer C, Holmér A, Saeed A, Fanaee-Danesh E, Zandl M, Albrecher NM, Björkhem I, Kostner GM, Dahlbäck B, Panzenboeck U (2017) Implications of cerebrovascular ATP-binding cassette transporter G1 (ABCG1) and apolipoprotein M in cholesterol transport at the blood-brain barrier. Biochim Biophys Acta. 1862(6):573-88. doi: 10.1016/j.bbalip.2017.03.003

5. Guillemot-Legris O, Mutemberezi V, Muccioli GG. Oxysterols in Metabolic Syndrome: From Bystander Molecules to Bioactive Lipids. Trends Mol Med. 2016; 22(7):594-614.
6. Zandl-Lang M, Fanaee-Danesh E, Sun Y, Albrecher NM, Gali CC, Čančar I, Kober A, Tam-Amersdorfer C, Stracke A, Storck SM, Saeed A, Stefulj J, Pietrzik CU, Wilson MR, Björkhem I, Panzenboeck U (2018) Regulatory effects of simvastatin and apoJ on APP processing and amyloid-β clearance in blood-brain barrier endothelial cells. Biochim Biophys Acta. 1863(1):40-60. doi: 10.1016/j.bbalip.2017.09.008