Novel Cytokines in Inflammatory Disease

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IL-33, a member of the IL-1 family, is the newly discovered ligand for the orphan receptor ST2 which is expressed on a subset of Th2, epithelial, endothelial and mast cells. IL-33 is also able to skew a predominantly Th1 cell population to a mainly Th2 cells phenotype in vivo. IL-33 could attenuate an on-going atherosclerosis in $ApE^{-/-}$ mice on high fat diet. Thus, IL-33 may be a potential therapeutic agent against atherosclerosis. However, IL-33 is a double-edged sword. IL-33 is expressed in synovial fibroblasts from patients with rheumatoid arthritis (RA). Mice lacking ST2 developed attenuated collagen-induced arthritis (CIA) and reduced ex vivo collagen-specific induction and antibody production.,of proinflammatory cytokines (IL-17, TNFα and IFNγ) Thus IL-33 is a critical pro-inflammatory cytokine for inflammatory joint disease. ST2-/- mice developed significantly attenuated eosinophilia and macrophage infiltration in the lungs following intranasal administration of IL-33 compared to WT mice. IL-33 changed the quiescent phenotype of alveolar macrophages towards alternatively activated phenotype (AAM) which expressed mannose receptor (MR), IL-4Rα, and produced high levels of Eotaxin-2 and TARC. These findings suggest that IL-33 may be a selective target for therapeutic intervention of inflammatory diseases.

IL-35 is the latest cytokine of the IL-12 family. It is formed by pairing Epstein-Barr virus-induced gene 3 (EBI3) and the p35 subunit of IL-12. The Fc fusion protein of IL-35 induced proliferation of murine $CD4^+CD25^+$ and $CD4^+CD25^-$ T cells when stimulated with immobilized anti-CD3 and anti-CD28 antibodies in vitro. The in vitro-expanded $CD4^+CD25^+$ T cells retained their suppressive functions against $CD4^+CD25^-$ effector cells. Furthermore, IL-35 inhibited the differentiation of Th17 cells in vitro. In vivo, IL-35 effectively attenuated established CIA in mice with concomitant suppression of IL-17 production but enhanced IFNγ synthesis. Thus IL-35 is a novel anti-inflammatory cytokine suppressing the immune response through the expansion of regulatory T cells and suppression of Th17 cell development.