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The γ_c Family of Cytokines: Basic Biology to Therapeutic Ramifications

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The common cytokine receptor γ chain, γ_c, is a component of the receptors for interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21. Mutation of the gene encoding γ_c results in X-linked severe combined immunodeficiency in humans, and γ_c family cytokines collectively regulate development, proliferation, survival, and differentiation of immune cells. Here, we review the basic biology of these cytokines, highlighting mechanisms of signaling and gene regulation that have provided insights for immunodeficiency, autoimmunity, allergic diseases, and cancer. Moreover, we discuss how studies of this family stimulated the development of JAK3 inhibitors and present an overview of current strategies targeting these pathways in the clinic, including novel antibodies, antagonists, and partial agonists. The diverse roles of these cytokines on a range of immune cells have important therapeutic implications.

Introduction

The common cytokine receptor γ chain (γ_c) family of cytokines includes interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21. This set of cytokines exhibits broad pleiotropic actions on the immune system, including both the innate and adaptive immune systems, with these cytokines collectively contributing to the development of T, B, natural killer (NK), and innate lymphoid cells (ILCs), promoting either cell survival or cell death of immune populations depending on the context, and critically modulating the differentiation of cellular populations into more terminally differentiated cells. Named based on the common usage of their shared receptor subunit, γ_c, this family of cytokines is vital for normal cellular function, and augmenting, inhibiting, or otherwise modulating the activities of these cytokines may offer therapeutic potential in a range of diseases. While this family of cytokines has been intensively studied, beginning more than four decades ago with the discovery in 1976 of its first member, IL-2, many new insights continue to be made regarding the biology of these cytokines and their mechanisms of action. The utility of IL-2 as a therapeutic agent for cancer was recognized early after its discovery, but new advances in this area continue. Moreover, basic insights from studies of γ_c family cytokines have allowed remarkable translational advances based on the targeting of the cytokines/cytokine receptors and downstream signaling pathways as well as gene therapeutic approaches. Work on γ_c family cytokines stimulated the development of a new class of widely used drugs, Janus kinase (JAK) inhibitors or (jakinibs), and increasingly sophisticated structural insights offer surprising new translational opportunities. It is timely to take stock of the advances over the last 40 years as well as to discuss current challenges and to predict the future. Given the thousands of papers on γ_c family cytokines, we cannot possibly be comprehensive; rather, we provide an overview with discussion topics we believe are particularly compelling at this time.

Overview and the Identification of the γ_c Family of Cytokines

Cytokines refer to molecules that are secreted by cells and act via specific receptors on target cells, with major actions within the immune system (Cohen et al., 1974). There are multiple families of cytokines, but in this review, we will focus on one family of type I four α-helical bundle cytokines known as the common cytokine receptor γ chain (γ_c) family of cytokines, which includes interleukins 2, 4, 7, 9, 15, and 21; the basis for this family is that each of these cytokines shares γ_c as a receptor component. We will review the historical basis for the identification of the family as well as the biological actions of its members. A timeline of some key discoveries is shown in Figure 1 and a schematic of the members of the family, receptors, signaling, and main biological actions are shown in Figures 2 and 3.

The first member of this family to be identified was IL-2, which was discovered as a T cell growth factor in 1976 (Morgan et al., 1976). IL-2 was subsequently found to have broad pleiotropic actions (reviewed in Liao et al., 2013), including the ability to augment the cytolytic activities of NK cells and cytotoxic T cells, to mediate antigen-induced cell death but also to be capable of promoting cell survival depending on the cellular and activation context, to augment immunoglobulin production by B cells, and to modulate the differentiation of T helper cells, augmenting T_H1, T_H2, and T_H9 differentiation but inhibiting T_H17 and T_{FH} differentiation. Importantly, IL-2 is a driver of regulatory T cell (Treg cell) development and expansion. As is discussed below, all γ_c family cytokines

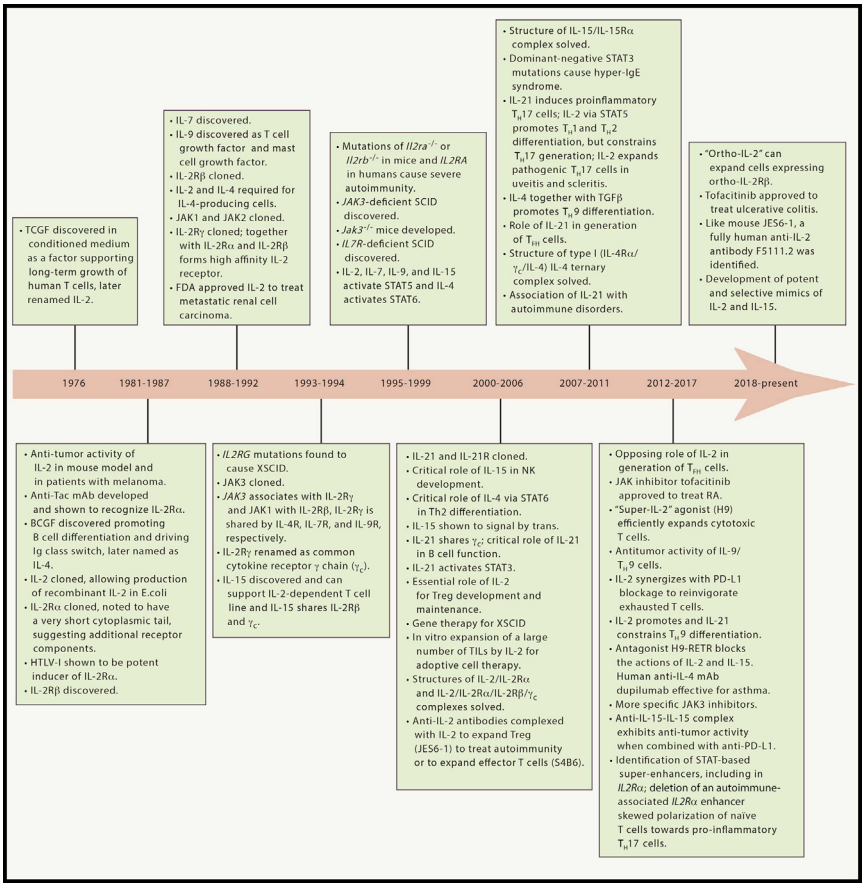

Figure 1. Timeline of Major Discoveries Related to γ_c Family Cytokines

Timeline of discoveries related to γ_c family cytokines, their receptors, major signaling molecules, their actions in immune cells, and some key reagents developed to modulate their actions.

exhibit pleiotropic actions, with each having more than one target cell.

IL-2 is historically important in that it was not only the first type I cytokine to be cloned (Kashima et al., 1985; Taniguchi et al., 1983), but it was also the first type I cytokine for which a receptor component, now known as the IL-2 receptor α chain, (IL-2Rα), was cloned (Cosman et al., 1984; Leonard et al., 1984; Nikaido et al., 1984). However, because IL-2Rα had a predicted cytoplasmic domain of only 13 amino acids including 6 positively charged residues that seemed more likely to serve a cytoplasmic anchoring function than to transduce signals into the cell (Cosman et al., 1984; Leonard et al., 1984; Nikaido et al., 1984), it was predicted that additional chains were needed. Moreover, IL-2Rα bound IL-2 with low affinity (K_d ~10^{-8} M), but both high- (K_d ~10^{-11} M) and low-affinity receptors were present on activated T cells, and intermediate-affinity receptors (K_d ~10^{-9} M) were present on other cells, such as MLA-144 cells and NK cells (Siegel et al., 1987; Tsudo et al., 1986). This led to the discovery of IL-2Rβ (Dukovich et al., 1987; Sharon et al., 1986; Teshigawara et al., 1987; Tsudo et al., 1986) and IL-2Rγ (Saito et al., 1991; Takeshita et al., 1990) and cloning of IL-2Rβ (Hatakeyama et al., 1989) and then subsequently IL-2Rγ (Takeshita et al., 1992), with studies revealing that IL-2Rα by itself accounted for the low-affinity receptors, the combination of IL-2Rβ and IL-2Rγ formed intermediate-affinity receptors, and all three chains combined to form high-affinity receptors (Takeshita et al., 1992).

IL-4 was discovered as a factor that could promote B cell differentiation and drive immunoglobulin class switch (Howard et al., 1982; Isakson et al., 1982; Vitetta et al., 1985), with augmented levels of IgG1 and IgE. It was shown to drive T_H2 differentiation (Le Gros et al., 1990; Swain et al., 1990) and promote T_H9 differentiation and to protect from helminth infection (Van Dyken and Locksley, 2013). IL-4 shares a number of its actions with IL-13 (Gieseck et al., 2018), a cytokine that also uses the type 2 IL-4 receptor (see below). Recently, IL-4 was suggested to contribute to Treg development (Owen et al., 2019) and to have a role in homeostasis and repair mechanisms (Harrison et al., 2019).

IL-7 was discovered as a stromal factor (Goodwin et al., 1989; Namen et al., 1988) that is essential for T cell development and that together with IL-15 mediates $CD8^+$ memory T cell homeostasis. IL-7 appears to also promote memory $CD4^+$ memory T cell homeostasis. In mice, IL-7 is an important pre-B cell growth factor (Peschon et al., 1994; von Freeden-Jeffry et al., 1995), but in humans, normal B cells develop even in the absence of IL-7 signaling (Giliani et al., 2005; Puel et al., 1998). It also can contribute to Treg cell development (Burchill et al., 2007; Mazzucchelli et al. 2008).

IL-9 was discovered as a late T cell growth factor (Schmitt et al., 1989; Uyttenhove et al., 1988) as well as a mast cell growth factor (Hültner et al., 1990). T_H9 differentiation is promoted not only by IL-2 but also by IL-1, IL-4, IL-25, IL-33, and type 1 IFNs and inhibited by IL-23 and IL-27, whereas depending on context, IL-6, IL-10, and IL-21 can either promote or inhibit this process (Kaplan et al., 2015). Importantly, this cytokine has been shown to exhibit anti-tumor activity (Lu et al., 2012; Purwar et al., 2012), to drive allergic inflammation as well as mucous production by goblet cells (Townsend et al., 2000), and to contribute to the pathogenesis of inflammatory bowel disease, where an association was observed between $IL\text{-}9^+$ T cells and the severity of disease (Gerlach et al., 2014; Nalleweg et al., 2015).

IL-15 is the dominant driving force for NK cell development and it augments memory $CD8^+$ T cell homeostasis (Kennedy et al., 2000; Lodolce et al., 1998). Like IL-2, IL-15 can augment NK and $CD8^+$ T cell cytolytic activity, but unlike IL-2, it does not mediate activation-induced cell death (AICD) (Marks-Konczalik et al., 2000). There have been reports of a role of IL-15 in Treg development (Burchill et al., 2007; Owen et al., 2018; Vang et al., 2008), but IL-2 is recognized as the more important driver of Treg

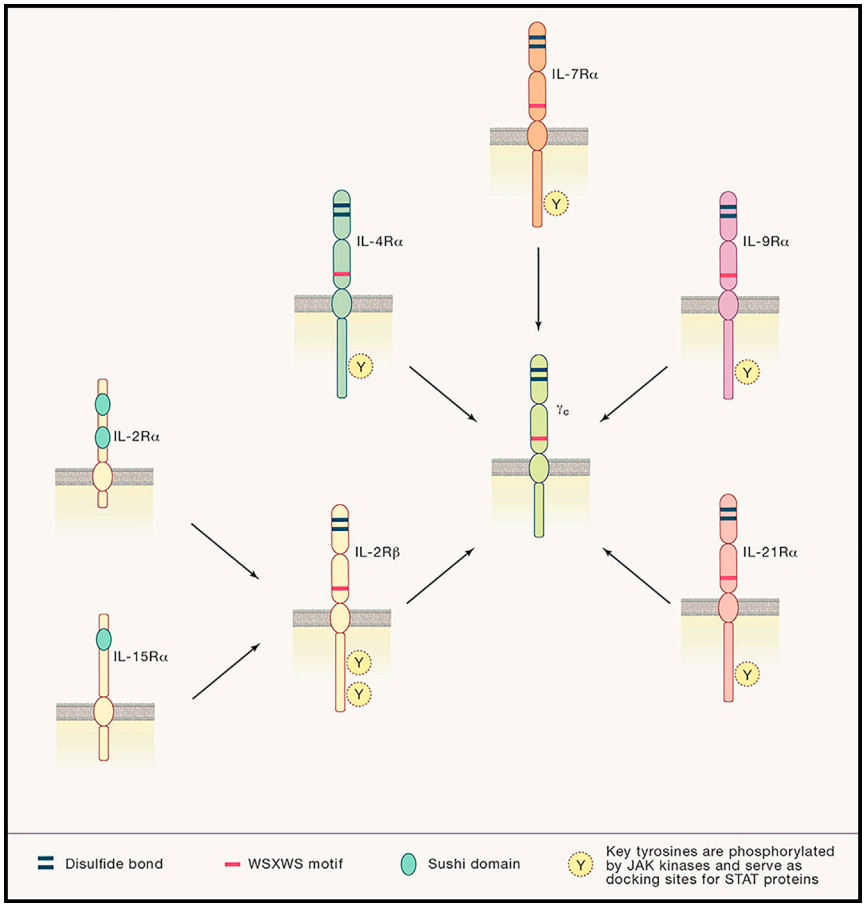

Figure 2. Schematic of γ_c Family Cytokine Receptor Chains

Shown are the unique receptors IL-2Rα for IL-2 and IL-15Rα for IL-15; unique receptors IL-4Rα, IL-7Rα, IL-9Rα, and IL-21Rα for their cognate cytokines; shared receptor IL-2Rβ by IL-2 and IL-15; and shared receptor γ_c by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Disulfide bonds are shown in the thick dark blue bar, WSXWS motif in the thick red bar, sushi domain in the green oval, and key tyrosine residues in cytoplasmic domain are indicated as Y with the yellow circle.

development, survival, and maintenance (Fontenot et al., 2005; Li and Rudensky, 2016; Malek and Castro, 2010; Waldmann, 2006).

IL-21 was discovered not as factor that mediated an activity but instead as the ligand for an orphan type 1 cytokine receptor that was most similar to IL-2Rβ (Ozaki et al., 2000; Parrish-Novak et al., 2000). Once cloned and characterized, however, IL-21 was found to explain some "missing" actions (Parrish-Novak et al., 2000; Ozaki et al., 2004, 2002; Kasaian et al., 2002). IL-21 is produced by T cells following antigen stimulation, but its richest sources appear to include T_H17, NKT, and T follicular helper (T_{FH}) cells (Spolski and Leonard, 2014) and in turn it acts on a broad array of populations, including but not necessarily limited to T cells, B cells including B10 cells, NK cells, DCs, macrophages, mast cells, and epithelial cells (Spolski and Leonard, 2014). IL-21 drives the expansion of $CD8^+$ T cells in combination with IL-7 or IL-15 (Zeng et al., 2005), contributes to $CD8^+$ T cell memory formation (Novy et al., 2011), and promotes the differentiation of T_{FH} (Nurieva et al., 2008) and T_H17 cells (Nurieva et al., 2007) while inhibiting the differentiation of Treg cells (Attridge et al., 2012) and T_H9 cells (Liao et al., 2014); in this regard, it opposes a number of the actions of IL-2. Like IL-4, IL-21 promotes the production of IgG1, but unlike IL-4, it represses rather than induces IgE production (Ozaki et al., 2002). In fact, defective IL-21 signaling appears to explain the elevated IgE observed in patients with autosomal dominant hyper-IgE syndrome (AD-HIES, also known as Job syndrome), which results from defective STAT3 signaling (Holland et al., 2007; Minegishi et al., 2007), the STAT protein that is most potently induced by IL-21 (Wan et al., 2015; Zeng et al., 2007). IL-21 also drives terminal B cell differentiation to plasma cells, but interestingly, IL-21 can also promote the apoptosis of incompletely activated B cells (Jin et al., 2004; Mehta et al., 2003; Ozaki et al., 2004), perhaps thereby limiting the possibility of autoimmunity. In fact, based on human GWAS studies as well as a range of animal models, IL-21 is an important contributor to the development of a range of autoimmune diseases. These include type 1 diabetes, systemic lupus erythematosus, and experimental allergic uveitis, indicating that IL-21 contributes to both antibody-mediated and T cell-mediated autoimmune diseases.

Thus, six different cytokines that are distinctive in function and that were discovered in different settings are linked together by a common receptor component. It is useful to first review how the linkage was discovered.

Relationship of IL-2Rγ to X-Linked Severe Combined Immunodeficiency and Discovering that IL-2Rγ Is a Common γ Chain, γ_c, Also Used by IL-4, IL-7, IL-9, IL-15, and IL-21

Whereas the genes encoding human IL-2Rα and IL-2Rβ map to chromosome 10p15.1 (Leonard et al., 1985) and 22q12.3 (Gnarra et al., 1990), respectively, the human *IL2RG* gene mapped to Xq13.1 (Noguchi et al., 1993b), at the locus for X-linked severe combined immunodeficiency (XSCID, also known as SCID-X1), and indeed patients with XSCID have mutations in *IL2RG* (Noguchi et al., 1993b). XSCID is a profound immunodeficiency characterized by dramatically diminished numbers of T cell and natural killer cells, and B cells, while present in normal numbers, are not functional. As a result of these immune system defects, historically, XSCID was typically fatal in the first year of life due to severe infections and became known as the "Bubble Boy disease" after David Vetter, who was kept alive for more than a decade in a protective germ-free "bubble" (Leonard, 2001). Subsequently, with the advent of bone marrow transplantation, individuals with XSCID could be successfully treated with dramatic improvement or normalization of immune function (Fischer et al., 2015).

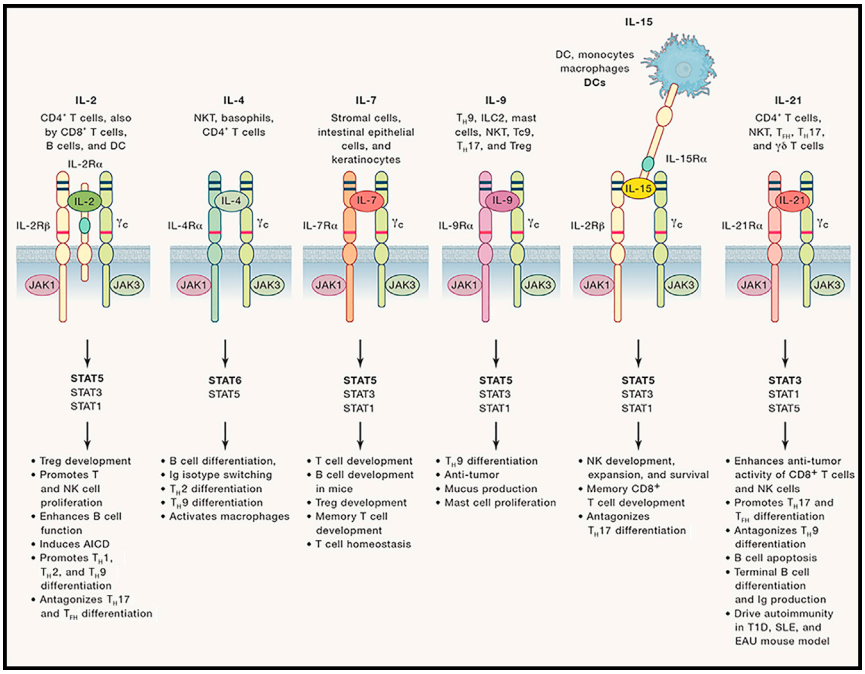

Figure 3. Schematic of the γ_c Family of Cytokines

Schematic of the major cellular sources of γ_c family cytokines; their receptor chains that JAK1 associates with IL-2Rβ, IL-4Rα, IL-7Rα, IL-9Rα, and IL-21Rα and JAK3 with γ_c; the STAT proteins activated (the STATs in bold are the major STAT activated for each cytokine; and the major actions of each cytokines.

The identification of *IL2RG* as the defective gene in XSCID not only represented a major scientific advance that indicated that this disease results from defective cytokine signaling, but it immediately allowed precise molecular diagnosis and paved the way to successful gene therapy for this disease (Leonard, 2001). At the same time, the finding presented a major conundrum in that it was clear that humans with defective production of IL-2 as well as mice with deletion of *Il2* (Sadlack et al., 1993), *Il2ra* (Willerford et al., 1995), or *Il2rb* (Suzuki et al., 1995) had much more normal T cell development, making it unlikely that the inactivation of IL-2 signaling could explain the defect in XSCID. Indeed, it was proposed that γ_c would be shared by additional cytokines in order to explain the defects associated with XSCID (Noguchi et al., 1993b). Such a model was consistent with the sharing of receptor components in other cytokine families, including the IL-3, IL-5, and GM-CSF hematopoietic cytokines that share a common β chain, β_c, and the IL-6 family of cytokines that share the signal transducing molecule gp130. Indeed, it was soon demonstrated that both IL-7 and IL-4 shared IL-2Rγ (Kondo et al., 1994, 1993; Noguchi et al., 1993a; Russell et al., 1993), leading to its being renamed as the common cytokine receptor γ chain, γ_c (Leonard, 1996; Noguchi et al., 1993a; Russell et al., 1993). This protein was subsequently shown to be shared by IL-9 (Kimura et al., 1995; Russell et al., 1994), IL-15 (Giri et al., 1994), and then by IL-21 (Asao et al., 2001), a cytokine that was not known at the time of the XSCID discovery. Thus, six different cytokine systems, IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, are disrupted in patients with XSCID (Noguchi et al., 1993b). Given the critical roles of IL-7 and IL-15 in T cell and NK cell development, respectively, these observations explain those major cellular defects in XSCID. Moreover, defective signaling by IL-4 and particularly IL-21 appear to explain the non-functionality of the B cells in this disease (Ozaki et al., 2002; Recher et al., 2011). Thus, although the discovery of the basis for XSCID evolved out of studies of IL-2, this cytokine is not "critical" for understanding the defects in XSCID, as cells on which it exerts its major actions do not develop due to the inactivation of the IL-7 and IL-15 systems. Interestingly, mutations in *IL2RG* have also been associated with less severe forms of immunodeficiency, such as a moderate form of X-linked combined immunodeficiency (XCID) (Russell et al., 1994), consistent with the fact that some mutations of γ_c attenuate rather than fully inactivate its function. A full range of *IL2RG* mutations in XSCID are available at https://www.ncbi.nlm.nih.gov/clinvar/?term=IL2Rg%5Bgene%5D.

Association of IL-2Rβ and γ_c with JAK1 and JAK3, Respectively, and the Discovery of *JAK3*-Deficient and *IL7R*-Deficient Forms of SCID

The cloning of cytokine receptor genes advanced our understanding of the relatedness of families of cytokines (Bazan, 1990a, 1990b). What was less clear was how engagement of cytokine receptors resulted in membrane to cytoplasmic signaling and the rapid induction of gene expression. For the interferons, key advances came from studies using a series of mutagenized cells lines that failed to signal via type I (IFN-α/β) and type II (IFN-γ) IFNs, culminating in the identification of the essential role of a new class of tyrosine kinases, Janus kinases (JAKs), for IFN signaling (Velazquez et al., 1992). Nearly concomitant with the discovery of JAKs, other studies allowed the discovery of STATs and their roles in IFN signaling, establishing the JAK-STAT paradigm (Shuai et al., 1993).

Studies of signaling then revealed that IL-2 could activate JAK1 and JAK3, and it was shown that JAK1 associated with IL-2Rβ (Miyazaki et al., 1994; Russell et al., 1994; Witthuhn et al., 1994) and JAK3 with γ_c (Miyazaki et al., 1994; Russell et al., 1994; Witthuhn et al., 1994). Because JAK3 was "downstream" of γ_c, it was hypothesized that mutations in the *JAK3* gene would cause a similar disease that phenocopies XSCID (Russell et al., 1994). Indeed, such patients were identified, and as anticipated, this disease occurred as an autosomal-recessive disease in both girls and boys (Macchi et al., 1995; Russell et al., 1995), given that the *JAK3* gene is at human chromosome 19p13.11 rather than on the X chromosome. The identification of humans with *JAK3* mutations provided the first evidence of the essential function of JAKs in cytokine signaling *in vivo*.

Given the relationship of IL-7 to T cell development, it was reasonable to speculate that mutations in *IL7* or *IL7R* might result in a T cell selective form of SCID, and indeed *IL7R*-deficient human SCID was identified as a disease in which T cells are profoundly diminished but NK-cell development remains intact (Puel et al., 1998); interestingly, *IL7*-deficient SCID has still not been identified despite the large numbers of SCID patients whose *IL7* gene has been sequenced. This might potentially result from the possibility that the *IL7* gene is not very susceptible to inactivating mutations, but it is also possible that the phenotype of such individuals is less severe than expected so that they do not come to medical attention or that the absence of *IL7* expression is unexpectedly associated with fetal lethality. Please see https://www.ncbi.nlm.nih.gov/clinvar/?term=JAK3%5Bgene%5D and https://www.ncbi.nlm.nih.gov/clinvar/?term=IL7R%5Bgene%5D, respectively, for the range of reported mutations in *JAK3* and *IL7R*.

Gene Therapy for XSCID

As noted above, the identification of *IL2RG* as the defective gene in XSCID paved the way toward gene therapy. Initially, proof-of-principle was established in curing *Il2rg*-deficient mice (Lo et al., 1999), a mouse model of XSCID. Subsequently, the first successful human gene therapy for XSCID was performed (Cavazzana-Calvo et al., 2000), where affected boys who lacked appropriate donors for bone marrow transplantation were treated by retrovirally mediated expression of an *IL2RG* cDNA. While successful in substantially improving immune function, two individuals developed acute lymphocytic leukemia resulting from retroviral insertion and activation of the *LMO2* proto-oncogene (Hacein-Bey-Abina et al., 2003). Fortunately, the leukemias in turn were successfully treated, but these serious adverse events resulted in work to develop alternative strategies to achieve the beneficial results while preventing or reducing untoward effects (Hacein-Bey-Abina et al., 2014; Clarke et al., 2018). Gene therapeutic approaches for *JAK3*-deficient and *IL7R*-deficient SCID are areas for future development. In addition, newer approaches such as gene editing are of obvious interest.

Receptor Structure of γ_c Family Cytokines and Other Downstream Signaling Pathways

Interestingly, as noted above, IL-2 has three classes of receptors binding IL-2 with low, intermediate, or high affinity. IL-4 has two types of receptors: the type I IL-4R on T cells comprising IL-4Rα + γ_c (Kondo et al., 1993; Russell et al., 1993) and the type II IL-4 receptor found on B cells and non-lymphoid cells compromising IL-4Rα + IL-13Rα1 (Aman et al., 1996; Hilton et al., 1996; Miloux et al., 1997); this latter receptor can also signal in response to IL-13 (Van Dyken and Locksley, 2013). The functional IL-7, IL-9, IL-15, and IL-21 receptors are IL-7Rα + γ_c (Noguchi et al., 1993a), IL-9Rα + γ_c (Kimura et al., 1995; Russell et al., 1994), IL-15Rα + IL-2Rβ + γ_c (Giri et al., 1994), and IL-21R + γ_c (Asao et al., 2001), respectively. IL-7R is also a functional part of the receptor for thymic stromal lymphopoietin (TSLP) (Pandey et al., 2000; Park et al., 2000), but rather than γ_c, this cytokine has TSLPR as its second component and thus is not a γ_c family cytokine. γ_c family cytokines generally signal in *cis*, meaning that they bind to and act on a cell expressing the receptor. However, IL-15 instead primarily signals in *trans* (Dugas et al., 1993), with IL-15 binding to IL-15Rα on one cell, which presents it to IL-2Rβ-γ_c on another cell. Whereas IL-2 can signal in *trans* (Wuest et al., 2011), it primarily signals in *cis*.

A large amount of information regarding receptors for γ_c family cytokines has accumulated over the years, including X-ray crystal structures for many of the receptors (Wang et al., 2009). IL-2Rβ, IL-4Rα, IL-7Rα, IL9Rα, IL-21R, and γ_c are all type I cytokine receptors, previously also called hematopoietin receptors, and share a characteristic cytokine-binding homology region (CHR) of approximately 200 amino acids that comprises two fibronectin FIII domains connected by a linker. They also contain the generally conserved WSXWS motif and four conserved cysteine residues involved in disulfide bonds that confer a characteristic overall conformation (Figure 2) (Bazan, 1990b). In contrast, IL-2Rα and IL-15Rα are not type I cytokine receptors but instead are distinctive sushi domain-containing proteins (Figure 2) (Lorenzen et al., 2006; Rickert et al., 2005).

In the case of IL-2, the mechanism underlying the assembly of the high-affinity receptor is now well-understood. IL-2 first interacts with IL-2Rα, which has rapid on- and off- rates of binding (Wang and Smith, 1987). Importantly, the association of IL-2 with IL-2Rα results in a conformational change in the structure of IL-2 so that it can then efficiently interact with IL-2Rβ, and finally, γ_c is recruited (Wang et al., 2005). The high affinity results from a combination of the rapid on-rate to IL-2Rα and the slower off rates from IL-2Rβ (Lowenthal and Greene, 1987; Wang and Smith, 1987). Although there are membrane proximal regions in the receptor chains that can interact with low affinity, assembly and stability of these complexes is primarily ligand driven. Knowledge of this system was important in the design of new cytokine variants (discussed below).

Interestingly, each γ_c family cytokine activates both JAK1 and JAK3, with JAK1 directly interacting not only with IL-2Rβ (Miyazaki et al., 1994; Russell et al., 1994; Witthuhn et al., 1994) but also with IL-4Rα, IL-7Rα, IL-9Rα, and IL-21Rα, and JAK3 interacting with γ_c (Figure 3) (Miyazaki et al., 1994; Russell et al., 1994; Witthuhn et al., 1994). Despite their activation of the same JAK kinases, γ_c family cytokines differ in terms of signaling. Of the seven STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6), IL-2, IL-7, IL-9, and IL-15 dominantly activate STAT5A and STAT5B, whereas IL-4 mainly activates STAT6 and IL-21 primarily STAT3 (Figure 3). Thus, STAT proteins partially explain the specificity of signaling by these cytokines. Moreover, for each cytokine, specificity is also conferred by when and where each cytokine is produced as well as the range of target cells expressing the cognate receptor at a given time, and the relative activation by each cytokine of additional signaling pathways

Beyond activation of JAKs and STATs, γ_c family cytokines activate other signaling pathways. For example, IL-2 activates MAP kinase- and phosphoinositol 3-kinase-dependent pathways (Ross and Cantrell, 2018), IL-7 activates PI 3-kinase (Jiang et al., 2005), and IL-4 induces phosphorylation of the adaptor molecule IRS2 to link to downstream signaling pathways (Paul, 2015). Analysis of the induced phospho-proteome coupled to JAK kinase inhibition suggested that ~90% of IL-2 signaling is JAK dependent (Ross et al., 2016). The contribution of STATs versus other pathways to metabolic changes is less well understood, and it will be important to identify the extent to which STAT proteins can explain the regulation of given genes as

they relate to metabolic control. Interestingly, IL-2-induced transcriptomic changes are regulated in part by glutamine and α-ketoglutarate, in part through changes in DNA and histone methylation states and genomic binding of CCCTC-binding factor (Chisolm et al., 2017).

It is important to also consider potential competition among the different γ_c family cytokines. Specifically, the sharing of γ_c could potentially help to explain why some of these cytokines share overlapping actions; alternatively, the sharing of γ_c might represent a mechanism for competition for γ_c, so that when more of one cytokine is produced, it potentially could "outcompete" other γ_c family cytokines for recruiting γ_c so that one cytokine dominates while simultaneously shutting off other cytokine signals (Leonard, 2001). This competition model makes the most sense in situations where γ_c is limiting. It is important to note that the two models are not mutually exclusive: sharing γ_c could help to explain shared actions, while competing for γ_c might be a mechanism for opposing actions.

Nonclassical Views of γ_c Cytokines

As γ_c family cytokines were discovered as lymphocyte growth factors, much of the research initially centered on actions related to adaptive responses. However, it also became clear that γ_c family cytokines have a major effect on the innate immune system, with IL-15 being critical for the development of NK cells and IL-7 and IL-15 having roles for innate lymphocytes (Robinette et al., 2017; Rochman et al., 2009). IL-15 induces T-bet in CD8αα$^+$ intraepithelial lymphocytes, which is essential for the development of this class of innate lymphocytes (Klose et al., 2014). Evidence has evolved in support of actions for γ_c family cytokines on neutrophils, macrophages, and other myeloid cells. For example, IL-4 antagonizes neutrophil expansion and activation (Impellizzieri et al., 2019; Woytschak et al., 2016) whereas IL-2 activates neutrophils to promote killing of Candida (Djeu et al., 1993).

Receptors for γ_c family cytokines are not restricted to immune cells. For example, IL-2R subunits and JAK3 are expressed by endothelial cells, which are mediators of capillary leak syndrome induced by IL-2, and osteoblasts can produce IL-9, which promotes megakaryopoiesis and can prevent chemotherapy-induced thrombocytopenia (Xiao et al., 2017). IL-4 and its close cousin IL-13, which is not a γ_c family cytokine as its receptor is comprised of IL-4Rα and IL-13Rα1 and not γ_c, have important metabolic actions affecting body heat, hepatic metabolism, peripheral nutrient metabolism, and insulin sensitivity (Van Dyken and Locksley, 2013). IL-4 and type 2 immune responses are important for tissue repair and the production of the epidermal growth factor-like molecule amphiregulin (Zaiss et al., 2015), which can be present in atypical CD8 cells in the skin (Harrison et al., 2019). IL-4 also can act on neurons to promote axonal repair in the setting of neuroinflammation (Vogelaar et al., 2018; Walsh et al., 2015), and moreover, type 2 cytokines including IL-4 also directly activate sensory neurons that elicit itch responses. Patients with chronic itch improve when treated with JAK inhibitors, and this is believed to occur based on the inhibition of IL-4 signaling (Oetjen et al., 2017).

Regulation of Expression of γ_c Family Cytokines

Much is known regarding the source of these cytokines being produced and the regulation of expression of γ_c cytokines, and indeed the regulation of IL-2, IL-4, IL-9, and IL-21 is fundamentally linked to T cell activation and helper cell differentiation (Figure 3). Consistent with its identification as an autocrine/paracrine T cell growth factor, considerable attention has been paid to the direct activation of the *Il2* gene by signals emanating from the T cell receptor (TCR) and costimulatory molecules that activate transcription factors including NF-κB, NFAT, Fos, and Jun (Liao et al., 2013).

The ability to comprehensively assess gene expression began with microarray technology and evolved with the development of RNA-Seq and then single cell RNA-Seq technologies. These data and new accessible platforms (e.g., Immgen, Biogps, etc.) provide different and more comprehensive pictures of gene expression compared to our conventional views. For example, *Il2* transcripts are produced not only by CD4$^+$ T cells, but also by CD8$^+$ T cells and dendritic cells and based on Immgen data, ILC2 and ILC3 are also producers of *Il2* mRNA (Crellin et al., 2010). However, whether ILCs substantially contribute to IL-2 protein production in immune responses is still poorly studied, although IL-2 produced by ILC3s was suggested to be a driver of eosinophilic pathology in pulmonary inflammation (Crellin et al., 2010; Roediger et al., 2015). Mice in which IL-2 is conditionally deleted (*Il2*$^{fl/fl}$ mice mated to Cre mice) have been generated (Owen et al., 2018), which should allow better assessment of the source of IL-2 in different tissues in different settings. Expression of *Il2* is highly dependent upon the cellular activation state, and in addition to transcriptional activation, post-transcriptional regulation also contributes (Lindstein et al., 1989).

IL-4 is produced mainly by T_H2 cells, NK T cells, basophils, and mast cells and its regulation has been intensively studied (Ansel et al., 2006; Nakayama et al., 2017). Analogous to the *Il2* gene being located adjacent to the *Il21* gene, the *Il4* gene is within the "T_H2 cluster" that also encompasses the *Il13* and *Il5* genes (Lee et al., 2003). The organization of this locus and the *Il2*/*Il21* locus suggests that these cytokines arose from duplication events during evolution.

IL-7 is produced by stromal and epithelial cells and by keratinocytes and hepatocytes, but unlike IL-2, IL-4, IL-9, and IL-21, it is not produced by lymphoid cells. While there are data indicating that IL-7 can be induced by inflammatory stimuli, the availability of IL-7 is also largely determined by lymphoid consumption of this cytokine (Martin et al., 2017).

IL-9 is produced not only by T_H9 cells but also by ILC2 cells, mast cells, and NK T cells (Kaplan et al., 2015). IL-2, IL-4, and thymic stromal lymphopoietin (TSLP), when combined with TGFβ, promote IL-9 production (Kaplan et al., 2015), as does the TNF family member TL1A in an IL-2 and STAT5-dependent manner (Richard et al., 2015). Production of IL-9 is also induced by the neuropeptides neuromedin U and calcitonin gene-related peptide (CGRP) (Klose et al., 2017; Mikami et al., 2013), whereas retinoic acid negatively regulates IL-9 production and allergic disease (Schwartz et al., 2019). Multiple transcription factors, including PU.1, NF-κB, NFAT, STATs, FOXO1, and IRF family members, have been reported to influence its expression. (Bi et al., 2017; Buttrick et al., 2018; Campos Carrascosa et al., 2017; Kaplan et al., 2015). Like other cytokine genes, the *Il9* locus has a complex enhancer structure (Koh et al., 2018; Schwartz et al., 2019).

Unlike IL-2, IL-4, IL-7, and IL-9, IL-15 mRNA is expressed by both hematopoietic and nonhematopoietic cells, with mature IL-15 being mainly produced by monocytes, macrophages, dendritic cells (Waldmann, 2006), and keratinocytes, but also by fibroblasts, myocytes, stromal cells, and nerve cells (Fehniger and Caligiuri, 2001; Tagaya et al., 1997; Waldmann and Tagaya, 1999). There are two splice variants of IL-15 mRNA, with expression being partially controlled by post-transcriptional mechanisms and intracellular trafficking (Abadie and Jabri, 2014; Waldmann and Tagaya, 1999).

IL-21 is expressed in $CD4^+$ T cells, NKT, T_{FH}, T_H17, and γδ T cells, although as noted above, these cells are not the exclusive source of IL-21. Not only is IL-21 implicated as contributing to the development of a range of autoimmune diseases, for example including systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes (Spolski and Leonard, 2014), but it also is induced in murine models of house dust asthma (Coquet et al., 2015). NKT cells, T_H17 cells, and intestinal $CCR9^+$ $CD4^+$ T cells and IFN-γ-expressing memory T cells can also be sources of IL-21, as well as "natural" T_{FH} cells that arise in the thymus (Marnik et al., 2017).

In the past, studies of cytokine and cytokine receptor gene regulation have largely focused on regulatory elements within either proximal promoters or in first introns of genes and the transcription factors that bind these elements, but next-generation sequencing has permitted a much broader view of the regulation of these genes, including the identification of superenhancers (Parker et al., 2013; Whyte et al., 2013). As noted above, the *Il2* and *Il21* genes are adjacent genes, and it is striking that IL-2 and IL-21 often exhibit opposing actions. For example, whereas IL-2 promotes T_H9 (Liao et al., 2014) and Treg (Burchill et al., 2007; Fontenot et al., 2005; Malek et al., 2002) differentiation and inhibits T_H17 (Laurence et al., 2007) and T_{FH} (Ballesteros-Tato et al., 2012; Johnston et al., 2012; Oestreich et al., 2012) differentiation, IL-21 has the opposite effects (Korn et al., 2007; Liao et al., 2014; Nurieva et al., 2008). Interestingly, a study using reporter mice indicated that $CD4^+$ T cells exposed to strong TCR signals produced IL-2 and were fated to become T_{FH} cells whereas those cells exposed to weaker TCR signals did not produce IL-2 and were destined to become non-T_{FH} cells (DiToro et al., 2018).

Regulation of Expression of Receptors for γ_c Family Cytokines

Like their ligands, cytokine receptors are encoded by genes that have a high degree of cell-specific expression and can be highly regulated by activation signals. For example, IL-2Rα is not expressed on resting T cells (except for Treg cells), but is potently induced after antigen activation, and it also can be induced by IL-2 itself, TNFα, and other activators of STAT5, STAT3, and NF-κB (Liao et al., 2013). *IL2RA* has been extensively studied, with the identification of multiple regulatory regions as well as a large STAT5-based super-enhancer that extends from the 5′ regulatory region into the first intron in both the human and mouse genes encoding IL-2Rα (Li et al., 2017; Simeonov et al., 2017).

Adjacent to *IL2RA* is the gene encoding IL-15Rα, *IL15RA*, which is expressed by a wide range of cells, including both immune cells and nonimmune cells. IL-15Rα can transmit IL-15 signals in *cis* (Carson et al., 1997), but it primarily acts to *trans*-present IL-15 to other cells expressing both IL-2Rβ and γ_c (Dubois et al., 2002; Lodolce et al., 1998). Given that these are both sushi domain-containing proteins that share structural similarities, it is possible that they also arose by gene duplication.

IL-4Rα is also broadly expressed on both lymphocytes and other hematopoietic as well as non-lymphohematopoietic cells. Type I IL-4 receptors are expressed on lympho-hematopoietic cells, whereas type II IL-4 receptors are expressed on some hematopoietic as well as nonhematopoietic cells (Paul, 2015). Adjacent to *IL4RA* is the *IL21R* gene (Ozaki et al., 2000). IL-21R mRNA is expressed on lympho-hematopoietic cells (Parrish-Novak et al., 2000) and is highly regulated in a cell- and activation-dependent manner (Coquet et al., 2007; Kim et al., 2005; Nurieva et al., 2007; Vogelzang et al., 2008).

IL-7Rα is expressed on both hematopoietic cells (to mediate effects of IL-7 and TSLP) but also on nonlymphoid cells such as dendritic cells to mediate effects of TSLP (West et al., 2012; Ziegler and Artis, 2010). IL-7Rα expression is dynamically regulated during lymphocyte development and in response to activation (Mazzucchelli and Durum, 2007). IL-7Rα is regulated by glucocorticoids in a diurnal pattern, facilitating the redistribution between lymph nodes, spleen, and blood, and in mice, nocturnal accumulation of T cells in the spleen enhances immune responses to systemic bacterial infection (Shimba et al., 2018). Interestingly, expression of IL-7Rα is downregulated by stimulation via the T cell receptor (Franchimont et al., 2002; Xue et al., 2002) or in response to γ_c family cytokines, including IL-2, IL-4, IL-7, and IL-15 (Mazzucchelli and Durum, 2007; Xue et al., 2002).

IL-9Rα is detected not only on T cells but also on nonhematopoietic cells, including airway and intestinal epithelial cells and smooth muscle cells (Goswami and Kaplan, 2011; Soussi-Gounni et al., 2001), consistent with its roles in allergic inflammation as well as mucous production by goblet cells.

Consistent with their dynamic regulation, *Il2ra*, *Il4ra*, and *Il7r* have also been shown to be located at superenhancer loci (Li et al., 2017; Vahedi et al., 2015). Cytokine and cytokine receptor genes can exhibit complex regulation, and polymorphisms in these loci can be associated with increased risk of disease in humans (Table 1). For example, IBD susceptibility has been linked to polymorphisms in *IL2, IL21, IL2RA,* and *IL15RA* (Jostins et al., 2012). Moreover, genome-wide association studies have implicated *IL2RA* non-coding variants as risk factors for multiple autoimmune disorders (Farh et al., 2015; Simeonov et al., 2017), including for a SNP that accounts for elevate risk of inflammatory bowel disease (Huang et al., 2017) but contributes to protection from type 1 diabetes (Huang et al., 2012; Maier et al., 2009; Onengut-Gumuscu et al., 2015), and furthermore, *IL4RA* polymorphisms are associated with asthma and allergy (Massoud et al., 2016). This is consistent with the concept that GWAS genetic variations are enriched within superenhancer loci (Hnisz et al., 2013; Parker et al., 2013; Vahedi et al., 2015), and it will be important to understand the mechanistic impact of genetic polymorphisms on each gene. A better understanding of these genetic elements, the transcription factors that act on these regions, and relevant signaling pathways will hopefully provide new therapeutic strategies.

Evolutionary Considerations

The genomic organizations of γ_c family cytokines are indicative of possible duplication events during evolution, an idea

Table 1. Disorders Associated with Mutations or Polymorphisms in γ_c Family Cytokines, Their Receptors, JAK Kinases, and STAT Proteins

Genetic changes	Genes	Phenotype
Gene mutation	*IL2*	Inflammation in patients with loss-of-function mutations
	IL2RA	Inflammation and autoimmunity in patients with loss-of-function mutations
	IL2RG	$T^-B^-NK^-$ XSCID in patients with loss-of-function mutations
	IL7R	$T^-B^+NK^+$ SCID in patients with loss-of-function mutations
	JAK3	$T^-B^-NK^-$ SCID in patients with loss-of-function mutations; gain-of-function mutations in some leukemias
	IL21RA	Defective T and B function and variable dysfunction of NK cells in patients with loss-of-function mutations
	STAT3	Immunodeficiency in patients with loss-of-function mutations and tumorigenesis in patients with gain-of-function mutations
		Autosomal-dominant hyper-IgE syndrome
	STAT5B	Growth retardation and immune dysfunction in patients with loss-of-function mutation and tumorigenesis in patients with gain-of-function mutations
Polymorphism	*IL4*	Asthma and allergic rhinitis
	IL9	Allergic rhinitis
	IL9R	Allergic rhinitis
	IL2	MS, T1D, IBD
	IL7	MS
	IL7R	MS, T1D
	IL21	SLE, IBD, T1D
	IL2RA	T1D, IBD, MS
	IL4RA	Asthma and allergy
	IL15RA	IBD
	IL21RA	SLE

supported by partially overlapping actions of these cytokines and their uniform utilization of JAK1 and JAK3. The time at which this family of cytokines evolved is not clear but appears to be more recent than IL-17 and IL-6. While type 3 immune responses (i.e., IL-17) appeared in invertebrates (Huang et al., 2015) and *Drosophilia* have an IL-6-related cytokine termed DOME, the evolution of γ_c family cytokines and their receptors is not evident in these species. Most γ_c cytokines, including IL-2, IL-4, IL-7, IL-15 and IL-21, are found in mammals, birds, and teleost and cartilaginous fish, with IL-2, IL-4, IL-7, and IL-21 present in the elephant shark genome (Redmond et al., 2018; Secombes, 2016). It is notable that the *IL2/IL21* and *IL4/IL13* gene clusters are conserved in mammals, birds, teleost fish, and the elephant shark, as is the gene encoding γ_c. Given the general role of γ_c family cytokines in lymphoid homeostasis and the fact that lymphocytes arose prior to the divergence of jawed and jawless fish, it seems likely that this family of cytokines may have arisen with lymphocytes during evolution. Interestingly, IL-9 has not been identified in the genomes of teleost and cartilaginous fish, perhaps suggesting that it arose after the other cytokines.

γ_c Family Cytokines and Fine-Tuning Cytokine Signals

As noted above, each γ_c family cytokine has pleiotropic actions and some of them have opposing actions to each other as well. The actions of γ_c family cytokines can be beneficial for maintaining normal immunity against pathologic insults, but as discussed above, genetic mutations and/or polymorphisms in genes encoding them and their signaling molecules can cause a range of disorders with devastating consequences, including severe immunodeficiency, autoimmunity, allergy, and malignancy (Table 1). Thus, it is vital to understand how the various actions and signals individually and collectively can be fine-tuned. Specificity is determined by expression of the cytokines, their receptors, and key signaling molecules, but there are additional mechanisms as well. To achieve these goals, efforts have been focused on fine-tuning the actions of γ_c family cytokine based on the knowledge of the biology of the system, in order to enhance therapeutic efficacy and dampen adverse side effects (Table 2).

There are multiple mechanisms for fine-tuning signals by cytokines. First, cytokines can be fine-tuned based on the differential use of STAT proteins. STAT protein activation is a basis for distinguishing some of the γ_c family cytokines from each other. For example, IL-2, IL-7, IL-9, and IL-15 primarily activate STAT5A and STAT5B and to some degree activate STAT3 and STAT1 (Demoulin et al., 1996; Lin et al., 1995); IL-4 dominantly activates STAT6, with some activation of STAT5 (Hou et al., 1994; Quelle et al., 1995; Rolling et al., 1996); and IL-21 primarily activates STAT3, with some activation of STAT5 proteins and STAT1 (Wan et al., 2015, 2013; Zeng et al., 2007). Thus, the major STAT that is activated clearly helps to distinguish among IL-2, IL-4, and IL-21. In addition, however, even for an individual cytokine, differential STAT activation can be important. For example, IL-21 induces different sets of genes via STAT3 versus STAT1, and the balance between the activation of these different STATs is a means for fine-tuning the system. Indeed, in autosomal dominant hyper-IgE syndrome, the *STAT3* gene is mutated (Holland et al., 2007; Minegishi et al., 2007), resulting in a hypomorphic state wherein expression of TBET, encoded by *TBX21*, a regulator of T_H1 differentiation, and IFNγ are augmented due to the relative increase in STAT1 versus STAT3 (Wan et al., 2015).

Table 2. Reagents Being Approved for Therapeutics or with Therapeutic Potentials

Type of Molecules	Molecules	Mechanisms of Action
Ligand	IL-2	Low dose to expand Treg cells
		High dose preferentially to expand effector T cells.
	IL-2 H9	Expands effector T cells
	H9-RETR	Blocks IL-2 and IL-15 signals, diminishes graft-versus-host disease, blocks the proliferation of chronic-smoldering adult T cell leukemia T cells.
	Ortho IL-2	Only acts on cells expressing Ortho IL-2Rb, an approach for transduction of TILs and selectively expanding them *in vivo*
Hybrid ligand	Neoleukin-2/15 (Neo-2/15)	Structural based synthetic molecule to mimic IL-2 and IL-15 with high stability and binding affinity and better anti-tumor activity in mouse model
Receptor-ligand	IL-15-IL-15Ra fusion protein (RLI)	Preferentially expands memory $CD8^+$ T cells but less efficiently expands exhausted T cells.
	IL-2-IL-2Ra fusion protein (FP)	Preferentially expands Treg cells.
MAb	Daclizumab	IL-2Ra blocking antibody approved for the treatment of renal allograft rejection and multiple sclerosis but voluntarily withdrawn from the market
	Dupilimab	Blocks both IL-4 and IL-13; approved for the treatment of moderate-to-severe asthma and atopic dermatitis
	JES6	Anti-IL-2; preferentially expands Treg cells when complexed with IL-2
	F5111.2	Anti-IL-2 human mAb similar to JES6
	S4B6	Anti-IL-2, preferentially expands effector T cells when complexed with IL-2
Small molecules	Tofacitinib	Inhibits JAK3 but also JAK1 and JAK2
	Baricitinib	Inhibits both JAK1 and JAK2
	Ruxolitinib	Inhibits both JAK1 and JAK2
	Oclacitinib	inhibits both JAK1 and JAK3
	JAK3i	Specifically inhibits JAK3 and preferentially the 2^{nd} wave of STAT5 activation by IL-2
	Peficitinib	Inhibits JAK3 and to a lesser extend also JAK1, JAK2, and TYK2

A second mechanism for fine-tuning is based on STAT dimerization versus tetramerization. The JAK-STAT paradigm involves the activation (i.e., phosphorylation) of STAT proteins by JAK kinases, allowing the formation of STAT dimers mediated by bivalent SH2-phosphotyrosine interactions (Leonard and O'Shea, 1998; Levy and Darnell, 2002). STAT dimers for STAT1, STAT3, STAT4, STAT5A, and STAT5B can bind to GAS (γ-IFN activated sequence, $TTCN_3GAA$) motifs, whereas STAT6 prefers a similar $TTCN_4GAA$ motif (Leonard and O'Shea, 1998). Additionally, however, it was shown initially for STAT1 and STAT4 that an additional N-terminal region (also called N-domain)-mediated interaction could result in dimerization of STAT dimers to form tetramers that could bind to tandemly linked GAS motifs (Soldaini et al., 2000; Vinkemeier et al., 1996; Xu et al., 1996). The binding is more stable but also there are sites that are divergent enough in the GAS motifs so that they cannot bind dimers even though they can bind tetramers. The ability to form STAT dimers and tetramers potentially allows for the evolutionary acquisition of more stable binding and sustained expression. Indeed, STAT5 tetramers are known to be vital for normal IL-2-induced T cell expansion (Lin et al., 2012) and IL-15-mediated NK cell survival (Lin et al., 2017), whereas STAT1 tetramers are required for a normal type 2 IFN response (Begitt et al., 2014).

Third, STAT-based superenhancers afford another mechanism for controlling cytokine signals. In addition to the binding of dimers versus tetramers, GAS motifs can be clustered throughout enhancer regions to form STAT-based superenhancers, which can serve to mediate the rapid and high inducibility of target genes (Li et al., 2017). The ability to identify these STAT-based superenhancers was greatly facilitated by chromatin immunoprecipitation coupled to massively parallel sequencing (ChIP-Seq) to identify cytokine-induced STAT binding sites throughout the genome. In conjunction with STAT knockout mice, it became possible to assess with new precision the direct impact of STATs on transcriptomic and epigenomic changes. These types of studies have provided a new view of cytokine-induced and regulated events (Li and Leonard, 2018). For example, these studies have revealed the functional cooperation of STAT3 and IRF4 in IL-21 signaling (Kwon et al., 2009) and additional complex sites known as AP1-IRF4 composite elements (AICEs) that control IL-21 signaling in T cells (Li et al., 2012), as well as genome-wide binding competition between GM-CSF-induced STAT5 and IL-21-induced STAT3 (Wan et al., 2013), opposing functions of STAT3 and STAT5 in *Il17a* and *Il17f* regulation (Yang et al., 2011), and competition between BLIMP1 and STAT5 (Poholek et al., 2016). Moreover, in the context of B cell acute lymphoblastic leukemia, STAT5 can antagonize the effects of NF-κB and Ikaros with high active STAT5 relative to these other factors, resulting in aggressive disease (Katerndahl et al., 2017).

Interestingly, there are two nearly identical STAT5 genes, *STAT5A* and *STAT5B*, which are highly conserved in human and mouse and encode proteins more than 90% identical at the amino acid level (Lin et al., 1996; Liu et al., 1995). Both

STAT5A and STAT5B are activated by IL-2, IL-7, IL-9, and IL-15. Of note, the abundance of total STAT5 protein is a critical factor in terms of functional specificity (Villarino et al., 2016; Villarino et al., 2017), but there also are important differences between STAT5A and STAT5B, which diverge at the C-terminal transactivation domain, with STAT5B having a stronger transactivation domain and representing the more important/dominant STAT5 protein for NK cell development (Imada et al., 1998; Nakajima et al., 1997). Thus, both the total level of STAT5 proteins and the specific amount of STAT5A versus STAT5B may be important, depending on the cell type and differentiation state, an area for additional investigation. STATs are also critical drivers of the active enhancer landscape and creation of superenhancer architecture, with STAT5 mediating IL-2-induced chromatin looping at superenhancers to preferentially regulate highly inducible genes (Li et al., 2017; Vahedi et al., 2015, 2012).

γ_c Family Cytokines and Translational Advances

At least four of the γ_c family cytokines have been reported to have anti-cancer activity: IL-2, IL-9, IL-15, and IL-21. The efficacy of IL-2 for the treatment of some forms of cancer has been established since the 1980s, with subsequent approval of IL-2 for the treatment of melanoma and renal cancer (Rosenberg, 2014). IL-2 is also used for therapeutic expansion of tumor infiltrating lymphocytes (TILs), which can then be adoptively transferred back into patients (Dudley et al., 2002). Importantly, however, T cells derived from tumors are often dysfunctional or "exhausted" (Lee et al., 1999), and low-dose IL-2 administration can enhance $CD8^+$ T cell responses. Indeed, in mouse models of chronic viral infections, virus-specific $CD8^+$ T cells express inhibitory receptors (Barber et al., 2006). The combination of IL-2 treatment with blockade of the PD-1 inhibitory pathway enhanced virus-specific $CD8^+$ T cell responses and decreased viral load (West et al., 2013). Additionally, terminally differentiated T cells may not be the most effective T cell product, and cells that retain stem-like properties are preferential for cell-based cancer therapies (Crompton et al., 2014). In this regard, exposure to IL-7, IL-15, or IL-21 during expansion protocols has been shown to preserve a less-differentiated state and improve *in vivo* persistence (Hinrichs et al., 2008; Russo et al., 2018; Santegoets et al., 2013; Xu et al., 2014). IL-7 has been evaluated to promote lymphoid reconstitution in the setting of stem cell transplant, but precisely how to use this and other γ_c cytokines most effectively are still under study (Mackall et al., 2011; Moutuou et al., 2018).

Because of the critical role for IL-2 in Treg cell homeostasis, IL-2 has also been considered in the treatment of autoimmunity (Sharabi et al., 2018). Administration of IL-2 to mice (alone or as an IL-2–anti-IL-2 antibody complex to increase its bioavailability) and humans can promote the expansion Treg cells in the periphery, and low dose IL-2 has been tested in hepatitis C-related vasculitis, graft-versus-host disease, and multiple autoimmune diseases, resulting in increased Treg cells (Koreth et al., 2011; Rosenzwajg et al., 2019; Saadoun et al., 2011; von Spee-Mayer et al., 2016); multiple trials are underway in subjects with autoimmune disease (NCT01988506, NCT03312335, NCT02424396, NCT02411253).

Interestingly, IL-21 has anti-cancer activity (Spolski and Leonard, 2014) and has been used in adoptive transfer experiments as noted above. IL-15 has been considered extremely promising as an anti-cancer agent, but some studies have indicated that it may be of greatest benefit in settings where IL-15 was combined with other approaches, including, for example, agents to relieve checkpoints, combination with anti-cancer monoclonal antibodies to augment ADCC, or in combination with agonistic anti-CD40 antibodies (Waldmann, 2018). IL-15 and IL-2 exhibit a range of differences, particularly *in vivo*, and antibody-bound IL-15 but not IL-2 could protect mice from cerebral malaria (Burrack et al., 2018).

A range of modified cytokines and newer molecules with therapeutic potential represent other ways of fine-tuning cytokine responses. As noted above, the interaction of IL-2 with IL-2Rα then allows its efficient interaction with IL-2Rβ. Various novel molecules have been designed that can affect signaling, including "superkines" and antagonists. A designer superkine for IL-2, also denoted as "super-2" or "H9," no longer needs IL-2Rα to efficiently interact with IL-2Rβ (Levin et al., 2012). As compared to wild-type IL-2, H9 has higher binding to cells with intermediate affinity receptors (e.g., resting T cells and NK cells) and has augmented activity on those cells (Figure 4). Moreover, H9 was then used as a platform for additional mutations that inhibited binding to γ_c and thus heterodimerization of IL-2Rβ and γ_c, resulting in potent antagonists of IL-2 and IL-15 signaling such as H9-RETR that could out-compete the endogenous cytokines (Mitra et al., 2015). Importantly, H9-RETR could block the *ex vivo* proliferation of cells from patients with the chronic-smoldering form of adult T cell leukemia as well as in a model of graft-versus-host disease (Mitra et al., 2015). It is possible that molecules that attenuate but do not abrogate the interaction of IL-2 with γ_c might exhibit partial agonism, with interesting biological effects. In addition to such partial agonists, an exciting "orthogonal" approach was used in which IL-2Rβ was mutated so that it could no longer recognize wild-type IL-2, and then a mutant IL-2 was created such that it could recognize the mutant but not wild-type IL-2Rβ (Sockolosky et al., 2018). By introducing the orthogonal IL-2Rβ into recipient target cells of interest, only those cells could respond to the orthogonal IL-2. Such an approach was effective in a mouse tumor model and might have promise for clinical therapy as well.

The activity of IL-2 also can be modulated by monoclonal antibodies, and the first blocking antibody for human therapy was daclizumab (Figure 4), a humanized form of anti-Tac monoclonal antibody to IL-2Rα (Berkowitz et al., 2014). Approved by the FDA for renal allograft rejection and the treatment of patients with relapsing forms of multiple sclerosis, the antibody was subsequently voluntarily withdrawn because of reports of encephalitis. Both the efficacy and adverse events associated with targeting IL-2Rα are likely indicative of the complex actions of IL-2 in terms of promoting and limiting immune responses.

Interestingly, in mouse studies, it was observed that the half-life of IL-2 can be prolonged by the addition of either of two "agonistic" monoclonal antibodies to IL-2, S4B6 or JES6 (Figure 4). Whereas S4B6 sterically blocks the interaction of IL-2 with IL-2Rα, stabilizing IL-2-IL-2Rβ interaction and favoring the expansion of cells with low expression of IL-2Rα (Boyman et al., 2006), JES6 sterically blocks the interaction of IL-2 with IL-2Rβ, resulting in preferential stimulation of IL-2Rα^{high} cells, including Treg cells (Boyman et al., 2006). Importantly, a human mAb similar to JES6, denoted F5111.2, has been identified

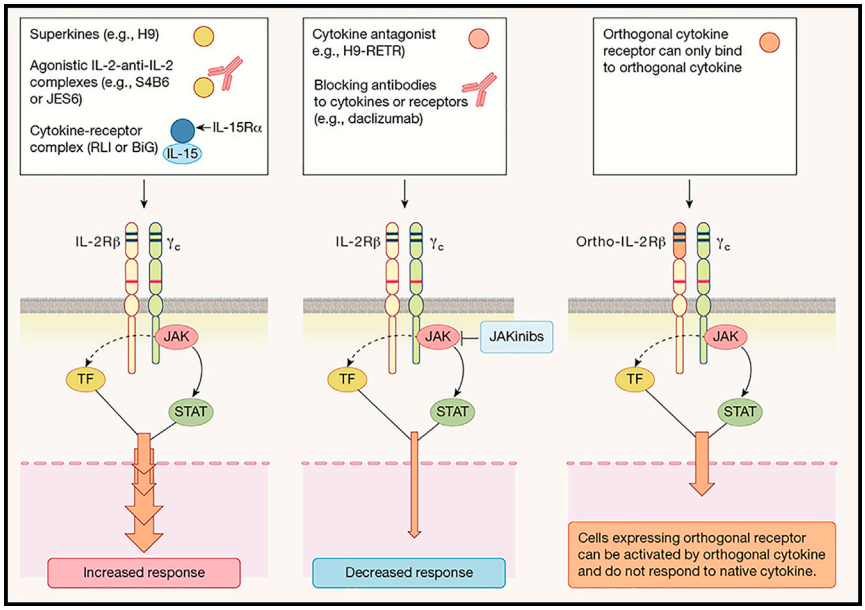

Figure 4. Approaches to Modulating the Actions of IL-2 or IL-15

On the left are shown IL-2 superkine (H9), anti-IL-2 antibody complexed with IL-2 (S4B6-IL-2 or JES6-IL-2), and IL-15Rα-IL-15 complex (RLI or BiG) enhancing the action. In the middle are shown IL-2 antagonist (H9-RETR), blocking antibodies daclizumab, or JAK inhibitors suppressing the action. On the right are shown cells expressing orthogonal IL-2Rβ only responding to orthogonal IL-2.

(Trotta et al., 2018), with potential benefit for the treatment of autoimmune disease. It maintains IL-2 in a conformation that results in preferential STAT5 phosphorylation of Treg cells *in vitro* and selective expansion of the cells *in vivo*. When complexed with human IL-2, F5111.2 induced remission of type 1 diabetes in the NOD mouse model, reduced disease severity in a model of experimental autoimmune encephalomyelitis, and protected mice against xenogeneic graft-versus-host disease. Because F5111.2 is a human mAb, it may hold potential therapeutic promise (Trotta et al., 2018).

Dupilumab is an anti-IL4Rα mAb that blocks both IL-4 and IL-13 signaling approved for the treatment of moderate to severe asthma and atopic dermatitis (Castro et al., 2018; Rabe et al., 2018; Simpson et al., 2016). Transient eosinophilia has been seen in dupilumab-treated patients. Curiously, both drug-induced alopecia and hair regrowth in patients with alopecia areata have been reported. The ability of IL-4 to limit type 1 and type 3 immune responses might explain the increase in autoimmune disease; conversely, with dupilumab the improvement in alopecia leads one to speculate that in some cases IL-4 is the driver of this disease. Interestingly, an antibody to IL-2Rβ, which targets IL-15 as well as IL-2, has shown efficacy in a preclinical model of vitiligo (Richmond et al., 2018).

Besides novel cytokines and antibodies, single-chain ligand-receptor molecules have distinctive properties. These have been generated for both IL-15 and IL-2. As noted above, IL-15 signals primarily in *trans*. A single chain IL-15/IL-15Rα fusion protein, denoted "RLI," was designed that can act as a super-agonist to preferentially expand memory phenotype $CD8^+CD44^{hi}$ T cells but not Treg or $CD4^+$ T cells, with augmented anti-tumor activity (Desbois et al., 2016) (Figure 4). Interestingly, however, RLI is relatively ineffective on exhausted T cells and accordingly is most effective when combined with anti-PDL1. Correspondingly to RLI, a single-chain IL-2/IL-2Rα agonist has also now been generated (Ward et al., 2018). Low-dose IL-2 represents an immunotherapy to selectively expand Treg cells to promote tolerance in patients with autoimmunity, and analogous to RLI, this IL-2-IL-2Rα fusion protein had greater *in vivo* efficacy for Treg expansion and control of autoimmunity than recombinant IL-2 (Ward et al., 2018). Biochemical and functional studies support a model in which IL-2 interacts with CD25 in *trans* to form inactive head-to-tail dimers that slowly dissociate into an active monomer. *In vivo*, the fusion protein is long-lived and selectively stimulates Treg cells. In female NOD mice, it increased Treg cells within the pancreas and reduced the instance of spontaneous diabetes, suggesting the potential for clinical development for use in autoimmunity or other disorders of an overactive immune response (Ward et al., 2018).

IL-2 and IL-15 exhibit different biological roles *in vivo* (Kennedy et al., 2000; Sadlack et al., 1994; Waldmann, 2006) yet share IL-2Rβ and γ_c and can induce similar gene expression patterns *in vitro* (Ring et al., 2012). Accordingly, they are both blocked by agents such as H9-RETR (Mitra et al., 2015), as described above. Recently, a novel computational approach took advantage of the knowledge of the structures for both IL-2 and IL-15 and how they bind to IL-2Rβ/γ_c receptors to *de novo* design a mimic of IL-2 and IL-15, denoted Neoleukin-2/15 (Neo-2/15) (Silva et al., 2019). This synthetic molecule retains the binding surface for IL-2Rβ/γ_c receptors but is very stable and binds with much higher affinity than either IL-2 or IL-15, without requiring either IL-2Rα or IL-15Rα, and it exhibited better antitumor activity than IL-2 in mouse models, was less toxic, and lacked detectable immunogenicity. It will be interesting to determine whether Neo-2/15 will be effective in clinical trials in humans. This type of approach may allow the design and production of novel molecules for both research and therapeutic purposes.

Chimeric antigen receptor (CAR) T cells represent an area of very active investigation. These cells are typically expanded in IL-2, but as indicated above for TILs, other cytokines may also have utility. Mimicking the effect of cytokines, a CD19 CAR was constructed to comprise a truncated cytoplasmic domain from IL-2Rβ that includes a STAT-binding motif, together with the more conventional TCR zeta and CD28 co-stimulatory domains (Kagoya et al., 2018). Given the toxicity associated with systemic IL-2, it has also been proposed that arming CAR T cells with IL-15 might retain beneficial effects while minimizing toxicity (Hurton et al., 2016).

JAK Inhibitors

Another major class of therapeutic molecules is JAK inhibitors. The discovery of *JAK3*-deficient SCID (Russell et al., 1994) revealed the critical role of JAK3 *in vivo* in humans. In *JAK3*-deficient SCID patients, analogous to the situation in XSCID, IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 were defective in their signaling, and it was proposed that JAK3 inhibitors would be immunosuppressive (Russell et al., 1994). Indeed, tofacitinib, which most potently inhibits JAK3 but also can inhibit JAK1 and JAK2 (Changelian et al., 2003), is approved by multiple agencies around the world for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis. Baricitinib, a JAK1/JAK2 inhibitor, was the second jakinib approved for RA. Ruxolitinib is another JAK1/JAK2 inhibitor approved for the treatment of myeloproliferative neoplasms based on the identification of *JAK2* gain-of-function mutations in polycythemia vera and related disorders (Kralovics et al., 2005).

The success of first generation jakinibs has spawned the development of more selective inhibitors that target individual JAKs. Because first generation jakinibs often target multiple JAKs, a broader range of cytokines is inhibited, with adverse effects including cytopenias, venous thromboembolism, hyperlipidemia, and infection. The hope is that more selective inhibitors will retain efficacy but have fewer side effects, and late-phase clinical trials suggest that selectivity can be achieved without loss of efficacy and with reduction in potential side effects like anemia and thrombocytopenia (Mease et al., 2018; O'Shea and Gadina, 2019; van der Heijde et al., 2018). A JAK3 selective covalent inhibitor, denoted JAK3i, was developed that interestingly was more selective for the later second wave of IL-2-induced STAT5 phosphorylation, whereas tofacitinib inhibited both waves (Smith et al., 2016). Another selective JAK3 inhibitor, PF-06651600, is also effective at inhibiting signaling by γ_c family cytokines and was shown to be effective in diminishing disease pathology in a rat model of adjuvant-induced arthritis and mouse experimental autoimmune encephalomyelitis (Thorarensen et al., 2017). In a phase 2a randomized double-blind, placebo-controlled trial, this inhibitor was reported to have efficacy for the treatment of alopecia areata (NCT02974868, NCT03732807); it is also being tested in rheumatoid arthritis, ulcerative colitis, and Crohn's disease (NCT02969044, NCT02958865, NCT03395184). Another study has led to the identification of cyanamide-based JAK3 covalent inhibitors (Casimiro-Garcia et al., 2018). Peficitinib, another Jakinib that appears to have moderate selectivity toward JAK3 but also can inhibit JAK1, JAK2, and TYK2, is being studied in rheumatoid arthritis and ulcerative colitis (Genovese et al., 2017; Sands et al., 2018). In principle, STAT proteins should be reasonable therapeutic targets as well.

Concluding Remarks

Each of the γ_c family cytokines was discovered in a distinctive context—related to T cells (IL-2), B cells (IL-4), thymocytes and pre-B cells (IL-7), T cells and mast cells (IL-9), NK cells (IL-15), and as an "orphan" (IL-21) —but they are linked not only by their sharing γ_c and being inactivated in patients with XSCID but also by their each activating JAK1 and JAK3. Fascinating biology continues to be learned, with elucidation of new shared or similar actions as well as contexts in which they can compete or have opposing actions, collectively modulating the development, survival, and/or differentiation of multiple cellular lineages, as well as on previously unappreciated cellular targets. Moreover, new insights into how cytokines achieve specificity undoubtedly will continue to be learned, including more about combinatorial actions of JAKs and STATs and also how these signaling pathways coordinate with others such as PI 3-kinase and ERK-dependent signaling pathways. Furthermore, the roles of these cytokines in modulating metabolism and gene regulation, including by influencing chromatin structure, are areas of excitement. Not only have great therapeutic strides been made such as precise diagnosis for XSCID, *JAK3*-deficient SCID, and *IL7R*-deficient SCID, gene therapy for XSCID, and the development of JAK inhibitors, but a great deal is being learned about mechanisms for augmenting, blocking, and balancing the actions of γ_c family cytokines. Designer cytokines including antagonists, partial agonists, and antibodies with distinctive properties are now being evaluated and some of these undoubtedly will realize therapeutic potential for allergy, immunodeficiency, autoimmunity, or cancer. It can be predicted that advances will continue to be made in achieving the effective modulation of actions of Treg versus T effector cells. In summary, the study of γ_c family cytokines has taught us a phenomenal amount about mammalian biology, signaling, and gene regulation, and it seems certain that new basic science surprises and novel therapeutics will continue to evolve out of research on this exciting family of cytokines.

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DECLARATION OF INTERESTS

W.J.L. is an unpaid member of the Scientific Advisor Committee of Medicenna. He has patents or is an inventor on patent applications related to γ_c family cytokines and antagonists/partial agonists. J.O'S. and W.J.L. hold a US Patent "Janus kinases and identification of immune modulators." J.O'S. and Pfizer hold a NIH Cooperative Research and Development Agreement.

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