Abstract

ORMDL proteins are regulators of serine palmitoyltransferase (SPT) enzyme, which catalyzes the first step of sphingolipid biosynthesis. Human and murine ORMDL family consists of three members, ORMDL1, ORMDL2 and ORMDL3. Human and murine ORMDLs exhibit high similarity between their amino acid sequences. ORMDL3 expression has been linked to several diseases, such as childhood-onset asthma, Crohn's disease, rheumatoid arthritis, type 1 diabetes, and primary biliary cirrhosis. High expression of ORMDL3 has been found in macrophages, T cells, eosinophils, epithelial cells and mast cells. ORMDL3 is a negative regulator of the high affinity IgE receptor I (FcεRI)-mediated signaling in mast cells. Mast cells have an important role in the acute phase of allergic reactions and are involved in eradication of multicellular parasites.

In the first part of this thesis we determined the expression of ORMDL family in peritoneal-derived mast cells (PDMCs) from *Ormdl3* knock out (KO) and wild type (WT) mice. Next we determined the roles of ORMD3 in FcεRI-mediated signaling in these PDMCs. Furthermore, we analyzed the relationship between expression of ORMDL family and SPT complex in bone marrow-derived mast cells (BMMCs) and bone marrow-derived mast cell line (BMMCL). We transduced BMMCL with vector coding SPTLC1 shRNA to induce SPTLC1 knock down (KD) and compared them with control BMMCL. Furthemore, we analyzed the expression of these proteins in BMMCs isolated from WT, *Ormdl2* KO, *Ormdl3* KO and *Ormdl2&3* double knock out (DKO) mice. In the final part of this thesis, we studied the role of ORMDL family in imiquimod (IMQ)-induced dermatitis, particularly in *Ormdl2* KO, *Ormdl3* KO, and *Ormdl2&3* DKO mice.

Keywords: ORMDL3, Mast cells, FcεRI, Imiquimod-induced skin inflammation