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The IL-12 Family of Cytokines & Mechanisms of Intestinal Inflammation

The IL-12 Family of Cytokines Regulates T Cell-Mediated Pro- & Anti-Inflammatory Immune Responses

Intestinal homeostasis relies on the ability of the intestinal immune system to tolerate commensal microflora, while providing protective immunity against invasive microbes. Under normal physiological conditions, gut-associated dendritic cells (DCs) preferentially induce the differentiation of regulatory T (Treg) cells that secrete immunosuppressive cytokines to prevent aberrant immune responses. Pathogenic microorganisms, or those that are typically nonpathogenic but elicit a response in genetically susceptible individuals, trigger immune cell activation and inflammation. These microbes activate DCs that promote the differentiation of naïve $CD4^+$ T cells to a Th1, Th2, or Th17 specific lineage. T helper cells, along with macrophages and DCs, secrete pro-inflammatory cytokines aimed at eliminating the causative pathogen. Breakdown of intestinal barrier function, altered immune cell reactivity to intestinal flora, or inappropriate or exaggerated T cell responses that Treg cells fail to suppress, are mechanisms that can lead to chronic inflammation and tissue destruction characteristic of inflammatory bowel disorders such as Crohn's disease and ulcerative colitis (❶-❹). While ulcerative colitis has been linked with increased levels of IL-13 and an excessive Th2 response, Crohn's disease is associated with an up-regulation of IL-12 family cytokines including IL-12 and IL-23, and increased Th1 and Th17 activities. IL-12 and IL-23 regulate the differentiation of Th1 and Th17 cells, and along with IL-27 and IL-35, play a crucial role in the balance of pro- and anti-inflammatory immune responses. For these reasons, they have become potential targets for inhibiting the pathogenesis of inflammatory bowel disorders.

Cytokine	Subunits	Receptors	Effect on T Cell Function
IL-12	p35 ⊂ p40	IL-12 Rβ2 ⊂ IL-12 Rβ1	■ Promotes Th1 Differentiation
IL-23	p19 ⊂ p40	IL-23 R ⊂ IL-12 Rβ1	■ Promotes Th17 Differentiation
IL-27	p28 ⊂ EBI3	gp130 ⊂ TCCR/WSX-1	■ Promotes Early Th1 Commitment ■ Inhibits Th17 Differentiation ■ Stimulates a Tr1-like Phenotype in Effector T Cells
IL-35	p35 ⊂ EBI3	Unknown	■ Promotes Treg Proliferation ■ Enhances Treg Suppressive Capacity

KEY: ■ Four α Helix Bundle ⊂ Ig-like Domain ● Cytokine Receptor Homology Domain ● Fibronectin-like Domain

This illustration represents general processes suggested in the scientific literature and is not to be considered comprehensive nor definitive.

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