LABORATORY OF

SIGNAL TRANSDUCTION

Plasma membrane signalosomes, membrane receptor signalling, immunoreceptor regulators, bacterial cytolysins, mast cells

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Our laboratory focuses on understanding the molecular mechanisms governing signal transduction from the plasma membrane receptors to the cytoplasm. We study mainly mast cells, potent immune modulators of the tissue microenvironment. In these cells, antigen-mediated aggregation of the immunoglobulin E receptor (FcεRI) results in degranulation and cytokines production. Increasing evidence suggests that an intricate network of inhibitory and activating receptors, together with lipids, governs the initiation of the mast cell's responsiveness to particular stimuli.

For our studies of plasma membrane signalling units, signalosomes, we use various techniques of molecular biology, immunology, and immunochemistry. Our principal approach lies in the production of cells or animals with increased or reduced expression of selected genes and comparing their properties with wild-type cells or wild-type animals.

Using mast cells from mice with ORMDL3 knockout (KO), we examined the role of ORMDL3 in mast cell activation. We found that the cells with ORMDL3 KO exhibited enhanced production of sphingolipids, as expected, because ORMDL3 is a negative regulator of the serine-palmitoyl transferase, a key enzyme in sphingolipid synthesis. Surprisingly, ORMDL-deficient cells also exhibited enhanced production of leukotrienes. We found that ORMDL3 physically interacts with 5-lipoxygenase, mediating enzyme conversion of arachidonic acid to leukotrienes. Several other experiments supported our hypothesis of physical and functional crosstalk between the leukotriene and sphingolipid metabolic pathways, leading to the production of lipid signalling mediators participating in signal transduction events and the development of several diseases.

An essential role of lipids was also demonstrated in our study examining the mechanism of the inhibitory effect of ursolic acid (UA) on the FcεRI-mediated activation of mast cells. UA has multiple biological activities. We found that UA rapidly reduced the mobility of plasma membrane components, including cholesterol and FcεRI. Based on our studies, we concluded that UA exerts its effects, at least in part, via lipid-centric plasma membrane perturbations, affecting the function of the FcεRI signalosome. These and other studies are directed to our long-term goal to contribute to the development of new, more potent, anti-allergic and anti-inflammatory drugs.

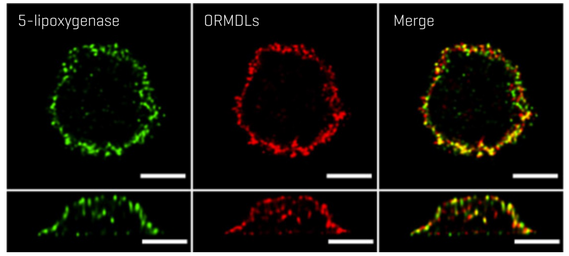

Figure 1. Data indicating that 5-lipoxygenase colocalizes with the ORMDLs on the endoplasmic reticulum membranes. Human mast cells HMC-1.1 were activated for 10 min with ionomycin and stained for 5-lipoxygenase and ORMDLs as described in Bugajev et al., J. Lipid Res., 2021. Co-localization is observed at both XY projections (top) and orthogonal projections (bottom).

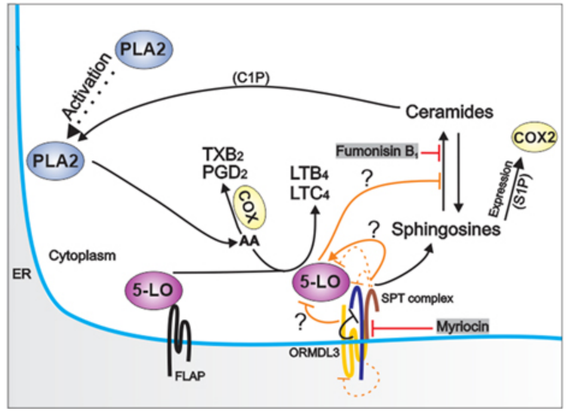

Figure 2. Scheme of the sphingolipid and eicosanoid metabolic pathway crosstalk. Interactions between the pathways seem to be mediated via metabolic mediators (ceramides, S1P, C1P) and physical interaction of the ORMDL3 with the SPT complex and 5-lipoxygenase. Details of the pathways are described in Bugajev et al., J. Lipid Res., 2021.

Selected publications:

1. Shaik GM, Draberova L, Cernohouzova S, Tumova M, Bugajev V, Draber P*. Pentacyclic triterpenoid ursolic acid interferes with mast cell activation via a lipid-centric mechanism affecting FcεRI signalosome functions. J Biol Chem 2022 298(11):102497.
2. Bugajev V*, Paulenda T, Utekal P, Mrkacek M, Halova I, Kuchar L, Kuda O, Vavrova P, Schuster B, Fuentes-Liso S, Potuckova L, Smrz D, Cernohouzova S, Draberova L, Bambouskova M, Draber P*. Crosstalk between ORMDL3, serine palmitoyltransferase, and 5-lipoxygenase in the sphingolipid and eicosanoid metabolic pathways. J Lipid Res 2021 62:100121.
3. Draberova L*, Tumova M, Draber P*. Molecular mechanisms of mast cell activation by cholesterol-dependent cytolysins. Front Immunol 2021 12:670205.
4. Bugajev V*, Halova I, Demkova L, Cernohouzova S, Vavrova P, Mrkacek M, Utekal P, Draberova L, Kuchar L, Schuster B, Draber P*. ORMDL2 Deficiency Potentiates the ORMDL3-Dependent Changes in Mast Cell Signaling. Front Immunol 2021 11:591975.
5. Redcenko O, Draberova L, Draber P*. Carboxymethylcellulose enhances the production of single-stranded DNA aptamers generated by asymmetric PCR. Anal Biochem 2020 589:113502.