Plectin confers mechanical stability of biliary epithelium

Katerina Nepomucka[1], Magdalena Prechova[1], Oldrich Benada[2], Gerhard Wiche[3], Martin Gregor[1]

[1]Dept. of Integrative Biology, IMG CAS, Prague, CZ, [2]Dept. of Transgenic Models of Diseases, IMG CAS, Prague, CZ; [2]Laboratory of Molecular Structure Characterization, Institute of Microbiology of the Czech Academy of Sciences, Prague, CZ; [3]Dept. of Biochemistry and Cell Biology, MFPL, University of Vienna, AT.

Plectin is ubiquitously expressed member of plakin family that interconnects all three cytoskeletal systems and links them to plasma membrane-bound junctional complexes. Plectin acts as a crosslinker and signalling scaffold, affecting mechanical as well as dynamic properties of the cytoskeleton.

To study the specific role of plectin in liver epithelia, we generated liver-specific Plectin KO mice. Plectin deficiency in hepatocytes and biliary epithelial cells caused aberrant organization of keratin filaments, biliary tree malformations and collapse of bile ducts and ductules. Plectin-deficient biliary epithelial cells formed compromised tight junctions, exhibited increased expression of the adherens junction protein E-cadherin and were inefficient in desmosomal protein desmoplakin upregulation upon cholestatic challenge.

To complement data obtained from mouse *in vivo* models, we generated by CRISPR/Cas9 targeting plectin-deficient immortalized mouse cholangiocytes. Both plectin-deficient primary hepatocytes and CRISPR/Cas9-generated plectin KO cholangiocytes revealed a higher susceptibility of keratin networks to stress-induced collapse. Plectin-deficient cholangiocytes also showed impaired functional integrity of intercellular junctions, measured by transepithelial electrical resistance and monolayer permeability for FITC-dextran upon hyper-osmotic shock.

These data demonstrate that plectin is required for proper keratin network cytoarchitecture, correct formation of cell-cell junctions and epithelial stability both *in vitro* and *in vivo*.

Acknowledgement: 17-31538A, RVO 68378050, COST Action CA15214-EuroCellNet, Strategy AV21 – QUALITAS, project LQ1604 BIOCEV-FAR, LM2015040, OP RDI CZ.1.05/2.1.00/19.0395.

Current Activities

During my PhD at University College London I have been working on regulation of actin cytoskeleton in Richard Treisman's laboratory in the Francis Crick Institute. I was mainly interested in regulation of cytoskeletal proteins dephosphorylation by Phactr1 phosphatase regulator from RPEL family that is known to be regulated by monomeric actin and thus works as a molecular sensor of cellular G-actin concentration. My work has provided a link between G/F actin cellular concentration and dephosphorylation of several cytoskeletal proteins, with implications in cell shape and signalling both in fibroblasts and primary neurons.

Recently, I have finished my PhD degree and joined Marin Gregor's laboratory in the Institute of Molecular Genetics in Prague. The main research interest of the group is focused on plectin-dependent regulation of the intermediate filament and actin cytoskeleton, cell junctions and cell motility, and its implication in diseases, such as liver fibrosis, cholestatic liver disease or cancer. I am in particular interested in plectin role in intercellular junctions formation and integrity.

My long-term scientific interest is centred on mechanotransduction and the connection between cytoskeleton and signalling. While during my PhD I was focused mainly on the actin cytoskeleton and its regulation, I have recently entered an exciting field of intermediate filaments. This conference is going to be a great opportunity for me to gain more knowledge about the latest intermediate filament-related research and to meet great scientists working in the field.