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 naive 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 pathogens. 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 (1-4). While ulcerative colitis has been linked with increased levels of IL-12 and an excessive Th1a response, Crohn's disease is associated with 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-22 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**

- IL-12: p40/p35
- IL-23: p19/p40
- IL-27: p35/p40

**Effect on T Cell Function**

- Promotes Th1 Differentiation
- Inhibits Th2 Differentiation
- Regulates Treg Cell Differentiation

**Mechanisms that Induce Intestinal Homeostasis**

1. Breakdown of Intestinal Barrier Function
2. Altered Immune Cell Reactivity
3. Impaired Regeneration
4. Regulated T Cell Differentiation

**The IL-12 Family of Cytokines**

- **IL-12** promotes Th1 differentiation and is produced by DCs and macrophages.
- **IL-23** promotes Th17 differentiation and is produced by DCs and intestinal epithelial cells.
- **IL-27** inhibits Th17 differentiation and is produced by intestinal epithelial cells.
- **IL-35** negatively regulates Th1 and Th17 cells.

**Regulatory T Cell Differentiation**

- Treg cells are induced by IL-2, IL-21, and TGF-β.
- Treg cells secrete IL-10 and TGF-β to suppress inflammation.

**Promoting the Differentiation of IL-12 R Family Cytokines**

- **IL-23** and **IL-27** promote the differentiation of Th17 cells.
- **IL-12** promotes the differentiation of Th1 cells.

**Inhibiting the Differentiation of IL-12 R Family Cytokines**

- **IL-35** inhibits the differentiation of Th17 cells.
- **IL-22** inhibits the differentiation of Th17 cells.

**The IL-23 Family of Cytokines**

- **IL-23** promotes the differentiation of Th17 cells and is produced by DCs and macrophages.
- **IL-27** inhibits Th17 differentiation and is produced by intestinal epithelial cells.

**TLR-Mediated Pro- & Anti-Inflammatory Immune Responses**

- TLRs are expressed on immune cells and recognize pathogen-associated molecular patterns.
- Activation of TLRs leads to the production of cytokines that promote or inhibit inflammation.

**Dietary Antigens**

- Dietary antigens trigger immune cell activation and inflammation.

**Intestinal Epithelial Cells**

- Intestinal epithelial cells secrete IL-23 and IL-27 to promote the differentiation of Th17 cells.

**Intestinal Lumen**

- The intestinal lumen contains commensal microflora and potential pathogenic microbes.

**Increased Leakage**

- Increased leakage of intestinal epithelial cells leads to the exposure of pathogenic microbes to the intestinal lumen.

**Breakdown of Intestinal Barrier Function**

- Breakdown of the intestinal barrier function allows pathogens to enter the intestinal lumen.

**Pathogen-Mediated Pro- & Anti-Inflammatory Immune Responses**

- Pathogens trigger immune cell activation and inflammation.

**Pro-Inflammatory**

- Th1 and Th17 cells secrete cytokines that promote inflammation.

**Anti-Inflammatory**

- Treg cells secrete cytokines that suppress inflammation.

**Conclusion**

- The IL-12 family of cytokines plays a crucial role in the balance of pro- and anti-inflammatory responses.

**References**


This diagram represents general processes suggested by the scientific literature and is not to be considered comprehensive or definitive.