Abstract

Background: Mast cells are key effector cells that elicit immunoglobulin E (IgE)-mediated allergic inflammations. Allergen cross-linking of IgE bound to the high-affinity IgE receptor, FcεRI, on mast cells triggers signaling cascades that activate signal proteins and evoke extracellular Ca^{2+} influx, which are crucial for cytokine production. The β2-adrenergic receptor (Adrb2) on mast cells negatively regulates FcεRI signaling, as demonstrated by the inhibition of IgE/antigen (Ag)-induced activation by Adrb2 agonists.

Objective: Although β2-adrenergic-related reagents are known to influence mast cell functions, the specific intrinsic role of Adrb2 in these cells is not fully understood, potentially because of off-target effects. In this study, the additional roles of Adrb2 in mast cells were investigated, specifically the involvement of Adrb2 in FcεRI signaling, using *Adrb2*$^{-/-}$ mice.

Methods: *Adrb2*$^{-/-}$ mice were used to investigate the roles of Adrb2 in mast cells by examining bone marrow-derived mast cells (BMMCs) for surface expression of mast cell markers, granule numbers, and gene expression of mast cell proteases. Cytokine production, Ca^{2+} influx, and nuclear factor of activated T cells (NFAT) nuclear translocation were measured in *Adrb2*$^{-/-}$ and *Adrb2*$^{+/+}$ BMMCs upon IgE/Ag stimulation.

Results: *Adrb2*$^{-/-}$ did not affect the generation of BMMCs, their surface expression of mast cell markers, granule numbers, or gene expression of mast cell proteases, indicating that the absence of Adrb2 had no adverse effect on mast cell development. However, *Adrb2*$^{-/-}$ BMMCs exhibited reduced tumor necrosis factor α (TNFα) production and diminished Ca^{2+} influx upon IgE/Ag stimulation, which correlated with decreased NFAT translocation. Restoration of Adrb2 in *Adrb2*$^{-/-}$ BMMCs rescued cytokine production. Notably, FcεRI-mediated phosphorylation of the phospholipase PLCγ1 and mitogen-activated protein kinases (MAPKs) remained unchanged in the absence of Adrb2.

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28 **Conclusion:** These results suggest that Adrb2 has a novel ligand-independent function, increasing Ca^{2+}

29 entry in mast cells when stimulated with IgE/Ag.