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Review

Common gamma chain cytokines in combinatorial immune strategies against cancer

Stephanie R. Pulliam[a,b], Roman V. Uzhachenko[a], Samuel E. Adunyah[a,b,**], Anil Shanker[a,b,c,*]

[a] Department of Biochemistry and Cancer Biology, School of Medicine, Meharry Medical College, Nashville, TN 37208, USA
[b] School of Graduate Studies and Research, Meharry Medical College, Nashville, TN 37208, USA
[c] Host-Tumor Interactions Research Program, Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN 37232, USA

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ABSTRACT

Common γ chain (γC) cytokines, namely IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 are important for the proliferation, differentiation, and survival of lymphocytes that display antitumor activity, thus stimulating considerable interest for the use of cytokines in cancer immunotherapy. In this review, we will focus on the γC cytokines that demonstrate the greatest potential for immunotherapy, IL-2, IL-7, IL-15, and IL-21. We will briefly cover their biological function, potential applications in cancer therapy, and update on their use in combinatorial immune strategies for eradicating tumors and hematopoietic malignancies.

Contents

* Corresponding author at: Laboratory of Lymphocyte Function, Department of Biochemistry and Cancer Biology, School of Medicine, Meharry Medical College, 2005 Harold D West Basic Sciences Bldg, 1005 Dr. DB Todd Jr. Blvd, Nashville, TN 37208, USA. Fax: +1 615 327 6442.
** Corresponding author at: Department of Biochemistry and Cancer Biology, School of Medicine, Meharry Medical College, 2104 Harold D West Basic Sciences Bldg, 1005 Dr. DB Todd Jr. Blvd, Nashville, TN 37208, USA. Fax: +1 615 327 6440.
E-mail addresses: sadunyah@mmc.edu (S.E. Adunyah), ashanker@mmc.edu (A. Shanker).

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1. Introduction

The myriad of cytokines that are produced in the tumor microenvironment play a profound role not only in cancer pathogenesis but also in cancer elimination when presented with appropriate immune stimulatory conditions. Cytokines that are secreted during inflammation aid in developing the host's innate and adaptive anti-tumor responses by enhancing tumor-recognition and stimulating lymphocyte effector function [1]. On the other hand, cytokines secreted by stromal and/or immune cells may also assist in tumor growth and promotion [2–6]. Therefore, understanding the relationship of cytokines with tumor cells as well as host immune cells will provide new opportunities for immunotherapy.

Several studies have shown the effectiveness of cytokines to increase the potential of cytotoxic lymphocytes capable of decreasing tumor size or sustaining remission. Cytokines that often display such effects belong to the γ-chain family consisting of interleukins IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [7–9]. These cytokines signal through a receptor complex sharing a common γ chain subunit (γC) generally implying signaling redundancy [8]. Building on the historical development of the γC-cytokines for clinical use, IL-2, IL-7, IL-15, and IL-21 demonstrate the greatest potential for immunotherapy [10–12] (Fig. 1). However, the use of these cytokines in combination with other therapeutics allowing for potential synergism will be the focus of this review. We will briefly cover the normal physiological function of these cytokines, potential role in immunotherapy, and the outcome of the most recent clinical trials on the use of these cytokines in combinatorial therapy involving the treatment of hematological malignancies and solid cancers.

2. Normal physiological functions of γchain cytokines

2.1. IL-2

Predominately produced by activated $CD4^+$ T cells under normal biological conditions, IL-2 is characterized for its ability to induce the expansion of $CD4^+$ and $CD8^+$ T cells [13,14], promote growth and differentiation of activated B cells [15], and encourage the cytotoxic activity of natural killer (NK) cells [16]. Both IL-2 and IL-4 are required for optimal $CD4^+$ development, whereby IL-2 maintains transcriptional accessibility to a portion of the *IL4* gene that in turn facilitates the differentiation of $CD4^+$ T cells [17]. IL-2 also induces the expression of IL-4Rα which further contributes to $CD4^+$ differentiation [18]. However, as a method to eliminate over-stimulation of T cells that may result in autoimmunity, IL-2 also induces Fas-mediated apoptosis in $CD4^+$ T cells [19]. Analysis of the gene promoter regions uncovered binding sites for various transcription factors including nuclear factor of activated T-cells (NFAT), NF-κB, and activator protein 1 (AP-1) [20] suggesting IL-2 is highly regulated transcriptionally and via mRNA stability. The IL-2 receptor (IL-2R) is a heterotrimeric complex consisting of IL-2Rα, IL-2Rβ, and γC subunits. As an additional mechanism of regulating immunity, IL-2Rα is highly expressed in $CD4^+CD25^+FoxP3^+$ regulatory T (Treg) cells [21] that suppresses potentially deleterious activities of T helper (Th) cells and maintains self-tolerance [22]. IL-2Rα does not contain a cytoplasmic signaling subunit; however, it is pertinent for high affinity binding of IL-2 to its receptor [23]. IL-2Rβ and γC are needed for signal transduction where IL-2Rβ associates with Janus tyrosine kinase-1 (Jak1) and γC is associated with Jak3 [24]. Upon activation of the IL-2R, Jak1 and Jak3 phosphorylate Signal Transducer and Activator of Transcription-5 (STAT5) [25]. Activation of Jak proteins also induces other signaling proteins such as phosphoinositide 3-kinase (PI3K) [26] and Src [27]. Further data indicate IL-2 activates STAT1 and STAT3 binding to IL-2Rβ in a different subdomain than STAT5, and this binding is independent of tyrosine residues [28]. IL-2-induced dimerization of STAT5a/b molecules results in the expression of pro-survival genes and FoxP3 transcription factor, master regulator of transcription program in Treg cells [29]. Also, formation of STAT5a/b di- or tetramers can alternate transcriptional programs depending on recruitment of transcription regulators with opposite action, histone acetyltransferase or methyltransferase as well as nuclear corepressor complex [30].

Further, IL-2 is linked to the suppression of Th17 differentiation that may be due to epigenetic suppression by competitive STAT5 binding to the IL-17 promoter [31]. Mutation within the IL-2 gene [32] or the IL-2Rα [33] are known to cause autoimmune diseases; while defects of signaling proteins such as γC are found in severe combined immunodeficiency disease (SCID) [34]. Paradoxically, IL-2 and IL-2R are expressed in cancer cells also. Reichert et al. documented increased expression of endogenous IL-2 and receptor subunits β and γ, when carcinoma cells are in the G2/M phase of the cell cycle as opposed to the G0/G1 phase. They were able to show IL-2 decreases expression of p27 and p21, negative regulators of cellular proliferation, thereby controlling cell cycle progression [35]. Despite this finding, it is important to stress that the mechanism of action of γC cytokines is not based on direct anticancer effects, but depends on immune-mediated pathways regulating the proliferation and survival of lymphocytes targeting tumor that will be discussed further in this review.