

Project for PhD thesis

Area: Cell biology, immunology, molecular medicine

Title: Proteolytic regulation of the DNA-degrading enzyme TREX1

Group leader: Prof. Dr. Bernd Schröder, Institute for Physiological Chemistry

Summary:

Cells have a surveillance pathway for cytosolic DNA, which can be pathogen-derived or from cell-intrinsic sources. If cytosolic DNA is sensed by the cGAS/STING pathway, an interferon response is initiated which plays major roles both in anti-viral but also anti-tumor activity. On the other hand, an uncontrolled activation of the cGAS/STING pathway is a hallmark of type I interferonopathies, hereditary autoinflammatory and autoimmune diseases characterized by chronic overproduction of type I interferon (IFN- α/β). This can, for example, occur due to loss of or inactivating mutations in the DNA-degrading enzyme TREX1. TREX1 is a protein anchored to the membrane of the endoplasmic reticulum with its DNase domain facing the cytosol. TREX1 clears DNA from the cytosol and by this means acts as a negative regulator of the cGAS/STING pathway. We have discovered that TREX1 can be proteolytically processed and regulated, leading to the generation of a soluble form of this protein. We want to understand the functional and pathophysiological implications of this process both for anti-viral immunity and specific types of interferonopathies as well as activation of immune responses by tumour cells. Therefore, this project addresses both mechanistic cell biology and translational aspects. Experimentally, cellular systems as well as animal models based on mice will be employed.

Recent publications of the group:

Ballin,M., Griep,W., Patel,M., Karl,M., Mentrup,T., Rivera-Monroy,J., Foo,B., Schwappach,B., and Schröder,B. (2022)The intramembrane proteases SPPL2a and SPPL2b regulate the homeostasis of selected SNARE proteins, in press.

Contreras,W., Wiesehöfer,C., Schreier,D., Leinung,N., Peche,P., Wennemuth,G., Gentzel,M., Schröder,B., and Mentrup,T. (2022) C11orf94/Frey is a key regulator for male fertility by controlling Izumo1 complex assembly. *Sci Adv* 8, eabo6049.

Mentrup,T., Stumpff-Niggemann,A.Y., Leinung,N., Schlosser,C., Schubert,K., Wehner,R., Tunger,A., Schatz,V., Neubert,P., Gradtke,A.C., Wolf,J., Rose-John,S., Saftig,P., Dalpke,A., Jantsch,J., Schmitz,M., Fluhrer,R., Jacobsen,I.D. and Schröder,B. (2022) Phagosomal signalling of the C-type lectin receptor Dectin-1 is terminated by intramembrane proteolysis. *Nat Comm* 13: 1880.

Mentrup,T. and Schröder,B. (2022)

Signal peptide peptidase-like 2 proteases: Regulatory switches or proteasome of the membrane? *Biochim. Biophys. Acta Mol Cell Res* 1869:119163.

Mentrup,T., Cabrera-Cabrera,F. and Schröder,B. (2021)

Proteolytic regulation of the Lectin-like oxidised lipoprotein receptor LOX-1 *Front Cardiovasc Med* 7: 594441.

Gradtke,A.C., Mentrup,T., Lehmann,C.H.K., Cabrera-Cabrera,F., Desel,C. Okakpu,D., Assmann, M., Dalpke,A., Schaible, U., Dudziak,D., and Schröder, B. (2021) Deficiency of the intramembrane protease SPPL2a alters anti-mycobacterial cytokine responses of dendritic cells. *J Immunol* 206, 164-180.