



# Laboratory of Transgenic Models of Diseases

Proteases and their inhibitors, epidermis, liver, IBD, colitis, transgenesis

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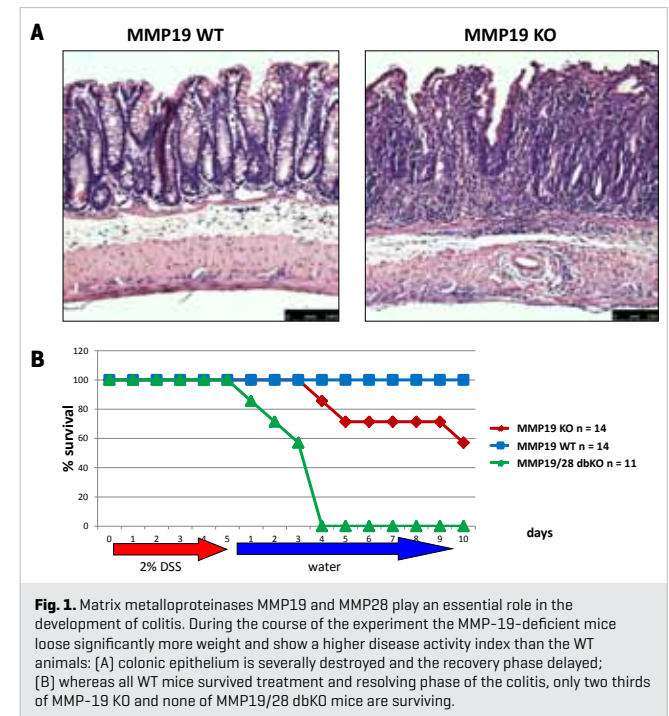
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Our work is focused on proteinases, especially metalloproteinases that process extracellular matrix [ECM] proteins or release [shed] ligands and their receptors from the cell surface. Interactions between cells and matrix control cell differentiation, survival, migration, and activation via cell surface receptors and adhesion molecules. Especially adhesion molecules sense changes in the composition of extracellular matrix that is affected by proteases and their inhibitors. Balance between these two molecule classes determines if tissues and organ architecture are to be built up or disrupted. Thus, this balance is pivotal for tissue homeostasis and disturbance may lead to development of various pathologies such as cancer, chronic inflammation, or fibrosis.

Our research activities focus on how proteases process ECM-proteins and how these changed matrix proteins [i.e. their fragments] affect the biology of various cell types. These investigations are focused specifically on several research areas: epithelium/epidermis and currently also liver and colon pathogenesis. Inflammatory reactions in these tissues are of our special interest as regulated proteolytic activity in the epidermis and many epithelia is crucial not only to maintenance of the body and organ barriers, but also to regulation of local inflammatory reactions. For instance, we are currently analysing the impact of matrix metalloproteinases 19 and 28 on development of

colitis in DSS-induced model using MMP-19- and MMP-28-deficient mice. The exacerbation of the colitis in the knockout mice together with elevated concentrations of pro-inflammatory cytokines derived from colonic tissue suggests that MMP-19 has a role in maintenance of intestinal homeostasis. According to these results we propose a protective effect of MMP-19 during colitis.

To understand development and progression of liver fibrosis and inflammation processes, our research in this area analyses the effects and consequences of metalloproteinase-mediated turnover of extracellular matrix and the release of regulatory molecules from the cellular surfaces, a process that is mediated by shedding proteases.



- GA CR, GC301/08/J053 – Mouse models for investigation of biological functions of novel Kazal-type protease inhibitors LEKTI-2 and LEKTI-3, 2008-2010, R. Sedláček
- AS CR, IAA500520812 – Investigating the pathologic role of metalloproteinases in liver using transgenic mice with conditional expression of transgenes, 2008-2012, R. Sedláček
- GA CR, GAP305/10/2143 – Generation of mouse models for targeting stellate cells and myofibroblasts in the liver, 2010-2013, R. Sedláček
- GA CR, GAP303/10/2044 – The impact of a liver-specific deficiency of growth factor sheddase ADAM10 on liver development and pathology, 2010-2013, R. Sedláček, M. Jiroušková



- Muller M, Beck IM, Gadesmann J, Karschuk N, Paschen A, Proksch E, Djonov V, Reiss K, Sedlacek R. MMP19 is upregulated during melanoma progression and increases invasion of melanoma cells. *Mod Pathol* 2010 23(4): 511-521.
- Lettau I, Hattermann K, Held-Feindt J, Brauer R, Sedlacek R, Mentlein R. Matrix metalloproteinase-19 is highly expressed in astroglial tumors and promotes invasion of glioma cells. *J Neuropathol Exp Neurol* 2010 69(3): 215-223.
- Beck IM, Ruckert R, Brandt K, Mueller MS, Sadowski T, Brauer R, Schirmacher P, Mentlein R, Sedlacek R. MMP19 is essential for T cell development and T cell-mediated cutaneous immune responses. *PLoS One* 2008 3(6): e2343.



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