LABORATORY OF

LEUKOCYTE SIGNALLING

Leukocyte signalling, membrane adaptor proteins, autoinflammation, haematopoiesis, myeloid cells

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The Laboratory of Leukocyte Signalling is studying the molecular mechanisms of signal transduction downstream of various leukocyte surface receptors. For a long time, our interest has been focused on membrane adaptor proteins and on the roles of these proteins in the regulation of leukocyte signalling and in leukocyte-driven pathologies. We also study plasma membrane separation into various micro or nanodomains and their relationship to the membrane protein distribution and function. In the recent years we have paid most attention to several so far poorly characterized membrane adaptor proteins. Among the most interesting was OPAL1, a membrane adaptor that is aberrantly expressed in childhood leukaemia. We found that it inhibits the activity of an important bone marrow homing receptor, CXCR4, in leukaemic cells as well as in myeloid progenitors. We also found that it regulates haematopoietic stem and progenitor cell mobilization and curtails bone marrow transplantation efficiency. These data helped us to better understand the regulation of these clinically important processes. Another interesting membrane adaptor is PSTPIP2. Its deficiency in mice results in an autoinflammatory disorder characterized by sterile inflammation of the bones and surrounding soft tissues. It is similar to several human bone diseases. We have discovered that the absence of PSTPIP2 results in exaggerated production of reactive oxygen species by neutrophil granulocytes early in the disease in the positions of future inflammatory bone lesions. Production of these toxic compounds then critically contributes to the bone damage accompanying this disease. We believe that this discovery will help in improving future treatment strategies for this class of disorders. Finally, within a long-lasting collaboration with the group of Marek Cebecauer at J. Heyrovsky Institute of Physical Chemistry, we also contribute to understanding the relationships between the structure and subcellular/nanoscopic localization of membrane adaptors and other membrane proteins.

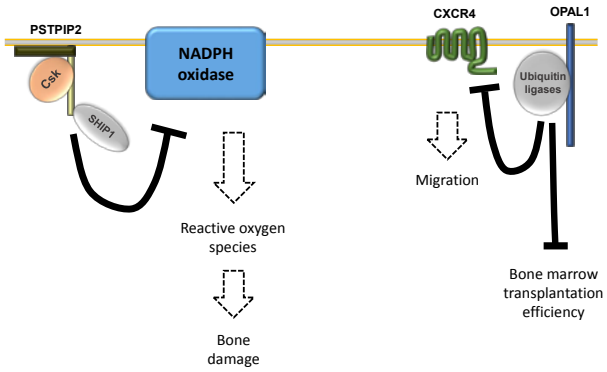

Figure 1. Schematic representation of the function of two membrane adaptor proteins, PSTPIP2 and OPAL1. PSTPIP2 (left) inhibits NADPH oxidase activity and consequently suppresses reactive oxygen species production and autoinflammatory bone damage. OPAL1 (right) recruits Nedd4-family ubiquitin ligases and negatively regulates CXCR4-driven migration and bone marrow transplantation efficiency.

Selected publications:

1. Kralova J, Drobek A, Prochazka J, Spoutil F, Fabisik M, Glatzova D, Borna S, Pokorna J, Skopcova T, Angelisova P, Gregor M, Kovarik P, Sedlacek R, Brdicka T* (2020) Dysregulated NADPH oxidase promotes bone damage in murine model of autoinflammatory osteomyelitis. *J Immunol*. doi: 10.4049/jimmunol.1900953. [Epub ahead of print]
2. Borna S, Drobek A, Kralova J, Glatzova D, Splichalova I, Fabisik M, Pokorna J, Skopcova T, Angelisova P, Kanderova V, Starkova J, Stanek P, Matveichuk OV, Pavliuchenko N, Kwiatkowska K, Protty MB, Tomlinson MG, Alberich-Jorda M, Korinek V, Brdicka T* (2020) Transmembrane adaptor protein WBP1L regulates CXCR4 signalling and murine haematopoiesis. *J Cell Mol Med*, **24**:1980-1992.
3. Angelisova P, Ballek O, Sykora J, Benada O, Cajka T, Pokorna J, Pinkas D, Horejsi V* (2019) The use of styrene-maleic acid copolymer (SMA) for studies on T cell membrane rafts. *Biochim Biophys Acta Biomembr*, **1861**:130-141.
4. Lukeš T, Glatzová D, Kvíčalová Z, Levet F, Benda A, Letschert S, Sauer M, Brdička T, Lasser T, Cebecauer M*(2017) Quantifying protein densities on cell membranes using super-resolution optical fluctuation imaging. *Nat Commun*, **8**:1731.

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