Common γ-Chain Family Cytokines Regulate Immune System Functions

γ-Chain Cytokines Have Unique & Overlapping Effects on Different Immune Cell Types

γ-Chain Cytokines belong to the common cytokine receptor γ-chain (gC) family, which 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 γc or γa subunit. The γ subunit associates with different cytokine-specific receptor subunits to form unique heterodimers, receptors for IL-4, IL-7, IL-9, and IL-21, or associates with both (IL-2, IL-15, IL-21) and δ subunits to form heterodimeric receptors for IL-2, IL-7, and IL-9. Cytokine receptors 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 γc-Chain cytokines.

Signaling through γc-Chain cytokines plays a major role in regulating the development, survival, proliferation, differentiation, and function of cells in the immune system. The importance of γc-Chain family cytokines for the establishment and maintenance of the immune system is emphasized by the fact that mutations in γc or γa in mice are associated with a disease known as a lethal/ recessive combined immunodeficiency (CIDS), which is characterized by the absence of T cells and natural killer (NK) cells, and the presence of non-functional B cells. Animal studies in mice have demonstrated that the lack of γc-Chain cytokine cell development in this disease can be primarily attributed to the respective lack of IL-7 and IL-15 signaling, while the loss of both IL-4 and IL-21 signaling leads to decreased 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 γc-Chain cytokines on different immune cell types have been documented. A number of these effects are highlighted here to demonstrate the central role that γc-Chain cytokines play in controlling immune system functions. Understanding the mechanisms by which these cytokines act and how their signaling pathways can be regulated may provide new therapeutic implications not only for a variety of immunodeficiency disease states, but also for disorders resulting from aberrant or exaggerated immune system activation.

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