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BIOLOGICAL CHEMISTRY AND NEUROSCIENCE

Project

Interleukin (IL)-18 in the Differentiation and Maturation of Mast Cells and Its Implication in Mast-Cell Mediated Pathology



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Recent studies have demonstrated a variety of roles for interleukin (IL)-18 in cytokine regulation and lymphocyte development, with results indicating roles in the development of both Th1 and Th2 responses depending on the other cytokines present. There is significant correlational evidence linking increased levels of IL-18 with allergic diseases in both human and animal models. Mast cells are major mediators of allergies; the cytokines, enzymes, and other molecules stored in mast cells effect an array of allergic and inflammatory processes when released. Therefore, the correlation between IL-18 and allergy suggests a possible role for the cytokine in mast cell pathology. Additionally, recent research has found IL-18 to induce the release of a variety of molecules from mast cells, such as Th2 cytokines, and found that IL-18 works in synergy with IL-3 to increase this release.

However, there is little evidence on the direct effects of IL-18 on mast cell differentiation and maturation, and the role of IL-18 on the in vivo accumulation of mast cells has shown conflicting results to date. This led us to investigate the effects of IL-18 on differentiation of mast cells from bone marrow precursors, maturation in vitro, and the synergy of IL-18 and IL-3. This also led us to investigate the role of IL-18 on in vivo accumulation of mast cells in the intestinal tract. Preliminary results indicate that IL-18 promotes differentiation and maturation, but not survival, of mast cells, and that overexpression of IL-18 results in a proliferation of mast cells in the intestinal tract. Ongoing projects are aimed at clarifying the interactions of IL-3 and IL-18 by using anti-IL-3 neutralizing antibodies and IL-18 knockout and transgenic IL-18 overexpressed mice for both in vivo and in vitro studies. This research will help guide future therapies to treat and prevent allergic diseases.