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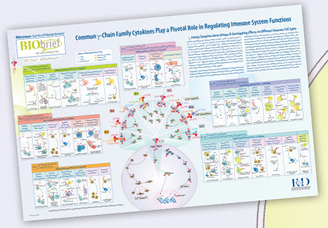
Common γ-Chain Family Cytokines Play a Pivotal Role in Regulating Immune System Functions



Common γ-Chain Family Cytokines Play a Pivotal Role in Regulating Immune System Functions

Different forms of severe combined immunodeficiency (SCID) diseases occur as a result of inactivating mutations in multifunctional immune system regulators. These mutations lead to developmental or functional defects in T lymphocytes, which can also be accompanied by variable defects in B lymphocytes and/or natural killer cells. The most common form of SCID, X-linked SCID (XSCID), is caused by mutations in the common cytokine receptor γ-chain (γ_c). The γ_c subunit is an essential component of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptor complexes, indicating that signaling by one or more of these cytokines is required for normal immune system development. Multiple studies have now demonstrated that cytokines belonging to the γ_c family serve as critical regulators of the development, survival, proliferation, differentiation, and/or function of cells of both the innate and adaptive immune systems. The unique and overlapping effects of these cytokines on different immune cell types are summarized here.

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γ_c FAMILY CYTOKINE-INDUCED EFFECTS ON:

- T Cells
- B Cells
- NK or NKT Cells
- Mast Cells or Basophils
- Dendritic Cells
- Epithelial Cells

IL-7 Receptor-expressing cells: T cells, pre-B cells, dendritic cells

PRIMARY BIOLOGICAL EFFECTS OF IL-7 SIGNALING

Promotes Human & Mouse T Cell Development	Promotes Naïve T Cell Homeostasis	Regulates Activated T Cell Proliferation	Regulates the Generation & Survival of Memory T Cells	Regulates V(D)J Recombination at the TCR & Distal Ig Heavy Chain Loci	Promotes Mouse B Cell Development
T CELL DEVELOPMENT	HOMEOSTATIC PROLIFERATION	PROLIFERATION/SURVIVAL	PROLIFERATION/SURVIVAL	V(D)J RECOMBINATION	B CELL DEVELOPMENT

IL-4 Receptor-expressing cells: T cells, B cells, NK cells, basophils, mast cells

PRIMARY BIOLOGICAL EFFECTS OF IL-4 SIGNALING

Regulates Activated T Cell Proliferation	Promotes Th2 or Th9 Differentiation	Promotes B Cell Proliferation	Regulates Ig Production & Class Switching	Promotes Mast Cell Survival & Proliferation	Regulates Priming & Chemotaxis of Mast Cells & Basophils
PROLIFERATION/SURVIVAL	Th2 or Th9 DIFFERENTIATION/ CLONAL EXPANSION	PROLIFERATION	IgG_1, IgG_{2a}, IgG_{2b}, IgG_3, IgE PRODUCTION	PROLIFERATION/SURVIVAL	MAST CELL & BASOPHIL PRIMING/CHEMOTAXIS

IL-2 Receptor-expressing cells: T cells, B cells, NK cells

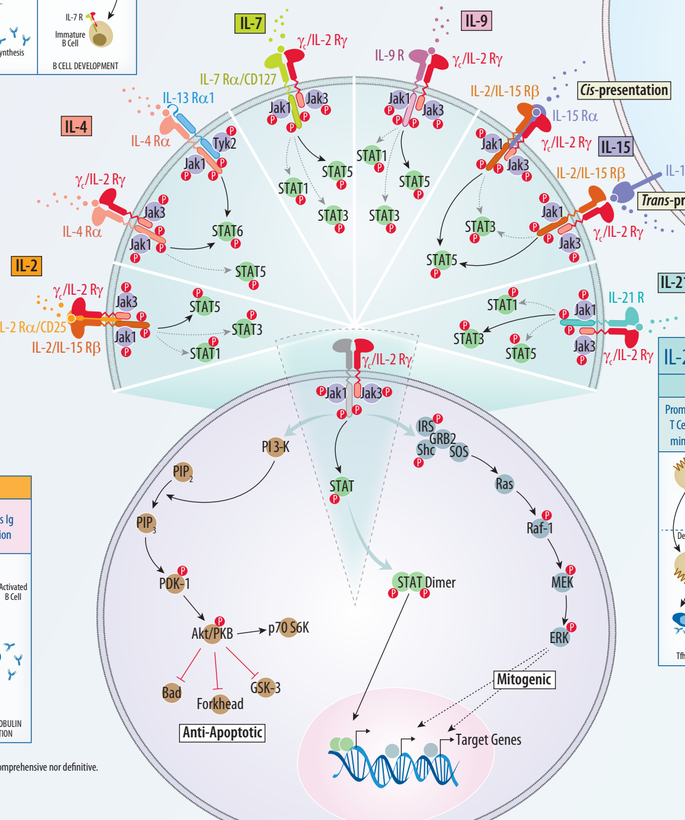
PRIMARY BIOLOGICAL EFFECTS OF IL-2 SIGNALING

Regulates Activated T Cell Proliferation	Promotes Activation-induced Cell Death (AICD)	Promotes Treg Cell Development, Survival & Maintenance	Inhibits Division of $CD8^+$ Memory T Cells	Promotes B Cell Proliferation	Promotes Ig Production
PROLIFERATION/SURVIVAL	AICD MAINTENANCE OF PERIPHERAL SELF-TOLERANCE	EFFECTS ON REGULATORY T CELLS	INHIBITS DIVISION	PROLIFERATION	IMMUNOGLOBULIN PRODUCTION

IL-9 Receptor-expressing cells: T cells, B cells, mast cells, eosinophils, macrophages, neutrophils, epithelial cells

PRIMARY BIOLOGICAL EFFECTS OF IL-9 SIGNALING

Regulates Activated T Cell Proliferation	Regulates Ig Production	Promotes Mast Cell Proliferation & Cytokine Secretion	Promotes Mucus Production
PROLIFERATION/SURVIVAL	IgG_1, IgG_{2a}, IgG_{2b}, IgG_3, IgE PRODUCTION	PROLIFERATION	MUCUS PRODUCTION



IL-15 Receptor-expressing cells: T cells, NK cells, NKT cells, dendritic cells, monocytes

PRIMARY BIOLOGICAL EFFECTS OF IL-15 SIGNALING

Regulates Activated T Cell Proliferation	Inhibits Activation-induced Cell Death (AICD)	Regulates the Maintenance of Naïve & Memory $CD8^+$ T Cells	Protects Intestinal Intraepithelial Lymphocytes	Promotes Expansion & Homeostasis of NKT Cells	Promotes NK Cell Development & Survival	Promotes Dendritic Cell Priming of NK Cell Activation
PROLIFERATION/SURVIVAL	INHIBITS AICD	PROLIFERATION/SURVIVAL	γδ T CELL SURVIVAL/EXPANSION	NKT CELL EXPANSION/HOMEOSTASIS	NK CELL DEVELOPMENT	NK-MEDIATED CELL DEATH

IL-21 Receptor-expressing cells: T cells, B cells, NK cells, NKT cells, dendritic cells, lymphoid tissues

PRIMARY BIOLOGICAL EFFECTS OF IL-21 SIGNALING

Promotes Follicular Helper T Cell Generation & Germinal Center Formation	Promotes Th17 Differentiation & Clonal Expansion	Enhances Cytotoxicity of $CD8^+$ T Cells, NK, & NKT Cells	Promotes B Cell Proliferation & Differentiation	Promotes B Cell Apoptosis in the Absence of BCR & T Cell Signals	Regulates Ig Production & Class Switching	Inhibits DC Maturation & Function
Tfh CELL DIFFERENTIATION	Th17 DIFFERENTIATION	INCREASED CYTOTOXICITY	B CELL EFFECTS	B CELL APOPTOSIS	IgG_1, IgG_{2a}, IgG_{2b}, IgG_3, IgE PRODUCTION	$CD4^+$ or $CD8^+$ T Cells INHIBITS T CELL RESPONSES

γ_c Family Cytokines Have Unique & Overlapping Effects on Different Immune Cell Types

Cytokines belonging to the common cytokine receptor γ-chain (γ_c) family include IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Members of this family signal through receptor complexes that contain the γ_c/IL-2 Rγ subunit. The γ_c subunit associates with different cytokine-specific receptor subunits to form unique heterodimeric receptors for IL-4, IL-7, IL-9, and IL-21, or associates with both IL-2/IL-15 Rβ and IL-2 Rα or IL-15 Rα to form heterotrimeric receptors for IL-2 or IL-15, respectively. γ_c family cytokines generally activate three major signaling pathways that promote cellular survival and proliferation, the PI 3-K-Akt pathway, the RAS-MAPK pathway, and the JAK-STAT pathway. Differences in the expression patterns of the cytokines or their unique receptor components, along with the activation of different STAT proteins may account for some of the distinct effects mediated by γ_c family cytokines.

Signaling by γ_c family cytokines plays a major role in regulating the development, survival, proliferation, differentiation and/or function of cells of the immune system. The importance of the γ_c family cytokines for the establishment and maintenance of the immune system is emphasized by the fact that mutations in γ_c/IL-2 Rγ in humans are associated with a disease known as X-linked severe combined immunodeficiency (XSCID), which is characterized by the absence of T cells and natural killer (NK) cells, and the presence of non-functional B cells. Knockout studies in mice have demonstrated that the lack of T cell and NK cell development in this disease can be primarily attributed to the respective loss of IL-7 and IL-15 signaling, while the loss of both IL-4 and IL-21 signaling leads to defective B cell function. Similar studies revealed that in contrast to humans, B cell development in mice also requires IL-7 signaling. Several additional unique and overlapping effects of the γ_c family cytokines on different immune cell types have been documented. A number of these effects are highlighted here to demonstrate the central role that γ_c family cytokines play in controlling immune system functions. Understanding the mechanisms by which these cytokines act and how their signaling pathways can be regulated may have therapeutic implications not only for a variety of immunodeficient disease states, but also for disorders resulting from aberrant or exaggerated immune system activation.

This illustration represents general processes suggested in the scientific literature and should be considered neither comprehensive nor definitive.

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