The Common Cytokine Receptor γ Chain Family of Cytokines

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Interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21 form a family of cytokines based on their sharing the common cytokine receptor γ chain (γc), which was originally discovered as the third receptor component of the IL-2 receptor, IL-2Rγ. The *IL2RG* gene is located on the X chromosome and is mutated in humans with X-linked severe combined immunodeficiency (XSCID). The breadth of the defects in XSCID could not be explained solely by defects in IL-2 signaling, and it is now clear that γc is a shared receptor component of the six cytokines noted above, making XSCID a disease of defective cytokine signaling. Janus kinase (JAK)3 associates with γc, and *JAK3*-deficient SCID phenocopies XSCID, findings that served to stimulate the development of JAK3 inhibitors as immunosuppressants. γc family cytokines collectively control broad aspects of lymphocyte development, growth, differentiation, and survival, and these cytokines are clinically important, related to allergic and autoimmune diseases and cancer as well as immunodeficiency. In this review, we discuss the actions of these cytokines, their critical biological roles and signaling pathways, focusing mainly on JAK/STAT (signal transducers and activators of transcription) signaling, and how this information is now being used in clinical therapeutic efforts.

Interleukin (IL)-2 is the prototype member of the γ chain (γc) family of cytokines. Initially identified as an activity present in the conditioned medium from normal human lymphocytes cultured with phytohemagglutinin (PHA) that could support the long-term in vitro culture of normal human T cells, IL-2 was initially known as T-cell growth factor (TCGF) (Morgan et al. 1976), but then subsequently renamed as IL-2 (Mizel and Farrar 1979). The cloning of complementary DNAs (cDNAs) encoding human (Taniguchi et al. 1983) and mouse (Kashima et al. 1985) IL-2 and the production of recombinant IL-2 allowed investigators to discover additional actions of IL-2 on T, B, and natural killer (NK) cells. Subsequent cloning of the human IL-2 receptor α chain (Leonard et al. 1984; Nikaido et al. 1984; Cosman et al. 1984) revealed that it had a short cytoplasmic tail with only 13 amino acids, making it unlikely to transduce IL-2 signals. This led to the search for additional IL-2 receptor components and the identification of IL-2Rβ (Sharon et al. 1986; Tsudo et al. 1986; Dukovich et al. 1987; Teshigawara et al. 1987) and subsequently IL-2Rγ (Takeshita et al. 1990; Saito et al. 1991) with eventual cloning of cDNAs encoding IL-2Rβ (Hatakeyama et al. 1989) and IL-2Rγ (Takeshita et al. 1992).

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IL2RG was localized to the X chromosome at Xq13, the disease locus for X-linked severe combined immunodeficiency ([XSCID], also known as SCIDX1), which then led to the discovery that *IL2RG* mutations indeed cause XSCID (Noguchi et al. 1993b), a disease characterized by the absence of T and NK cells with nonfunctional B cells (Fischer et al. 2005). This finding was immediately important as it allowed earlier and more precise diagnosis of XSCID and also paved the way for successful gene therapy (Leonard 2001; Hacein-Bey-Abina et al. 2002). However, there were other major scientific implications of the XSCID discovery as well. Given that T- and NK-cell development was normal in *IL2*-deficient patients (Pahwa et al. 1989; Weinberg and Parkman 1990) and *Il2* knockout (KO) mice (Schorle et al. 1991), it was hypothesized that IL-2Rγ was a shared receptor component for other cytokines as well (Noguchi et al. 1993b), leading to the eventual demonstration that IL-2Rγ is indeed a shared receptor component for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 (Rochman et al. 2009). Thus, it was renamed as the common cytokine receptor γc (Noguchi et al. 1993a; Russell et al. 1993), and cytokines using γc are now known as γc family cytokines. The inactivation of signaling by six cytokines in XSCID underscores that it is indeed a disease of defective cytokine signaling (Leonard 1996).

γc family cytokines all share similar three-dimensional structural features and are four α-helix-bundle type I cytokines (Bazan 1990). Although all of these cytokines were initially discovered based on specific actions for either the development or function of T, B, and NK cells (except for IL-21, which was identified based on its binding to an orphan receptor, as will be discussed below), we now know that each cytokine is pleiotropic with broad roles in the development of immune cells or related to immune responses, including some actions beyond the immune systems.

In this review, we discuss the molecular and cellular biology of this family of cytokines, their signaling pathways, actions, and the interplay among them during the development of immune cells and immune responses. We will also discuss the emerging promising approaches for rationally modulating the actions of these cytokines for treating patients with immunodeficiency, autoimmune disorders, infectious diseases, allergic conditions, and malignancies. Needless to say, the number of studies performed and wealth of information on γc family cytokines is enormous, with a huge number of publications in the field (see Fig. 1 for the number of publications just in the period from 2010 to 2017). We have necessarily been selective in our discussion, trying to highlight important early studies as well as some of the exciting progress in this field, and apologize in advance for being unable to cite large numbers of superb studies on these cytokines. However, many other articles in this collection also cover aspects of γc family cytokines, and the reader is directed to those as well.

γc FAMILY CYTOKINES—AN OVERVIEW

γc family cytokines collectively mediate biological actions on a range of immune cells (Fig. 2). $CD4^+$ T cells are the main producers of IL-2 in response to T-cell receptor (TCR) stimulation, whereas $CD8^+$ T cells, NK cells, and NK T (NKT) cells can also produce IL-2 but at much lower levels (Liao et al. 2013). Although IL-2 was initially discovered as a T-cell growth factor

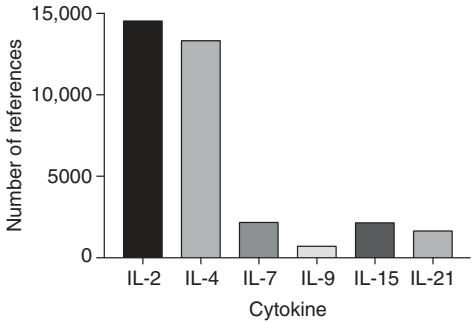

Figure 1. PubMed search results of γ chain (γc) family cytokines between 2010 and 2017. The search was performed using EndNote X7.7.1 with the key words IL-2 or interleukin 2, IL-4 or interleukin 4, IL-7 or interleukin 7, IL-9 or interleukin 9, IL-15 or interleukin 15, and IL-21 or interleukin 21, respectively, under Abstract, 2010–2017 under Year, and English under Language.

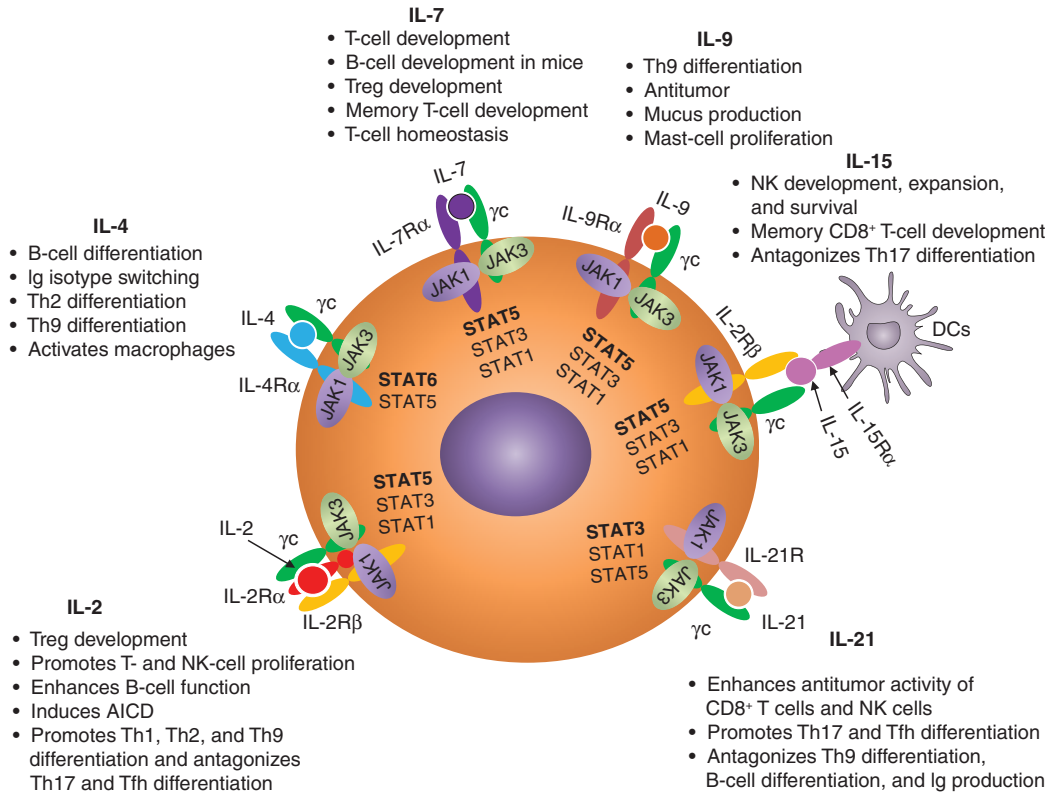

Figure 2. Schematic of γ chain (γc) family cytokines and their receptors. Shown are how Janus kinase (JAK)1 and JAK3 associate with each receptor, the signal transducers and activators of transcription (STAT) proteins activated by each cytokine, and the major actions of these cytokines on the development and function immune cells. The STAT proteins predominantly activated by each cytokine are in bold. IL, Interleukin; Th, T helper; Tfh, T follicular helper; Treg, regulatory T; NK, natural killer; Ig, immunoglobulin; DCs, dendritic cells; AICD, activation-induced cell death.

(Morgan et al. 1976), it can also promote the growth and differentiation of B cells that are stimulated by anti-immunoglobulin (Ig)M or CD40 ligand (Armitage et al. 1995) and promote NK-cell proliferation and enhance NK-cell cytotoxicity (Siegel et al. 1987). In addition to its potent proliferative activity for T cells in vitro, IL-2 can induce activation-induced cell death (AICD) (Lenardo 1991) of $CD4^+$ T cells, which is important for the maintenance of peripheral self-tolerance. In addition to its actions as a T-cell growth factor, an essential role of IL-2 in vivo is to promote the development and maintenance of regulatory T (Treg) cells whose suppressive activity is vital to control pathologic inflammatory responses (Malek et al. 2002). In addition, IL-2 promotes the differentiation of T helper (Th)1 (Liao et al. 2011), Th2 (Zhu et al. 2003; Cote-Sierra et al. 2004; Liao et al. 2008), and Th9 (Liao et al. 2014) cells, whereas it suppresses the differentiation of Th17 (Laurence et al. 2007; Liao et al. 2011) and T follicular helper (Tfh) (Ballesteros-Tato et al. 2012; Johnston et al. 2012; Oestreich et al. 2012) cells. As is discussed below, IL-2 has been extensively used as an anticancer agent and for modulating the immune responses.

IL-4 was first identified as a B-cell differentiation factor(s) produced by T cells, which induces Ig isotype switch (Howard et al. 1982; Isakson et al. 1982). IL-4 is a signature cytokine for Th2 responses that are essential for the con-

trol of extracellular parasites infection and contribute to allergic reactions (Paul 2015). IL-4 also induces the generation of M2 (M-IL-4) macrophages, which are essential for macrophage-mediated control of infection with the protozoan *Trypanosoma cruzi* (Wirth et al. 1989). In addition, IL-4 promotes the generation of IL-9$^+$ IL-10$^+$ T cells in the presence of transforming growth factor (TGF)-β, which are subsequently designated as Th9 cells and suppress TGF-β-induced Foxp3$^+$ Treg-cell generation (Dardalhon et al. 2008). With its key roles in mediating allergic responses, modulating IL-4 activity is now of considerable therapeutic interest (see below).

In contrast to the production of IL-2 and IL-4 by T cells, IL-7 was discovered as a stromal-cell-derived factor that supported the growth of pre-B cells (Namen et al. 1988; Goodwin et al. 1989). IL-7 signaling also plays an essential, nonredundant role in the development of T cells in humans (Puel et al. 1998; Giliani et al. 2005) and of both B and T cells in mice (Peschon et al. 1994; von Freeden-Jeffry et al. 1995). Unlike other γc family cytokines, the expression level of IL-7 is relatively stable. IL-7 by itself does not promote proliferation of naïve T cells but is essential to ensure sustained expression of antiapoptotic proteins BCL2 and MCL1, and thereby long-term in vivo survival of T cells (Rathmell et al. 2001; Opferman et al. 2003; Sprent and Surh 2011). To maintain long-term memory-T-cell survival, IL-7-induced expression of the glycerol channel aquaporin 9 in antigen-specific memory CD8$^+$ T cells is essential for IL-7-directed glycerol uptake, and this is required for triglyceride synthesis and lipid storage to maintain the longevity of memory CD8$^+$ T cells after viral clearance (Cui et al. 2015). Although IL-7 is not required for the development of conventional NK cells (He and Malek 1996; Puel et al. 1998), it plays a critical role in the homeostasis of thymic NK cells (Vosshenrich et al. 2006). Interestingly, either osteoblast ablation or deletion of *Il7* in osteoblasts of adult mice results in significantly lower numbers of common lymphoid progenitors (CLPs) without affecting hematopoietic stem-cell numbers, and administration of IL-7 can restore normal numbers of CLPs (Terashima et al. 2016).

IL-9 was discovered as a T-cell-derived growth factor for certain Th-cell clones in the absence of either antigen or antigen-presenting cells (APCs) (Uyttenhove et al. 1988; Schmitt et al. 1989) and then shown to also be a growth factor for bone marrow mast cells (Hultner et al. 1990). Although IL-9 was initially considered to be a Th2 cytokine (Gessner et al. 1993), it is now recognized as the signature cytokine for Th9 cells, whose differentiation is induced when naïve CD4$^+$ T cells are cultured with IL-2, IL-4, and TGF-β (Schmitt et al. 1994) or when Th2 cells are cultured with TGF-β (Dardalhon et al. 2008; Veldhoen et al. 2008). IL-9 can enhance IL-4-induced IgE and IgG production (Dugas et al. 1993; Petit-Frere et al. 1993), supports innate lymphoid-cell (ILC) survival, and induces cytokine production by these cells (Wilhelm et al. 2011; Turner et al. 2013). IL-9 can also be produced by Th17 cells and can promote the expansion of these cells (Elyaman et al. 2009; Nowak et al. 2009). Expression of IL-9 in NKT cells can be enhanced by IL-2 but not IL-15 (Lauwerys et al. 2000). As discussed below, IL-9 also has anticancer activity.

IL-15 was codiscovered as a T-cell growth factor activity present in the supernatants from a simian kidney epithelial line CV-1/EBNA (Grabstein et al. 1994) and HTLV-1-transformed HUT-102 leukemia cells (Bamford et al. 1994; Burton et al. 1994). Although many different cell types can express IL-15 messenger RNA (mRNA), IL-15 protein is mainly produced by dendritic cells (DCs) and monocytes in response to Toll-like receptor (TLR) activation and binds to receptors on these cells (Waldmann 2006). IL-15 plays critical roles in the development and/or maintenance of memory CD8$^+$ T cells and preferentially can expand central memory phenotype T cells in vivo, with *Il15*$^{-/-}$ or *Il15ra*$^{-/-}$ mice having profound loss of memory phenotype CD8$^+$ T cells, intestinal intraepithelial lymphocytes, NKT cells, and NK cells (Lodolce et al. 1998; Kennedy et al. 2000). Although IL-2 and IL-15 both share IL-2Rβ and γc and activate the same Janus kinase (JAK)1/JAK3/signal transducers and activators of transcription (STAT)5 pathway, IL-15 can inhibit IL-2-induced AICD, and the addition of blocking

antibodies to IL-15 restores IL-2-induced AICD of these $CD4^+$ T cells (Marks-Konczalik et al. 2000). As discussed below, IL-15 is under active evaluation as an anticancer agent.

IL-21 was identified by expression cloning (Parrish-Novak et al. 2000) as the ligand for a novel "orphan" type I cytokine receptor, originally also denoted as "novel interleukin receptor" (NILR) in addition to the IL-21R (Ozaki et al. 2000; Parrish-Novak et al. 2000). Interestingly, the genes encoding IL-2 and IL-21 are adjacent on human chromosome 4q27 and mouse chromosome 3. IL-21 has significant homology with IL-2, IL-4, and IL-15 (Parrish-Novak et al. 2000), is expressed by Tfh, NKT, Th1, Th2, and Th17 cells, is the key γc family cytokine that contributes to Tfh-cell differentiation in vivo, and it can also promote Th17 differentiation (reviewed in Spolski and Leonard 2014). Although IL-21 alone does not show proliferative activity for either B or T cells, it can potentiate the proliferation of human B cells stimulated by anti-CD40 (Parrish-Novak et al. 2000). IL-21 plays complex roles in the differentiation and function of B cells. For example, IL-21 can promote B-cell proliferation in the presence of anti-CD40 or anti-IgM, whereas it can induce death of resting B cells or B cells stimulated with lipopolysaccharide (LPS) or CpG (Mehta et al. 2003; Jin et al. 2004; Ozaki et al. 2004). IL-21 transgenic mice or wild-type (WT) mice overexpressing IL-21 by hydrodynamic-based gene delivery of IL-21 plasmid DNA show increased numbers of immature B cells, memory B cells, and plasma cells, with elevated serum IgG and IgM levels (Ozaki et al. 2004). IL-21, together with IL-4, plays a vital role in B-cell differentiation and Ig production (Ozaki et al. 2002). In addition to its direct role in the inhibition of Treg differentiation by suppressing Foxp3 expression (Nurieva et al. 2007), IL-21 can diminish Treg homeostasis through inhibiting IL-2 production by T cells (Attridge et al. 2012). IL-21 can also increase the numbers of $CD56^+$ $CD16^{high}$ human NK cells generated from $CD34^+$ human hematopoietic progenitor cells cultured with IL-15 and Flt3 ligand (FLt3L) (Parrish-Novak et al. 2000). IL-21 by itself does not significantly promote the growth of naïve or memory $CD8^+$ T cells, but it can greatly synergize with IL-15 and to a lesser extent with IL-7, but not with IL-2, to enhance the proliferation of these cells (Zeng et al. 2005). These cells develop normally in mice lacking IL-21R, indicating that this cytokine is not required for their development but rather contributes to their expansion. As discussed below, IL-21 is a potent inducer of IL-10 and can drive the production of regulatory B cells and, moreover, IL-21 promotes autoimmune disease and has anticancer activity.

RECEPTORS USED BY γc FAMILY CYTOKINES

Most of the receptors for γc family cytokines (IL-2Rβ, IL-4Rα, IL-7Rα, IL-9Rα, and IL-21R, and γc) are type I cytokine receptors and share an approximately 200-amino-acid-long cytokine-binding homology region (CHR) consisting of two fibronectin type III (FNIII) domains connected by a linker (Bazan 1990). These proteins have four conserved cysteine residues at the N-terminal domain, which can form interstrand disulfide bonds, and a WSXWS (tryptophan-serine-any amino acid-tryptophan-serine) motif near the C terminus (Bazan 1990; Wang et al. 2009). IL-2Rα and IL-15Rα do not contain the CHR module and instead have "Sushi" domains that mediate ligand binding but with very different affinities (Rickert et al. 2005; Lorenzen et al. 2006). Interestingly, in addition to sharing γc, IL-2 and IL-15 receptors additionally share IL-2Rβ (Bamford et al. 1994; Giri et al. 1994).

IL-2 receptors are expressed mainly by lymphoid cells. In the absence of stimulation, IL-2Rα is mainly expressed on Treg cells and not expressed on naïve T cells, but it is potently induced on T-cell activation (Leonard et al. 1985; Malek and Castro 2010; Liao et al. 2013). IL-2Rβ and γc are constitutively expressed on some resting T cells, especially NK cells, $CD8^+$ T cells, B cells, macrophages, monocytes, and DCs. Like IL-2Rα, IL-2Rβ can be further induced on stimulation of these cells, either by antigen or by IL-2. Three IL-2 receptor chains, IL-2Rα, IL-2Rβ, and IL-2Rγ, form three different types of IL-2 receptors, binding IL-2 with low affinity (IL-2Rα only, $K_d \approx 10$ nM), intermediate affinity (IL-2Rβ + IL-2Rγ, $K_d \approx 1$ nM), and high affinity (IL-2Rα

+ IL-2Rβ + IL-2Rγ, $K_d \approx 10$ pM) (Malek and Castro 2010; Liao et al. 2013). Although IL-2Rα and IL-2Rβ together can form pseudo-high-affinity IL-2 receptors ($K_d \approx 100$ pM), they cannot transduce IL-2 signals because of the lack of γc (Arima et al. 1992). The intermediate-affinity and high-affinity IL-2 receptors are the functional receptors (Malek and Castro 2010; Liao et al. 2013). Although IL-2 mainly signals via IL-2 receptor chains coexpressed on the same cell (*cis* signaling), antigen-specific $CD25^+$ mature DCs that lack IL-2Rβ can *trans*-present IL-2 to $CD25^-$ T cells, which can be blocked by declizumab, a humanized antihuman CD25 antibody (Wuest et al. 2011).

Unlike IL-2 receptor chains, IL-4Rα is expressed on both lymphohematopoietic and non-lymphohematopoietic cells, with ~300 IL-4 binding sites on resting lymphocytes and 10-fold more upon activation (Paul 2015). IL-4 receptors are also present on macrophages and mast cells (Ohara and Paul 1987). There are two types of IL-4Rs: type I IL-4 receptors on lymphohematopoietic cells are composed of IL-4Rα and γc (Kondo et al. 1993; Russell et al. 1993), whereas in nonhematopoietic cells, type II IL-4 receptors comprise IL-4Rα plus IL-13Rα1, which is also the functional receptor for IL-13 (Aman et al. 1996). In reconstitution experiments using COS-7 cells, IL-4 binds to IL-4Rα with high-affinity ($K_d \approx 266$ pM) and in the presence of γ_c, the binding affinity is further increased ($K_d \approx 79$ pM) (Russell et al. 1993). The direct interaction of the IL-4Rα chain with γc is very weak (K_d in the μM range) (LaPorte et al. 2008).

The IL-7 receptor consists of IL-7Ra and γc (Noguchi et al. 1993a; Kondo et al. 1994), and IL-7Ra) is also a component of the receptor for thymic stromal lymphopoietin (TSLP), in that context cooperating with the direct TSLP-binding protein, TSLPR (Pandey et al. 2000; Park et al. 2000). IL-7Rα is expressed on both hematopoietic cells and cells of nonlymphoid origin (Jiang et al. 2005). The expression of IL-7Rα is dynamically regulated during lymphocyte development and in response to TCR or cytokine stimulation, and IL-7Rα regulation is the major mechanism for regulating IL-7 responses (Mazzucchelli and Durum 2007). IL-7Rα can be induced by FLT3 ligand, glucocorticoids, type I interferons (IFNs), and tumor necrosis factor (TNF), whereas it is suppressed by two γc family cytokines, IL-2 and IL-7, as well as by IL-6 (Xue et al. 2002; Mazzucchelli and Durum 2007). Both high-affinity ($K_d \approx 65$ pM) and low-affinity ($K_d \approx 100$ nM) IL-7 receptors can be detected on peripheral blood lymphocytes, and a reconstitution experiment in COS-7 cells showed that IL-7 binds to IL-7Rα with an intermediate affinity ($K_d \approx 250$ pM) that is enhanced to high affinity when γc is present (Noguchi et al. 1993a).

IL-9 receptors contain IL-9Rα chain and γc (Russell et al. 1994; Kimura et al. 1995). A single class of IL-9 receptor with high affinity ($K_d \approx 100$ pM) can be detected on T cells, mast cells, and macrophages (Druez et al. 1990). Interestingly, IL-9Rα is also detected in nonhematopoietic cells, including airway and intestinal epithelial cells and smooth muscle cells (Goswami and Kaplan 2011; Kaplan et al. 2015). The human *IL9R* gene is located on the X chromosome, and at least four *IL9R* pseudogenes are localized at the pseudoautosomal region of X and Y chromosomes (Kermouni et al. 1995; Vermeesch et al. 1997). A study of the single-nucleotide polymorphisms (SNPs) shows that a specific haplotype of IL-9Rα gene is protective against wheezing in boys but not in girls and provides weak protection against sensitization to inhalant and/or food allergens (Melen et al. 2004).

IL-15 receptors are composed of IL-15Rα, IL-2Rβ, and γc (Bamford et al. 1994; Giri et al. 1994; Grabstein et al. 1994). IL-15Rα is expressed on a wide range of cells, including immune cells (T cells, B cells, macrophages, and stromal-cell lines) and nonimmune cells (keratinocytes and skeletal muscle cells) (Grabstein et al. 1994). IL-15 binds to IL-15Rα with high affinity ($K_d \approx 25$ pM), much higher than the affinity of IL-2 for IL-2Rα, whereas IL-15 binds IL-2Rβ and γc with a $K_d \approx 1$ nM, similar to the affinity of IL-2 to IL-2Rβ and γc. Like IL-2Rα, IL-15Rα does not transduce IL-15 signals, but IL-15Rα-expressing APCs, such as DCs and monocytes, can bind IL-15 and *trans*-present the cytokine to lymphocytes that express IL-2Rβ and γc; this *trans* signaling is the dominant mode for IL-15 action (Dubois et al. 2002).

IL-21 receptors consist of IL-21Rα chain and γc (Asao et al. 2001). IL-21Rα mRNA is expressed on lymphohematopoietic cells and is potently induced on stimulation of human peripheral blood mononuclear cells with PHA (Ozaki et al. 2000) and TCR (Wu et al. 2005). At the amino acid level, IL-21Rα is most similar to IL-2Rβ (29% identity, 46% similarity), and its cytoplasmic domain is more similar to that of IL-9Rα, whereas its overall domain organization (a single cytokine-binding domain followed by a transmembrane domain and a relatively long cytoplasmic domain) is most similar to IL-4Rα (Parrish-Novak et al. 2002). IL-4Rα and IL-21R are encoded by the adjacent genes (Ozaki et al. 2000).

SIGNALING PATHWAYS USED BY γc FAMILY CYTOKINES

Unlike most growth factor receptors, type I cytokine receptors do not have intrinsic protein kinase activity in their cytoplasmic domains. Thus, the association of nonreceptor JAK1 with the cytokine-specific receptor chains (IL-2Rβ, IL-4Rα, IL-7Rα, IL-9Rα, and IL-21R but not IL-2Rα and IL-15Rα) and JAK3 with γc is essential for transducing the signals induced by γc family cytokines (Fig. 2) (Leonard and O'Shea 1998). Because JAK3 interacts with and is "downstream" from γc (Boussiotis et al. 1994; Russell et al. 1994; Kawahara et al. 1995), it was hypothesized (Russell et al. 1994) and then shown that mutations in *JAK3* cause a form of $T^-B^+NK^-$ SCID that phenocopies XSCID (Macchi et al. 1995; Russell et al. 1995). Each γc cytokine induces the juxtaposition of the cytoplasmic domain of its cytokine-specific receptor chain with γc to trigger the activation of JAK1 and JAK3 (Nakamura et al. 1994; Nelson et al. 1994), which then phosphorylates the key tyrosine residues in the cytoplasmic domain of each unique receptor chain (IL-2Rβ, IL-4Rα, IL-7Rα, IL-9Rα, and IL-21Rα), providing the phosphotyrosine docking site(s) for STAT proteins via their SH2 domains; the STAT proteins can then be phosphorylated by JAK kinases (Leonard and O'Shea 1998). Tyrosine-phosphorylated STAT proteins dimerize via bivalent interactions between the C-terminal phosphotyrosine on each monomeric STAT protein and the SH2 domain on the other monomeric STAT protein (Fig. 3). STAT dimers then translocate to the nucleus to bind to IFN-γ-activated site (GAS) motifs, activating the transcription of their target genes (Darnell et al. 1994; Leonard and O'Shea 1998). The docking site(s) for STAT proteins on the cytoplasmic domains of each cytokine receptor determine which STAT protein will be activated by a given cytokine (Lin et al. 1995; Demoulin et al. 1996). For example, IL-2, IL-7, IL-9, and IL-15 predominantly activate STAT5A and STAT5B and to a lesser extent STAT3 and STAT1 (Lin et al. 1995; Demoulin et al. 1999), IL-4 mainly activates STAT6 and to a lesser extent STAT5 (Hou et al. 1994; Quelle et al. 1995; Rolling et al. 1996), and IL-21 activates STAT3 and to a lesser extent STAT1 and STAT5 (Fig. 2) (Zeng et al. 2007; Wan et al. 2013; Wan et al. 2015).

An early study of the IFN-γ enhancer revealed cooperative binding of STAT proteins and the recognition of STAT tetramers. STAT tetramers form based on interactions via their highly conserved N-terminal regions ("N-domains") in addition to the SH2-phosphotyrosine interactions required for dimerization, thus allowing the dimerization of dimers. Tetramers can bind to less-well-conserved STAT-binding motifs (Vinkemeier et al. 1996; Xu et al. 1996; Soldaini et al. 2000), and the cooperative binding of STAT proteins in this context is caused by N-domain-mediated tetramerization (Vinkemeier et al. 1996; Xu et al. 1996). The crystal structure of the STAT4 N-domain identified the key residues involved in the N-domain-mediated interactions (Vinkemeier et al. 1998; Chen et al. 2003). The nonredundant in vivo function of STAT dimers and tetramers was shown in STAT5 tetramer-deficient mice (Lin et al. 2012). Whereas a complete deletion of both *Stat5a* and *Stat5b* results in fetal lethality, at least in part caused by defective erythropoietin-based STAT5 activation and red-cell formation (Socolovsky et al. 1999; Yao et al. 2006), STAT5 tetramer-deficient mice are viable, indicating STAT5 tetramers are dispensable for survival of mice (Lin et al.

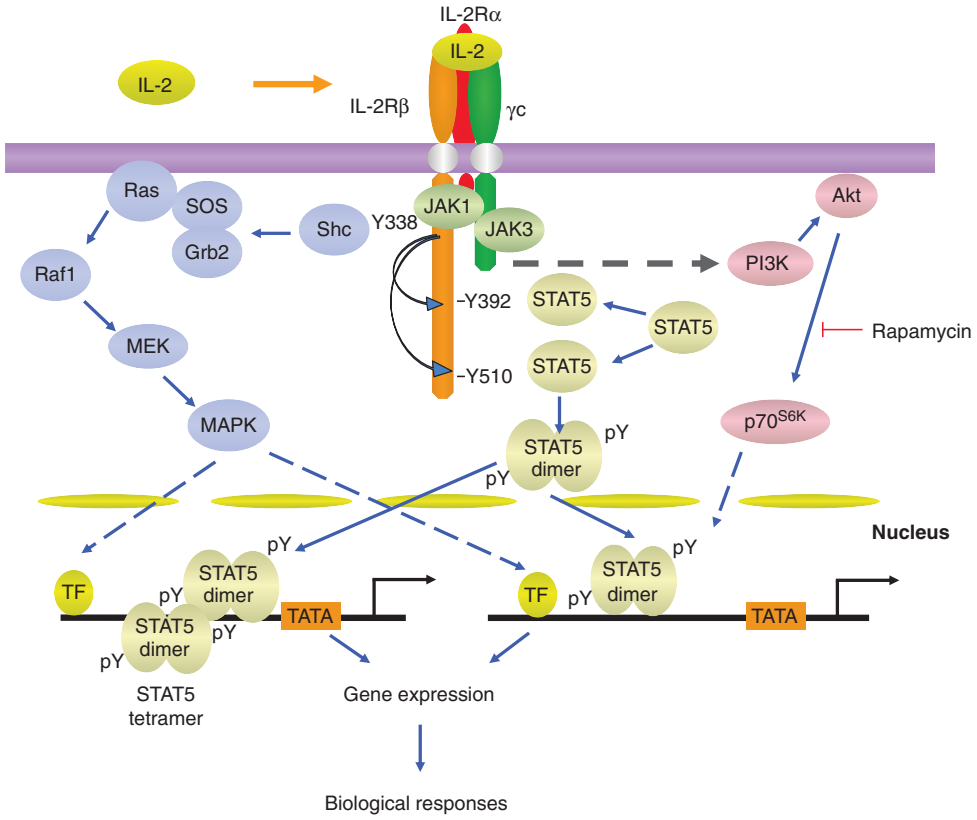

Figure 3. The interleukin (IL)-2 signaling pathway. Activation of Janus kinase (JAK)/signal transducers and activators of transcription (STAT), mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K) pathways by γ chain (γc) family cytokines. As indicated in the text, IL-7 was reported to not activate the MAPK pathway. TF, Transcription factor.

2012). Moreover, STAT5 tetramers are not required for the development of B cells, $CD4^+$, $CD8^+$, and $CD4^+Foxp3^+$ T cells, but are required for normal numbers of peripheral $CD8^+$ T-cell and NK-cell numbers, in vitro proliferation of $CD8^+$ T cells stimulated by IL-2 or IL-15, and homeostasis of $CD4^+$ and especially $CD8^+$ T cells in lymphopenic hosts (Lin et al. 2012). In addition, STAT5 tetramer-deficient virus antigen-specific $CD8^+$ T cells show decreased expansion in response to lymphocytic choriomeningitis virus (LCMV) or adenovirus 5. Consistent with the potent induction of IL-2Rα mRNA by IL-2, ~13 major STAT5-binding sites were identified in the *Il2ra* gene by ChIP-Seq analysis, but only a few of them bind to STAT5 tetramers. Interestingly, IL-2-induced *Il2ra* mRNA is markedly decreased in STAT5-tetramer-deficient T cells, indicating that STAT5 tetramers are essential for normal *Il2ra* transcription (Lin et al. 2012). Despite the normal numbers of $CD4^+Foxp3^+$ T cells in STAT5 tetramer-deficient mice, IL-2Rα expression in these cells is greatly diminished and STAT5-tetramer-deficient Treg cells show decreased suppressive activity in an adoptive transfer colitis model (Lin et al. 2012). Interestingly, STAT1-tetramer-deficient mice have also been generated and show normal type I IFN responses and antiviral activity, but abolished IFN-γ signaling and antibacterial immunity (Begitt et al. 2014). Thus, there are key roles for STAT1 and STAT5 dimers versus tetramers in mediating cytokine signaling, indicating that targeting the forma-

tion of STAT tetramers could be a means of modulating cytokine actions.

JAK/STAT signaling is critical for a broad range of cellular functions, including proliferation, survival, and differentiation, but γc family cytokines, except IL-7, have been shown to activate mitogen-activated protein kinase (MAPK) to promote cell growth, and all γc family cytokines activate phosphatidylinositol 3-kinase (PI3K) to support cell survival (see Fig. 3 for IL-2 activation of these signaling pathways). IL-4 (Wang et al. 1993) and IL-9 (Yin et al. 1995) additionally activate insulin receptor substrates (IRSs) in a manner that is dependent on JAK1 (Yin et al. 1995; Nelms et al. 1999).

To further characterize IL-2 signaling, mass-spectrometry-based quantitative phosphoproteomics were used to identify IL-2 signaling networks in preactivated mouse $CD8^+$ T cells that were cultured in IL-12 to keep the cells viable (Ross et al. 2016). An IL-2-JAK-dependent network appeared to account for most the phosphoproteins identified, including those crucial for the cellular fitness and functions, such as transcription factors, regulators of chromatin structure, mRNA translation machinery, GTPases, vesicle trafficking, and the actin and microtubule cytoskeleton. About 10% of the phosphoproteins identified in these cells were JAK-independent (tofacitinib resistant), comprising those involved in the generation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and the AKT pathway.

Although tofacitinib was developed as a JAK3 inhibitor (Changelian et al. 2003), it also inhibits JAK1 and JAK2 as well as JAK3. A recent study using a more specific JAK3 inhibitor, JAK3i (3000-fold more selective for JAK3 than for JAK1, JAK2, and TYK2), unexpectedly revealed biphasic catalytic activity of JAK3 in STAT5 activation in $CD4^+$ T cells stimulated by IL-2 (Smith et al. 2016). Interestingly, the second wave is required for the expression of cyclins and cell-cycle progression to the S phase, and more sensitive than the first wave of STAT5 activation to JAK3i (Smith et al. 2016). Additional work is needed to clarify the role of the first wave in IL-2 action and whether the second wave is directly or indirectly activated by IL-2. Recently, an additional JAK3-specific inhibitor has been reported (Telliez et al. 2016).

GENE EXPRESSION MEDIATED BY γc FAMILY CYTOKINES

STAT-mediated activation by γ_c family cytokines is vital for the development and function of immune cells. As discussed below, STAT6 activated by IL-4 and STAT3 activated by IL-21 play essential roles in B-cell differentiation and Ig switching (Linehan et al. 1998; Diehl et al. 2012); STAT5 plays nonredundant roles in T- and B-cell development (IL-7) (Yao et al. 2006), in NK-cell development, expansion, and survival (IL-15) (Yao et al. 2006), and in Treg development (IL-2) (Burchill et al. 2007). STAT5 is also critically important for T-cell homeostasis (IL-7) in peripheral and for T-cell expansion in response to antigen stimulation (IL-2 and IL-15). Furthermore, STAT activation by this family of cytokines is also critical for $CD4^+$ Th-cell differentiation. For example, STAT3 activated by IL-21 is vital for Tfh differentiation (Nurieva et al. 2008), STAT5 activated by IL-2 is required for normal Th1, Th2, and Th9 differentiation (Zhu et al. 2003; Liao et al. 2008, 2011, 2014), and STAT6 activated by IL-4 is essential for Th2 and Th9 differentiation (Kuperman et al. 1998; Goswami et al. 2012).

In addition to promoting $CD4^+$ T-cell differentiation, IL-21-activated STAT3 and IL-2-activated STAT5 show opposing actions on Th9, Th17, and Tfh differentiation (Laurence et al. 2007; Yang et al. 2011; Johnston et al. 2012; Liao et al. 2014). These opposing actions of IL-2 and IL-21 during Th17 differentiation can be achieved either by IL-2-mediated inhibition of *Il6ra* and *Il6st* expression or enhanced T-bet (Liao et al. 2011), which should augment binding of RUNX1, thereby diminishing association of RUNX1 with RORγt (Lazarevic et al. 2011), or by competition between STAT3 versus STAT5 for binding to GAS (IFN-γ-activated sequence, $TTCN_3GAA$) motifs on *Il17a* and *Il17f* (Yang et al. 2011). Because the GAS motifs recognized by STAT proteins are fairly conserved,

except for STAT6 using the motif $TTCN_4GAA$ (with N_4 instead of N_3) (Leonard and O'Shea 1998), binding of STAT3 versus STAT5 is likely influenced by the local concentration of each STAT protein. For Th9 differentiation, BCL6 expression suppressed by IL-2 and enhanced by IL-21 are at least, in part, attributed to their opposing actions (Liao et al. 2014). For Tfh differentiation, induction of BLIMP1 via IL-2-activated STAT5 and maintaining BCL6 levels via IL-21-activated STAT3 are responsible for the opposing actions of these cytokines (Johnston et al. 2012; Oestreich et al. 2012). Thus, STAT proteins activated by γc family cytokines are essential to restrain the inflammation triggered by immune responses and to protect the host from harm by controlling the balance between Treg and Th cells.

In addition to the activation of different STAT proteins by different γc family cytokines, different STAT proteins activated by the same cytokine can also result in distinct biological actions. For example, IL-21 activates both STAT3 and STAT1 in mouse $CD4^+$ T cells, with STAT1 promoting expression of the *Ifng* and *Tbx21* genes and STAT3 inhibiting their expression. Correspondingly, expression of *IFNG* and *TBX21* genes are higher in patients with loss-of-function mutation in STAT3 or with gain-of-function mutation in STAT1 (Wan et al. 2015). Moreover, STAT proteins are involved in the assembly of complexes of transcription factors at enhancers, as first shown for IL-21-induced expression of the *Prdm1* gene, which requires STAT3 and IRF4 to act in concert and cooperatively binding during Tfh differentiation (Kwon et al. 2009). Such assembly is essential to initiate and maintain the transcription program during Th differentiation (Ciofani et al. 2012; Vahedi et al. 2012). Moreover, during Th17 differentiation, IL-21 signals via AP1-IRF composite elements (AICEs) (Li et al. 2012) and binding of large complexes of factors (e.g., STAT3, Jun family proteins, basic leucine zipper ATF-like transcription factor (BATF), RORγt, c-Maf, p300, and CTCF) to the regulatory regions of key Th17 genes is required for the initiation and maintenance of the Th17 transcription program (Ciofani et al. 2012).

γc FAMILY CYTOKINES AND T-CELL DEVELOPMENT

The essential roles of γc family cytokines in the development, homeostasis, and survival of T cells are shown by the findings in humans with gene mutations in either the human *IL2RG* gene encoding γc or the *JAK3* gene, as well as in corresponding KO mice. IL-7 is the most critical cytokine for the development of T cells in both humans and mice, with normal T-cell development in *Il2* (Schorle et al. 1991), *Il4* (Kuhn et al. 1991), *Il9* (Townsend et al. 2000), *Il15* (Kennedy et al. 2000), and *Il21* (Nurieva et al. 2007) KO mice.

IL-7Rα is mainly expressed on CLPs, pre–T cells, and thymic and peripheral $CD4^+$ and $CD8^+$ single-positive T cells. The key roles for IL-7 in T-cell development are to maintain the expression of the antiapoptotic protein, BCL2, for double-negative (DN) thymocyte survival, and of *Rag1* for the rearrangement of T-cell antigen receptors in thymic $CD4^-CD8^-$ DN T cells (Mazzucchelli and Durum 2007). The absence of γδ T cells in $Il7ra^{-/-}$ mice and the observation that they cannot be restored by expression of a *Bcl2* transgene show the indispensable role of IL-7 in RAG-mediated rearrangement of TCR-γ (Maki et al. 1996; Mazzucchelli and Durum 2007). Regulation of the accessibility of the *Tcrg* locus to recruit STAT5 proteins activated by IL-7 and other cofactors is attributed to the essential role of IL-7 in T-cell development (Ye et al. 2001). In addition, there is a profound decrease in αβ T-cell numbers in $Il7^{-/-}$ or $Il7ra^{-/-}$ mice (Peschon et al. 1994; von Freeden-Jeffry et al. 1995), but normal T-cell numbers could be restored by a *Bcl2* transgene or partially restored by the deletion of the gene encoding pro-apoptotic BAX in $Il7ra^{-/-}$ mice (Akashi et al. 1997; Khaled et al. 2002). The absence of γδ T cells but presence of some αβ T cells results from the lack of initiation of recombination of the *Tcrg* locus, with normal recombination of Vβ2 but greatly reduced recombination of Vβ14 (Schlissel et al. 2000).

Interestingly, the defect in T-cell development appears somewhat less severe in $Il7^{-/-}$ mice than in $Il7ra^{-/-}$ mice (Peschon et al.

1994; von Freeden-Jeffry et al. 1995), and TSLP also uses IL-7Rα as a receptor component, even though it is not a γc family cytokine. Despite normal development of T cells in *Crlf2*$^{-/-}$ (TSLPR KO) mice, TSLP contributes to T-cell development to some degree as *Il2rg*$^{-/y}$*Crlf2*$^{-/-}$ mice display a greater defect in T-cell development than observed in *Il2rg*$^{-/y}$ mice (Al-Shami et al. 2004).

The levels of expression of cytokine receptors is well-correlated with mature T-cell homeostasis. For example, naïve T-cell homeostasis is predominantly dependent on survival signals provided by IL-7, with high expression of IL-7Rα but very low expression of IL-2Rα and IL-2Rβ on these cells. TCR activation of naïve T cells results in decreased expression of IL-7Rα but potently induces IL-2Rα and IL-2Rβ, and IL-2 and IL-15 can also support memory T-cell homeostasis (Surh and Sprent 2008).

γc FAMILY CYTOKINES AND Treg-CELL DEVELOPMENT AND BIOLOGY

Approximately 10% of peripheral mature CD4$^+$ T cells express IL-2Rα (CD25), and these Treg cells show potent suppressive activity as shown by the ability of adoptively transferred CD4$^+$CD25$^+$ T cells to prevent CD4$^+$CD25$^-$ T-cell-induced autoimmunity in athymic nude mice (Sakaguchi et al. 1995). Naturally occurring Treg cells constitutively express the forkhead family transcription factor FOXP3. Treg cells play essential roles in the maintenance of a balanced immunity under various physiological and pathophysiological conditions (Ohkura et al. 2013; Li and Rudensky 2016). For example, they are essential for suppressing autoreactive T cells that have escaped negative selection in the thymus, controlling potentially harmful excessive immune responses, and suppressing the antitumor immunity that helps tumors to escape immune surveillance. The gene encoding FOXP3 is localized on the X chromosome, and FOXP3 is vital for the development and function of Treg cells. Mutation of the *FOXP3* gene in humans causes severe autoimmune disease (Bennett et al. 2001), and a truncation mutation of the mouse *Foxp3* gene caused by a frameshift attributed to an insertion of two nucleotides in exon VIII (*Scurfy* mouse) results in fatal lymphoproliferative disorders (Brunkow et al. 2001). FOXP3 is required for the development of these cells in the thymus, as shown by the complete absence of CD4$^+$CD25$^+$ Treg cells in *Foxp3*-deficient mice (Fontenot et al. 2003). STAT5 proteins are required for optimal expression of FOXP3 in vitro, with binding of STAT5 to three GAS motifs in the *Foxp3* gene from CD4$^+$CD25$^+$ but not from CD4$^+$CD25$^-$ splenic T cells (Yao et al. 2007).

Finding that *Il2*, *Il2ra*, and *Il2rb* KO mice do not show defective T-cell development but rather have lymphoproliferative autoimmune disorders caused by dysregulated expansion of effector phenotype CD4$^+$ T cells (Sadlack et al. 1993; Suzuki et al. 1995; Willerford et al. 1995) was unexpected, given that IL-2 can potently promote the in vitro proliferation of T cells that express IL-2 receptors. However, this can be explained by markedly decreased Treg-cell numbers in these mice. Importantly, the severe autoimmunity in *Il2rb*$^{-/-}$ mice can be corrected either by thymic-specific expression of IL-2Rβ or by adoptive transfer of normal Treg cells into *Il2rb*$^{-/-}$ newborn mice (Malek et al. 2000, 2002; Malek and Castro 2010), demonstrating the important roles of IL-2 in the development and/or homeostasis of Treg cells in vivo. Subsequent studies showed that IL-2 signaling is critical for the expansion and survival of Treg cells (Bayer et al. 2005, 2007; Fontenot et al. 2005; Setoguchi et al. 2005) but is not required for their suppressive function, given that the residual Treg cells from *Il2*$^{-/-}$ or *Il2ra*$^{-/-}$ mice show similar suppressive activity in vitro as cells from WT mice (Fontenot et al. 2005). Together with TGF-β, IL-2 also plays important roles in the generation of inducible Treg (iTreg) cells from naïve CD4$^+$ T cells, especially in peripheral mucosal tissues like lungs and gut (Davidson et al. 2007; Zheng et al. 2007).

Foxp3$^+$ Treg cells are essentially absent in thymus and spleen of *Il2rg*$^{-/-}$, *Jak3*$^{-/-}$, or *Stat5*$^{-/-}$ mice (Fontenot et al. 2005; Mayack and Berg 2006; Yao et al. 2007), indicating the vital roles of γc family cytokines in the development and homeostasis of Treg cells in vivo. However, although CD4$^+$Foxp3$^+$ Treg cells are

markedly decreased in *Il2*$^{-/-}$, *Il2ra*$^{-/-}$, or *Il2rb*$^{-/-}$ mice, some Treg cells are still present, suggesting the involvement of other γc family cytokine(s) in maintaining normal Treg numbers. Indeed, there is a moderate decrease of both thymic and splenic CD4$^+$Foxp3$^+$ Treg cells in *Il7ra*$^{-/-}$ mice (Burchill et al. 2007), and the severity of the Treg defects in *Il2rb*$^{-/-}$*Il7ra*$^{-/-}$ double KO mice is similar to that observed in *Il2rg*$^{-/Y}$ mice, whereas *Il2rb*$^{-/-}$*Il4ra*$^{-/-}$ double KO mice had more Treg cells than *Il2rg*$^{-/Y}$ mice (Bayer et al. 2008; Vang et al. 2008), indicating that IL-7R-dependent signaling also contributes to normal Treg numbers. In addition, both IL-7 and IL-15, but not TSLP, can induce the differentiation of Treg cells from CD4$^+$CD25$^+$Foxp3$^-$ thymic Treg progenitor cells in vitro, although less potently than IL-2 (Vang et al. 2008). IL-9 was also reported to enhance in vitro Treg function, as a neutralizing antibody to IL-9 blocked such a function (Elyaman et al. 2009). Consistent with this finding, *Il9ra*$^{-/-}$ mice show decreased in vivo Treg function in a mouse experimental autoimmune encephalomyelitis (EAE) model, and injection of anti-IL-9-blocking antibodies in WT mice also have diminished Treg function (Elyaman et al. 2009).

THE ROLES OF γc FAMILY CYTOKINES IN CD4$^+$ T HELPER–CELL DIFFERENTIATION

The adaptive immune system plays major roles in eliminating pathogens and protecting the host from harm. Key components of this system include peripheral naïve CD4$^+$ T cells, which in response to antigen stimulation can differentiate into at least five types of Th cells, including Th1, Th2, Th9, Th17, and Tfh cells (Fig. 4). Which cells form is determined based on the type and strength of the antigen encountered, the presence of cytokines produced by innate immune cells, key transcriptional profiles, and the signature cytokines produced by these cells. Although IL-4 and IL-9 are the only γc family cytokines to serve as signature cytokines (for Th2 and Th9, respectively), other γc family cytokines play indispensable roles in these processes as well, either to facilitate or antagonize a given differentiation process (Fig. 4).

Th1 responses are critical for controlling intracellular pathogens and serve major roles in developing inflammatory disorders. STAT4-dependent IL-12-induced T-bet expression is a key step for the differentiation of naïve CD4$^+$ T cells into Th1 cells, ensuring expression of IFN-γ, and suppressing the expression of IL-4 and IL-17. Among γc family cytokines, IL-2 plays critical roles in promoting Th1 differentiation. IFN-γ production is markedly impaired in *Jak3*$^{-/-}$ or *Stat5*$^{fl/fl}$CD2-Cre$^+$ CD4$^+$ T cells, despite intact IFN-γ-STAT1 and IL-12-STAT4 signaling pathways in these cells. Moreover, antibodies to IL-2, IL-2Rα, and IL-2Rβ also greatly diminish IFN-γ expression under Th1 differentiation conditions in WT CD4$^+$ T cells (Shi et al. 2008). IL-7 can partially restore the decreased IFN-γ expression when IL-2 signaling is blocked, but the effect is only partial, correlating with less potent STAT5 activation by IL-7 than by IL-2. IL-2 induces the expression of IL-12Rβ2 as well as IFN-γ and T-bet, at least in part via STAT5 binding to the regulatory regions of these genes (Liao et al. 2011). The importance of IL-2-induced IL-12Rβ2 expression in Th1 differentiation is further shown by the ability of retroviral transduction of IL-12Rβ2 into *Il2*$^{-/-}$ CD4$^+$ T cells to restore impaired Th1 differentiation in these cells. Interestingly, the anti-inflammatory cytokine IL-27 inhibits Th1 differentiation, limiting the production of IL-2 during Th1 differentiation (Villarino et al. 2006).

Th2 differentiation is critical for eliminating extracellular parasites and involves the production of the signature Th2 cytokines IL-4, IL-5, and IL-13. Together, these cytokines play important roles in Ig isotype switch, IgG1 and IgE production, and mediate allergic inflammatory responses, including asthma and atopic dermatitis. Both the sustained expression of GATA3, at least in part via STAT6 (activated by IL-4) and STAT5 proteins (activated by IL-2 or potentially other γc family cytokines), are essential to initiate and maintain Th2 differentiation (Zhu et al. 2003, 2004; Pai et al. 2004). Early findings that the neutralization of IL-2 inhibited in vivo IL-4 production and that overexpression of constitutively activated STAT5A restored defective IL-4 production in the ab-

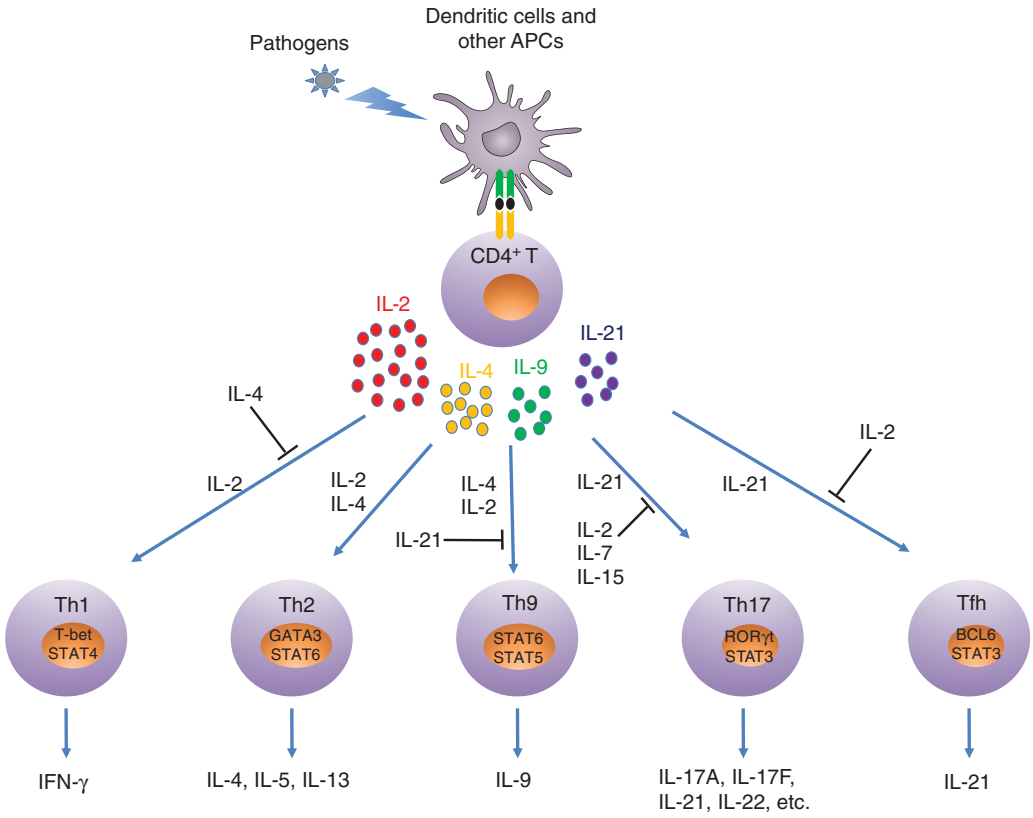

Figure 4. Schematic of roles of γ chain (γc) family cytokines in T helper (Th) differentiation. On antigen stimulation, $CD4^+$ T cells can produce interleukin (IL)-2, IL-4, IL-9, and IL-21. Under different differentiation conditions, each γc family cytokine can either promote or suppress a given differentiation process. APCs, antigen-presenting cells; Tfh, T follicular helper; STAT, signal transducers and activators of transcription; IFN, interferon.

sence of IL-2 signaling demonstrate the indispensable role of IL-2 for normal Th2 differentiation (Cote-Sierra et al. 2004). These results were extended by the findings that early during the Th2 differentiation, IL-2 potently induces the expression of IL-4Rα chain in both WT and *Il4*$^{-/-}$ $CD4^+$ T cells activated by TCR stimulation, and that this is critical for the cells to respond to IL-4 for sustained GATA3 expression. The induction of IL-4Rα by IL-2 is attributed to the direct binding of STAT5 proteins to the GAS motifs in the first intron of the *Il4ra* gene, and, under Th2 differentiation conditions, retroviral transduction of *Il4ra* cDNA into *Il2*$^{-/-}$ $CD4^+$ T cells could fully restore the defective IL-4 expression in these cells (Liao et al. 2008). These findings together show essential roles for both IL-4 and IL-2 for normal Th2 differentiation.

Th9 cells express the signature cytokine IL-9, which is involved in inflammatory disorders, including allergic inflammation, autoimmunity, and antitumor immunity. A number of transcription factors are required for Th9 differentiation, including SMAD family proteins, E-26-specific (ETS) family proteins, IRF4, and the BATF (Kaplan et al. 2015). IL-4 and IL-2 are the key γc family cytokines required for Th9 differentiation, as evidenced by the greatly diminished IL-9 expression in *Stat6*$^{-/-}$ (Goswami et al. 2012) or *Il2*$^{-/-}$ $CD4^+$ T cells (Liao et al. 2014). Although IL-7, IL-9, and IL-15 can also induce IL-9 expression in *Il2*$^{-/-}$ $CD4^+$ T cells in the presence of IL-4 and TGF-β, they

are much less potent than IL-2 (Liao et al. 2014). Both IL-4-STAT6 and IL-2-STAT5 pathways promote Th9 differentiation through the regulation of different transcription factors. IL-4-STAT6 induces IRF4 to increase IL-9 expression while suppressing the expression of FOXP3 and T-bet to inhibit Treg and Th1 differentiation, respectively (Goswami et al. 2012), whereas IL-2-STAT5 suppresses BCL6 to antagonize the potent inhibitory action of IL-21 on Th9 differentiation, indicating that IL-2-STAT5 and IL-21-STAT3 signaling pathways differentially regulate Th9 differentiation via their opposing effect on BCL6 expression (Liao et al. 2014). In addition, IL-2-STAT5 can promote IL-9 production by directly regulating IRF4 and IL-9 expression (Gomez-Rodriguez et al. 2016). Furthermore, the progressive loss of IL-9 production during in vitro Th9 differentiation is observed in WT but not in *Stat3*$^{-/-}$ cells, suggesting that the diminished IL-9 results from IL-10-induced activation of STAT3 (Ulrich et al. 2017).

In a mouse melanoma model, IL-9 and Th9 cells show potent antitumor activity (Lu et al. 2012; Purwar et al. 2012). IL-1β can also potentiate Th9 differentiation via activation of STAT1, which in turn induces the expression of IRF1 and thereby IRF1 binding to regulatory regions in both the *Il9* and *Il21* genes, with augmented expression of both IL-9 and IL-21. The indispensable role of IL-21 in the antitumor activity of Th9 cells is shown by the ability of an anti-IL-21 antibody to abolish the antitumor activity of Th9 cells induced by IL-1β (Vegran et al. 2014).

Both Th2 and Th9 cells are involved in the clearance of parasite infections, but IL-9 is expressed in vivo earlier during *Nippostrongylus brasiliensis* infection than are IL-4, IL-5, and IL-13 (Licona-Limon et al. 2013). In fact, IL-9 expression is required for IL-5 and IL-13 expression, with impaired expression of these cytokines in *Il9*$^{-/-}$ mice. Moreover, adoptive transfer of Th9 cells, but not Th2 cells, improves worm expulsion in *Rag2*$^{-/-}$ mice and the administration of neutralizing IL-9 antibody to these mice abolishes the ability of adoptively transferred Th9 cells to clear worm infection, leading to the conclusion that Th9 cells more efficiently clear worm infection than Th2 cells (Licona-Limon et al. 2013).

Th17 cells express transcription factor RORγt and the signature cytokines IL-17A and IL-17F, as well as other cytokines, to eliminate extracellular pathogens and fungal infections. Early during Th17 differentiation, the cooperative binding of BATF and IRF4 to their target genes plays crucial roles for chromatin accessibility and the subsequent binding of STAT3 activated by IL-6 and IL-21 and other transcription factors to initiate the Th17 transcriptional program (Ciofani et al. 2012; Li et al. 2012). Depending on how Th17 cells are generated, they can be either pathogenic and mediate autoimmune disorders or nonpathogenic and protect the host from harm caused by inflammation. For example, nonpathogenic Th17 cells are generated in the presence of IL-6 and TGF-β (McGeachy et al. 2007), whereas pathogenic Th17 cells are generated when proinflammatory IL-23 is additionally present, thereby inhibiting Th17 cells from producing IL-10 and up-regulating granulocyte macrophage colony-stimulating factor (GM-CSF) (Codarri et al. 2011; El-Behi et al. 2011). In contrast to the positive effects of IL-2 on Th1, Th2, and Th9 differentiation described above, IL-2 suppresses Th17 differentiation as shown by the observation that *Il2*$^{-/-}$ CD4^{+} T cells or blocking IL-2 signaling in WT CD4^{+} T cells results in increased Th17 differentiation (Laurence et al. 2007). Similarly, IL-15 can also inhibit Th17 differentiation as evidenced by the lower IL-17A expression observed when IL-15 is added and increased IL-17A seen when anti-IL-15 antibody is added to neutralize IL-15 produced by APC or as is observed in *Il15*$^{-/-}$ or *Il15rα*$^{-/-}$ CD4^{+} T cells (Pandiyan et al. 2012). The inhibitory effects of IL-2 and IL-15 on Th17 differentiation can potentially be attributed to the competition of the shared binding sites in *Il17* by STAT3 activated by IL-6 and IL-21 versus STAT5 activated by IL-2 and IL-15 (Laurence et al. 2007; Yang et al. 2011; Pandiyan et al. 2012) as well as to the suppressive effect of IL-2 on the expression of IL-6Rα and the IL-6 signal-transducing molecule, gp130, which is shown by the finding that retroviral transduction of gp130 can partially

reverse the inhibitory effect of IL-2 on Th17 differentiation (Liao et al. 2011). In contrast to its inhibitory actions on Th17 differentiation, IL-2 can expand Th17 cells isolated from peripheral blood of healthy human donors or patients with scleritis and increase IL-17 expression in these cells (Amadi-Obi et al. 2007). It was also reported that IL-2, IL-7, and IL-15 can each enhance the expression of IL-17A, IL-17F, IL-22, and IL-26 in $CCR6^+$, but not in $CCR6^-$, human $CD4^+CD45RO^+$ $CD25^-$ memory T cells, and this was attributed to the ability of these cytokines to activate PI3K, as inhibition of PI3K signaling selectively abolished the expression of IL-17 signature cytokines induced by these γc family cytokines (Wan et al. 2011). In addition, memory phenotype Th17 cells isolated from human peripheral blood constitutively express low levels of IL-2, and an IL-2-neutralizing antibody can induce apoptosis of these cells, indicating a critical role for IL-2 in Th17-cell survival as well (Yu et al. 2011). Although IL-6 and TGF-β can initiate Th17 differentiation, IL-21 produced by TCR stimulation also contribute to Th17 differentiation, with impaired in vitro differentiation of Th17 cells in *Il21*$^{-/-}$ $CD4^+$ T cells; IL-21 can also partially compensate for the absence of IL-6 signaling during Th17 differentiation (Korn et al. 2007; Nurieva et al. 2007; Zhou et al. 2007).

Tfh cells are localized in germinal centers and are characterized by coexpression of transcription factor BCL6, inhibitory receptor PD1, IL-21, the chemokine receptor CXCR5, and costimulatory protein ICOS, but these cells do not express BLIMP1 (Crotty 2014; Qi 2016). Tfh cells play crucial roles in T-cell-dependent humoral immunity by directing B-cell differentiation into plasma cells, the selection of affinity-matured antibody-producing B cells, Ig isotype switch, and production of Ig (Crotty 2014; Qi 2016). BCL6 is the key regulator that promotes Tfh differentiation, whereas BLIMP1 antagonizes BCL6 and thus suppresses Tfh differentiation (Johnston et al. 2009). ICOS ligand, IL-6, IL-21, and STAT3 are all required for the development of Tfh cells; indeed, the lack of any of these proteins in mice impairs the development of $CD4^+CXCR5^+$ T cells after immunization (Nurieva et al. 2008). Interestingly, IL-21 uniquely up-regulates the expression of both BCL6 and BLIMP1, which result in different outcomes: germinal center B-cell maintenance mediated by BCL6 (Johnston et al. 2009; Yu et al. 2009) versus plasma-cell differentiation mediated by BLIMP1 (Shaffer et al. 2002). IL-21-induced BLIMP1 expression requires the cooperative binding of STAT3 and IRF4 in the regulatory region of *Prdm1* (gene encoding for BLIMP1) (Kwon et al. 2009). In contrast, IL-2 potently suppresses Tfh-cell differentiation by activating STAT5 and thereby inducing BLIMP1, which down-regulates BCL6 (Johnston et al. 2009, 2012; Ballesteros-Tato et al. 2012; Oestreich et al. 2012). In addition, quenching IL-2 from activated $CD4^+$ T cells by soluble IL-2Rα produced by Tfh-cell-priming $ICOSL^{hi}CD25^+$ DCs favors Tfh-cell differentiation at the follicle outer T-cell zone (Li et al. 2016). Interestingly, IL-2-activated AKT and mTORc1 kinases play a critical role in determining Th1 versus Tfh differentiation. The lower levels of IL-2 expression in Tfh cells are correlated with lower proliferation, glycolysis, and mitochondrial respiration than is observed in Th1 cells during acute LCMV infection (Ray et al. 2015). Down-regulation of BCL6 in Tfh cells late after immunization correlates with decreased proliferation and increased IL-7 responses, in part via increased IL-7Rα expression in these cells (Kitano et al. 2011); however, unlike IL-2, IL-7 does not increase BLIMP1 expression (McDonald et al. 2016).

Besides their opposing actions on Tfh cells, IL-2 and IL-21 regulate Tfh-cell function through differential actions on follicular regulatory T (Tfr) cells, which suppress Tfh-cell-mediated Ig production by B cells (Sage and Sharpe 2015). In addition to other signature molecules expressed by Tfh cells, Tfr cells additionally express $Foxp3^+$ and high levels of ICOS and PD1 (Chung et al. 2011; Linterman et al. 2011). A transcriptomic analysis of Tfh cells in response to Tfr cells revealed that transcription factors essential for Tfh cells, including *Bcl6*, *Ascl2*, and *Tcf1*, are not affected by Tfr-cell suppression, whereas *Prdm1* and especially *Il4* and *Il21* mRNA levels in Tfh cells are markedly reduced

(Sage and Sharpe 2016). In addition, Tfr cells alter Myc signals and mechanistic target of rapamycin (mTOR) pathway in B cells. Importantly, IL-21 or IL-6, but not IL-4, can rescue Tfh- and B-cell functions suppressed by Tfr cells (Sage et al. 2016). In human patients with loss-of-function mutations in *IL21RA* (Kotlarz et al. 2013; Stepensky et al. 2015), there are increased numbers of IL-2-dependent total Treg and Tfr cells in peripheral blood (Jandl et al. 2017). Correspondingly, in the mouse, IL-21 suppresses the expansion of Tfr cells by down-regulating IL-2Rα expression, which is mediated by BCL6 (Jandl et al. 2017). Thus, IL-2 and IL-21 act either directly on Tfh cells or on Tfr cells to maintain B-cell functions via their opposing actions.

ROLES OF IL-2, IL-7, IL-15, AND IL-21 IN THE DEVELOPMENT AND DIFFERENTIATION OF CD8$^+$ T CELLS

IL-2, IL-7, IL-15, and IL-21 play important roles in the homeostasis, expansion, survival, and function of CD8$^+$ T cells. IL-2 and IL-15 potently promote CD8$^+$ T-cell proliferation and induce effector molecules and inflammatory cytokines (Waldmann 2006; Liao et al. 2013), and IL-7 is essential for the survival and homeostasis of naïve CD8$^+$ T cells (Schluns et al. 2000); IL-15 can also promote naïve CD8$^+$ T-cell homeostasis albeit less potently (Kennedy et al. 2000; Berard et al. 2003). IL-7 also regulates the homeostasis of memory CD8$^+$ T cells after viral infection (Kaech et al. 2003), whereas IL-2 can suppress the homeostasis and function of memory CD8$^+$ T cells by Treg cells (Ku et al. 2000; Murakami et al. 2002; Waldmann 2006). When combined with IL-15 or to a lesser extent with IL-7 but not with IL-2, IL-21 can synergistically expand CD8$^+$ T cells in vitro, and the combination of IL-21 and IL-15 potently increases antigen-specific CD8$^+$ T-cell numbers in vivo and inhibits tumor progression in a B16 melanoma model (Zeng et al. 2005). IL-2 and IL-15 enhance expression of transcription factor eomesodermin (*Eomes*) by antigen-primed CD8$^+$ T cells and their development into effector CD8$^+$ T cells, whereas IL-21 induces *Tcf7* and *Lef1* while suppressing Eomes and effector CD8$^+$ T-cell development (Hinrichs et al. 2008). Moreover, antigen-primed CD8$^+$ T cells cultured with IL-21 but not with IL-2 or IL-15 show enhanced antitumor activity when adoptively transferred into B16 melanoma-bearing mice (Hinrichs et al. 2008).

Cytotoxic CD8$^+$ T cells can directly kill virus-infected cells via perforin and granzymes. During LCMV infection, a sustained presence of IL-2 up-regulates Eomes and perforin but down-regulates expression of BCL6 and IL-7Rα, resulting in the expansion of effector cells while suppressing the development of memory cells (Pipkin et al. 2010). Dynamic expression of IL-2Rα in antigen-specific CD8$^+$ T cells appears to correlate with the fate of CD8$^+$ T-cell differentiation in response to LCMV infection. IL-2Rα^{low} CD8$^+$ T cells expressing high levels of IL-7Rα and CD62L show enhanced survival and are thought to become long-lived functional memory cells, whereas IL-2Rα^{high} CD8$^+$ T cells expand more rapidly but are more susceptible to apoptosis (Kalia et al. 2010). In chronic viral infections, including human immunodeficiency virus (HIV) in humans and LCMV in mice, CD8$^+$ T cells become exhausted (Zajac et al. 1998), and this is characterized by their greatly diminished secretion of IL-2 and decreased proliferation but increased expression of the inhibitory receptor PD1 (Barber et al. 2006). Besides PD1, transcription factor BATF is coexpressed, potently suppressing T-cell proliferation and cytokine secretion, whereas BATF small interfering RNA (siRNA) can rescue the defective secretion of IL-2 in T cells from HIV patients (Quigley et al. 2010). Furthermore, in mice chronically infected with LCMV, low-dose IL-2 can enhance CD8$^+$ T-cell responses, decrease PD1 expression, and increase IL-7Rα and CD44 expression on virus-specific CD8$^+$ T cells. Moreover, a combination of IL-2 with anti-PD-L1 greatly enhances virus-specific CD8$^+$ T-cell responses (West et al. 2013).

ROLES OF IL-4, IL-7, AND IL-21 IN THE DEVELOPMENT AND BIOLOGY OF B CELLS

B-cell numbers in *Il2rg*$^{-/-}$ and *Jak3*$^{-/-}$ mice are markedly diminished, and the cells that develop

are nonfunctional because of the lack of T-cell help, given the defective T-cell development in these animals (Cao et al. 1995; Nosaka et al. 1995). IL-7 is the key γc family cytokine for mouse B-cell development, with a severe block at the early stages of B-cell development in mice deficient in either IL-7 or IL-7Rα, including in CLPs and during the transition from pro-B cells to pre-B cells, with absent mature follicular B cells in both *Il7*- or *Il7r*-deficient mice (Peschon et al. 1994; von Freeden-Jeffry et al. 1995). Interestingly, B-cell development is more defective in *Il7ra*$^{-/-}$ mice than in *Il7*$^{-/-}$ mice, suggesting that TSLP, which also uses IL-7Rα as a receptor component, might also be involved. However, unlike the observation indicating a role for TSLP in T-cell development, B-cell development is similar in *Il7*/*Tslpr* double KO mice and *Il7* KO mice, indicating that TSLP may not be involved in B-cell development (Jensen et al. 2008). Unlike its ability to restore αβ T-cell development in *Il7r*$^{-/-}$ mice, expression of the *Bcl2* transgene could not rescue B-cell development defect in the absence of an IL-7 signal (Maraskovsky et al. 1998). However, the *Bcl2* transgene could compensate for the markedly decreased expression of antiapoptotic protein MCL1 and restore pro-B-cell development in the absence of STAT5 (Malin et al. 2010). IL-7 produced by bone marrow endothelial cells is crucial in B-cell lymphogenesis, as the conditional deletion of *Il7* in mouse mesenchymal progenitor cells results in a decrease of both pro- and pre-B-cell numbers in bone marrow (Cordeiro Gomes et al. 2016). In contrast to its importance for B-cell development in the mouse, IL-7 signaling is not essential for human B-cell development, as patients with mutations in *IL7RA* have normal B-cell numbers, although these B cells are not functional because of severe defects in T cells (Puel et al. 1998; Giliani et al. 2005). Thus, either IL-7 does not contribute to human B-cell development or there is a redundant pathway.

IL-4 signaling is not involved in B-cell development but rather is crucial for the differentiation of mature B cells, Ig isotype switching, and IgE production, as *Il4*$^{-/-}$ and *Il4ra*$^{-/-}$ mice show normal development of T and B cells but diminished IgG1 production, greatly diminished IgE production, and normal levels of IgM and other Ig isotypes after infection with *N. brasiliensis* (Kuhn et al. 1991; Noben-Trauth et al. 1997). Similarly, the development of T and B cells are normal in *Il21r*$^{-/-}$ mice but IgG1 levels are greatly diminished, indicating the involvement of IL-21 in Ig switch as well. However, IL-21 is also required for IgG3 production by CD40-activated naïve human B cells (Pene et al. 2004; Avery et al. 2008). Interestingly, IL-4 favors the production of IgG1, whereas IL-21 favors the IgG3 production by CD40-activated naïve human B cells (Avery et al. 2008). However, unlike the mice lacking IL-4 signaling, IgE levels are actually elevated in *Il21r*$^{-/-}$ mice after immunization (Ozaki et al. 2002), possibly caused by an inhibitory effect of IL-21 on IL-4-induced germ line Cε transcription (Suto et al. 2002). Possible cooperative actions between IL-4 and IL-21 for Ig production are further provided by the findings of a pan-hypogammaglobulinemia and poorly organized germinal centers in mice lacking both IL-4 and IL-21 signaling (Ozaki et al. 2002). These observations indicate that both IL-4 and IL-21 contribute to the differentiation of B cells into plasma cells, Ig isotype switch, and Ig production. In addition to actions of IL-21 on T cells to promote B-cell function, a study using a mouse multiple sclerosis (MS) model showed that IL-21 and CD40 are required for the expansion and maturation of regulatory B cells into IL-10-producing effector "B10" cells to inhibit autoimmune disorders by suppressing effector T (Teff)-cell function (Yoshizaki et al. 2012).

As discussed above, IL-4 and IL-21 are the most important γc family cytokines for promoting Tfh development and function, which are essential for B-cell differentiation and Ig isotype switching and production (Ozaki et al. 2002) and they play nonredundant roles in these processes (Ozaki et al. 2004). However, the kinetics of when each of these two key γc family cytokines is expressed during Tfh differentiation was unclear. By using mice expressing IL-21 and IL-4 reporters, it was shown that Tfh cells in germinal centers go through different transcriptional and functional stages to provide different signals

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for B-cell differentiation and function in germinal centers. For example, cells secreting only IL-21 are most efficient at promoting somatic hypermutation and affinity maturation in B cells, whereas cells expressing only IL-4 are more efficient at promoting plasma-cell differentiation and IgG1 class switch, and cells expressing both IL-4 and IL-21 can serve both functions (Weinstein et al. 2016). During LCMV infection, IL-21 signaling is dispensable for Tfh differentiation but is required for the generation of long-lived plasma cells and sustained antibody production (Rasheed et al. 2013).

Defective T cells in *IL2RG*- or *JAK3*-deficient patients can be reconstituted after hematopoietic cell transplantation, but B cells are still not functional in a significant portion of patients who require Ig replacement therapy. Interestingly, the naïve B cells from these patients respond well to IL-4 plus CD40L, but respond poorly to IL-21 plus CD40L, indicating that IL-21 is the major γc family cytokine to initiate humoral immunity in humans (Recher et al. 2011). Consistent with this, *IL7R*-deficient SCID patients, where IL-21 signaling is intact, show more efficient reconstitution of normal B-cell function after bone marrow transplantation (Buckley 2011).

ROLES OF γc FAMILY CYTOKINES FOR NK-CELL DEVELOPMENT AND CYTOLYTIC ACTIVITY

Unlike T and B cells, NK cells can rapidly secrete inflammatory cytokines, chemokines, and, importantly, proteinases on encountering virus-infected cells or tumor cells to eliminate these cells (Vivier et al. 2011; Cerwenka and Lanier 2016). The essential roles of γc family cytokines in the maturation, expansion, and survival of NK cells are shown by the profoundly decreased numbers of immature and mature NK cells in *Il2rg*$^{-/Y}$ mice. However, NK progenitor numbers in mutant mice are similar to those in WT mice, indicating that γc family cytokines are dispensable for NK-cell commitment in bone marrow. IL-15 is the principal γc family cytokine for the generation and maintenance of normal numbers of immature and mature NK cells, as *Il15*$^{-/-}$, *Il15ra*$^{-/-}$, and *Il2rb*$^{-/-}$ mice each show profoundly decreased NK-cell numbers (Vosshenrich et al. 2005). IL-7 is dispensable for conventional NK-cell development, as mice deficient in either *Il7* or *Il7ra* show normal bone marrow and splenic NK numbers (He and Malek 1996; Moore et al. 1996), but IL-7 plays an important role in thymic NK-cell homeostasis, as there is a higher frequency but lower number of thymic NK cells in *Il7*$^{-/-}$ mice (Moore et al. 1996) and nearly a complete absence of IL-7Rα^{+} NK cells in *Rag2*$^{-/-}$*Il7*$^{-/-}$ mice (Vosshenrich et al. 2006).

Although IL-2, IL-4, and IL-21 are dispensable for the generation, differentiation, expansion, and survival of NK cells in vivo, they can nevertheless either promote NK-cell proliferation and survival or enhance NK-cell function. In mice infected with *Leishmania major*, IL-2 and IL-12, but not IL-4 produced by antigen-specific CD4^{+} T cells, are required for early IFN-γ production by NK cells, which depends on the presence of CD40/CD40L (Bihl et al. 2010). In response to virus rechallenge after vaccination, IL-2 secreted by human memory T cells can potently induce a sustained cytokine secretion and degranulation by NK cells, indicating the important roles of IL-2-induced NK-cell function in the initial control of the viral infection after vaccination (Horowitz et al. 2010). Wiskott–Aldrich syndrome protein (WASp) is an actin regulator, and NK cells from patients with loss-of-function mutations in WASp cannot form lytic synapses because of decreased degranulation and expression of IFN-γ (Huang et al. 2005; Orange et al. 2011). IL-2-treated WASp KO NK cells can rescue the defective NK function to eliminate major histocompatibility complex (MHC) class I negative hematopoietic tumor cells (Kritikou et al. 2016). Overexpression of IL-4 in mice results in altered expression of cell-surface markers and function of conventional NK cells via a cooperation with macrophage-produced IL-15, with lower expression of CD11b and IL-18Rα but increased expression of IFN-γ, IL-10, and GM-CSF. These IL-4-stimulated NK cells show higher cytotoxicity than conventional NK cells, and NK cells with a phenotype similar

to the IL-4-stimulated NK cells are found in mice following infection with *N. brasiliensis* (Kiniwa et al. 2016), suggesting the involvement of NK cells in Th2 responses during the clearance of this parasite.

IL-21 can promote differentiation and expansion of bone marrow human NK progenitors in the presence of Flt3L and IL-15, and it can also enhance NK cytotoxicity, albeit less potently than IL-2 or IL-15, and IL-21 has a cooperative effect when combined with IL-2 or IL-15 (Parrish-Novak et al. 2000). NK function in human patients with loss-of-function mutations in IL-21R is variable, ranging from normal to profoundly impaired NK-cell cytotoxicity (Kotlarz et al. 2013); the reason(s) for this variation in NK function remains unclear. Interestingly, IL-21-dependent expansion of the IFN-γ-producing memory-like NK cells during bacille Calmett–Guérin (BCG) vaccination is important for protective immunity against *Mycobacterium tuberculosis* (Venkatasubramanian et al. 2017).

ROLE OF IL-4 IN MACROPHAGE BIOLOGY

Activation of macrophages by cytokines and TLRs is important for host defense and immunity. IL-4-activated macrophages play a role in type 2 immunity in allergic inflammation, helminth infection, and wound healing, and these cells are referred to as M2 or M(IL-4) macrophages (Van Dyken and Locksley 2013; Wynn and Vannella 2016; Eming et al. 2017). M(IL-4) macrophages also play a critical role in wound repair following helminth infection (Chen et al. 2012) and are involved in the repair of infarcts in the adult mouse heart (Shiraishi et al. 2016). Tumor-associated macrophages (TAMs) share the immune tolerance and immunosuppressive phenotype with M2 macrophages and are associated with tumor progression (Wynn et al. 2013). Local injection of IL-21 into tumors can suppress the expression of genes associated with M2 macrophages in TAMs, including *Vegf* and *Tgfb*. In contrast, *Ccl2* expression is associated with tumor-inhibiting M1 macrophages, which then act through $CD8^+$ T cells to enhance antitumor therapy (Xu et al. 2015).

ROLES OF IL-15 AND IL-21 IN DENDRITIC CELL FUNCTION

DCs play vital roles in both innate and adaptive immunities and can be divided in two major types based on the cell-surface markers and their functions, including conventional DCs (cDCs) and plasmacytoid DCs (pDCs) (Pulendran 2015; Durai and Murphy 2016). cDCs, which can be subdivided into cDC1 and cDC2 cells and express high levels of MHC class II molecules, are professional APCs, whereas pDCs rapidly secrete high levels of type I IFNs on encountering pathogens mediated by activation of TLRs. γc family cytokines critically regulate the development and function of DCs. For example, IL-15 can promote the differentiation of monocytes into Langerhans cells in the presence of GM-CSF (Mohamadzadeh et al. 2001), a subset of immature DCs, and can support the maturation of monocytes into DCs (Saikh et al. 2001). IL-15 also promotes DC activation and maturation, whereas IL-21 inhibits these processes and blocks the maturation and activation of LPS-induced DCs (Brandt et al. 2003). In addition, IL-21 induces apoptosis of splenic cDCs but not GM-CSF-induced DCs, and this is dependent on its activation of STAT3 and increased expression of proapoptotic protein BIM. GM-CSF via STAT5 activation can antagonize the apoptotic effect of IL-21 on cDCs (Wan et al. 2013). Although IL-21 does not affect expression of type I IFNs, IL-6, or TNF-α nor the maturation of pDCs, it can potently induce granzyme B (GZMB) expression in human pDCs via a STAT3-dependent pathway. Increased GZMB production induced by IL-21 in pDC is, at least in part, responsible for the inhibition of $CD4^+$ T-cell proliferation mediated by TLR-activated pDCs (Karrich et al. 2013).

γc FAMILY CYTOKINES AND AUTOIMMUNE DISEASES: KEY ROLES FOR IL-2 AND IL-21

As discussed above, γc family cytokines are essential for the development of T and NK cells and the function of B cells and other immune cells and are involved in every aspect of the im-

mune response. Balanced actions of these cytokines are crucial for protecting the host from harm, not only by pathogens but also by inflammation caused by an immune response. Accumulating evidence has shown that effector $CD4^+$ T cells play key roles in mediating autoimmune pathology, whereas Tregs play important roles in controlling the immune response (Grant et al. 2015; Suarez-Fueyo et al. 2017). Dysregulated signals by γc family cytokines are significantly associated with the progression and outcome of the human autoimmune disorders (Spolski and Leonard 2014; Tangye 2015; Suarez-Fueyo et al. 2017); thus, modulating γc family signals is an important means to manage autoimmunity.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown cause, characterized by massive production of autoantibodies and proinflammatory cytokines and can affect every organ. A study of 1318 SLE patients and 1318 matched controls found that two of three SNPs in the introns of *IL21* were significantly associated with SLE (Sawalha et al. 2008). Another study in two large cohorts found that one of the 17 SNPs in the *IL21RA* gene was significantly associated with SLE (Webb et al. 2009). There is also a significant association of the decreased expression of IL-21Rα in peripheral B cells with nephritis and high-titer anti-double-stranded DNA antibodies in SLE patients. B cells from some SLE patients fail to proliferate in response to IL-21 plus anti-CD40 antibody stimulation (Mitoma et al. 2005). Increased IL-21 mRNA levels were also detected in skin biopsies of SLE patients (Caruso et al. 2009). In addition to this association in human SLE, IL-21 was shown to play a vital role in the development of SLE in mouse models. In the BXSB-*Yaa* mouse model of SLE, both IL-10 and IL-21 levels are elevated and the increased IL-21 is not produced by Th17 cells but instead is from $ICOS^+CD4^+$ T cells, and increased IL-10 production by T cells requires IL-21 (Pot et al. 2009; Spolski et al. 2009). Importantly, $Il21r^{-/-}$ BXSB-*Yaa* mice have decreased antinuclear antibodies, do not develop histological and immunological characteristics of SLE, and survive for more than 250 days (Bubier et al. 2009), and blocking IL-21 signaling in SLE-prone MRL-Fas^{lpr} mice with an IL-21R-Fc fusion protein can reduce disease progression (Herber et al. 2007). IL-21 also plays a pathological role in mouse experimental autoimmune uveitis (EAU), which shares the pathological features with human uveitis and is a Th17-cell-related disease, with attenuated EAU in $Il21r^{-/-}$ mice as compared with WT mice (Wang et al. 2011).

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder characterized by autoantibody-induced joint inflammation and systemic inflammation. A number of proinflammatory cytokines are associated with the development and disease activity of RA, although the exact etiology of RA is still not understood. IL-21 is associated with pathogenesis of RA. For example, expression of IL-21Rα was detected in synovial fibroblasts and synovial macrophages of RA patients (Jungel et al. 2004), and IL-21 expression in synovial fluid and peripheral blood in RA patients correlates with the presence of Th17 cells (Niu et al. 2010). In addition, increased plasma IL-21 level correlates with the disease activity of RA (Rasmussen et al. 2010). Interestingly, treatment with tocilizumab, a blocking antibody to the IL-6 receptor, selectively reduced IL-21 and IgG4 anti-CCP autoantibody levels, with an improved RA disease activity (Carbone et al. 2013). Based on mass cytometry, multidimensional cytometry, transcriptomics, and functional assays, a marked increase was noted in $PD1^{hi}CXCR5^-CD4^+$ T cells in the synovium of RA patients. These cells express IL-21, CXCL13, ICOS, and MAF and induce plasma-cell differentiation to promote B-cell responses and Ig production only within pathologically inflamed nonlymphoid tissues (Rao et al. 2017). Autoantibodies can be detected years before the onset of RA, but titers do not well correlate with disease activity. A strong correlation was noted between the expression levels of IL-17 and increased Th17-cell numbers and the systemic disease activity in both the onset and the progression of RA (Leipe et al. 2010). In a mouse RA model, IL-23 can suppress the expression of *St6gal1*, which encodes for a rate-limiting enzyme to control the IgG glycosylation in antibody-producing cells during plasma-cell development. The suppressive effect of *St6gal1*

by IL-23 is mediated by IL-21 and IL-22, but not by IL-17A, IL-17F, or GM-CSF (Pfeifle et al. 2017).

Although the etiology for MS is not fully understood, infiltration of the central nervous system (CNS) by autoreactive T cells is important for the initiation of chronic inflammation and neurodegeneration causing damage to myelin and axons. Among the factors associated with MS, Th1- and Th17-mediated inflammation in both peripheral tissues and CNS play important roles in the pathogenesis of MS. Among proinflammatory cytokines and chemokines aberrantly produced during inflammation, IL-2 and IL-21 are the only γc family cytokines. Interestingly, genome-wide association studies (GWAS) reveal that genetic variations in *IL2RA*, *IL7*, *IL7R*, *STAT3*, *STAT4*, and *TYK2* are risk factors that confer susceptibility in MS patients (International Multiple Sclerosis Genetics et al. 2011, 2013). Furthermore, in mouse EAE, a mouse model of MS, mice with *Stat3*-deficient $CD4^+$ T cells are resistant to EAE owing to defective Th17 differentiation (Liu et al. 2008), and, unexpectedly, mice with *Stat5* deleted in $CD4^+$ T cells also show diminished development of EAE because of their impaired expression of GM-CSF in $CD4^+$ T cells activated by IL-7 (Sheng et al. 2014). To dampen IL-2's potent proliferative activity on IL-2Rα^{high} Teff cells during inflammation mediated by T cells, a humanized neutralizing IgG1 monoclonal antibody to IL-2Rα (daclizumab) was developed (Queen et al. 1989). Daclizumab is well tolerated and results in a significant improvement in treating relapsing-remitting or secondary progressive forms of MS (Bielekova et al. 2004), which account for a majority of MS patients. Daclizumab treatment causes a gradual decrease in circulating T-cell numbers and significantly expands $CD56^{bright}$ NK-cell numbers, which correlates with a positive response to daclizumab therapy (Bielekova et al. 2006; Wynn et al. 2010). In 2016, daclizumab (Zinbryta; previously known as daclizumab high-yield process) was approved by the European Medicines Agency and the U.S. Food and Drug Administration (FDA) for the treatment of relapsing forms of MS in adults (Shirley 2017a).

Inflammatory bowel diseases (IBDs) are characterized by chronic inflammation in the intestine and are mediated by increased proinflammatory cytokine secretion. Environmental, genetic, and commensal microbial factors are involved in the development of IBD. Crohn's disease (CD) and ulcerative colitis (UC) are two major forms of IBD and a meta-analysis identified 163 IBD susceptibility loci, including signaling molecules for cytokines *STAT1*, *STAT3*, *STAT4*, and *JAK2* and γc family cytokines and cytokine receptors *IL2*, *IL21*, *IL2RA*, and *IL15RA* (Jostins et al. 2012). In addition to genetic and environmental factors, T cells play important roles in the outcome of IBD. As discussed above, mice with defective IL-2 signaling spontaneously develop severe colitis (Sadlack et al. 1993; Suzuki et al. 1995; Willerford et al. 1995). A homozygous mutation of *IL21* (c.T147C, p.Leu49Pro) was identified in early-onset IBD patients with decreased circulating B-cell numbers, including naïve and memory B cells and increased transitional B-cell numbers. Although the mutant IL-21 was predicted to have decreased protein stability, in vitro–produced IL-21^{Leu49Pro} cannot activate STAT3, promote normal B-cell proliferation, nor mediate B-cell activation in vitro, suggesting that the mutant IL-21 may not be able to stably bind to the IL-21 receptor. Indeed, the B cells from these patients show normal B-cell activation and Ig class switch in response to either WT IL-21 plus CD40L or IL-4 plus CD40L stimulation, indicating that the defective B-cell function is not caused by intrinsic B-cell defects (Salzer et al. 2014).

Type I diabetes (T1D) is a chronic autoimmune disease characterized by the loss of insulin-producing pancreatic β cells, and both genetic susceptibility and environmental factors contribute to the onset of T1D. Inflammatory processes driven by self-reactive T cells in response to infectious agents and commensal organisms can either be pathogenic or protective (Herold et al. 2013). In human GWAS, among γc family cytokine and cytokine receptor gene loci, *IL2RA*, *IL2*, *IL21*, and *IL7RA* are risk loci for T1D patients (Todd et al. 2007; Concannon et al. 2009). The essential role of IL-2 in Treg cells was further shown by the findings that the

ratios of Treg and Teff cells progressively decrease in inflamed pancreatic islets but not in pancreatic lymph nodes. A low dose of IL-2 promotes survival of Treg cells and protects nonobese diabetic (NOD) mice from T1D onset (Tang et al. 2008; Grinberg-Bleyer et al. 2010). In addition, injection of NOD mice with anti-IL-7Rα antibody alone can reverse established T1D (Lee et al. 2012). Treg cells from either healthy individuals or from T1D patients can respond to IL-2 at a 10-fold lower concentration than that required for memory T cells (Yu et al. 2015). Low-dose IL-2 mainly increases Treg-cell numbers and suppresses IFN-γ production by pancreas-infiltrating T cells, whereas anti-IL-7Rα antibody reduces Th1 and Tc1-cell numbers and increases PD1 expression in Teff cells. In addition, circulating anti-IL-2 autoantibodies are also detected in NOD mice and patients with T1D, and their titer is positively correlated with age and disease onset (Perol et al. 2016). The *Il2*/*Il21* loci are within the diabetes-associated *Idd3* locus, and increased levels of IL-21 were detected in NOD mice, suggesting that IL-21 is a pathogenic cytokine in this model of T1D. Indeed, NOD mice crossed with *Il21r*$^{-/-}$ mice show low lymphocyte infiltration into the pancreas and reduced Th17 cells, indicating critical roles of IL-21 in the development of T1D in NOD mice (Spolski et al. 2008; McGuire et al. 2009). Incubation of bone marrow from NOD mice with CpG can induce a B-cell population that resembles innate pro-B cells (Montandon et al. 2013). Adoptive transfer of these CpG-induced pro-B cells can protect NOD mice from disease onset, which is attributed to the ability of these CpG-pro-B to suppress the proliferation of Teff cells and induce their apoptosis. Furthermore, the expression of IL-21 by Teff cells cocultured with CpG-induced pro-B cells was markedly reduced, but the expression of IL-2 and IL-10 were increased (Montandon et al. 2013).

MODULATION OF γc FAMILY CYTOKINE SIGNALING AND THERAPEUTIC RAMIFICATIONS

Given their indispensable roles in the development and function of T, B, and NK cells and broad actions on the immune response, rationally modulating the actions of γc family cytokines has become an important approach for managing patients with a range of diseases, including immunodeficiency, allergy, infection, autoimmune disorders, transplant rejection, and cancer. For example, giving cytokines can enhance their actions, whereas blocking antibodies against cytokines or cytokine receptors, or small molecules that either inhibit cytokine production or kinase activity like JAK inhibitors, can dampen their actions to protect the host from harm mediated by overreactive immune responses. Indeed, γc family cytokines have been effective in completed and/or ongoing clinical trials for cancer immunotherapy (Rosenberg 2014; Spolski and Leonard 2014; Waldmann 2015; Pulliam et al. 2016; Tran et al. 2017). Moreover, blocking IL-4 signaling is effective for treating adult patients with moderate-to-severe atopic dermatitis (Wenzel et al. 2013; Beck et al. 2014) and adult patients with uncontrolled persistent asthma (Wenzel et al. 2016).

IL-2's potent ability to expand Teff cells and enhance NK-cell cytotoxicity led to the use of high-dose recombinant IL-2 (proleukin) to treat metastatic melanoma and renal-cell carcinoma. Although 15% of the patients with melanoma or renal-cell carcinoma responded well to the treatment and some of them had a long-term tumor-free period, the use of high-dose IL-2 therapy was limited because of its severe side effects, including vascular leak syndrome (VLS) and increased serum creatinine and bilirubin levels (Rosenberg 2014). However, adoptive cell transfer of autologous tumor-infiltrating lymphocytes (TILs) expanded in vitro by IL-2 also results in significant improvement in treating patients with metastatic melanoma (Rosenberg 2014; Tran et al. 2017).

The discovery of IL-2's essential role in Treg function led to observations that low-dose IL-2 preferentially expands Treg cells in vivo, thereby suppressing graft-versus-host disease (GVHD) (Koreth et al. 2011; Asano et al. 2017) and autoimmune disorders, like T1D (Hartemann et al. 2013; Yu et al. 2015) and SLE (He et al. 2016). Importantly, when combined with IL-2, two monoclonal antibodies against mouse IL-2

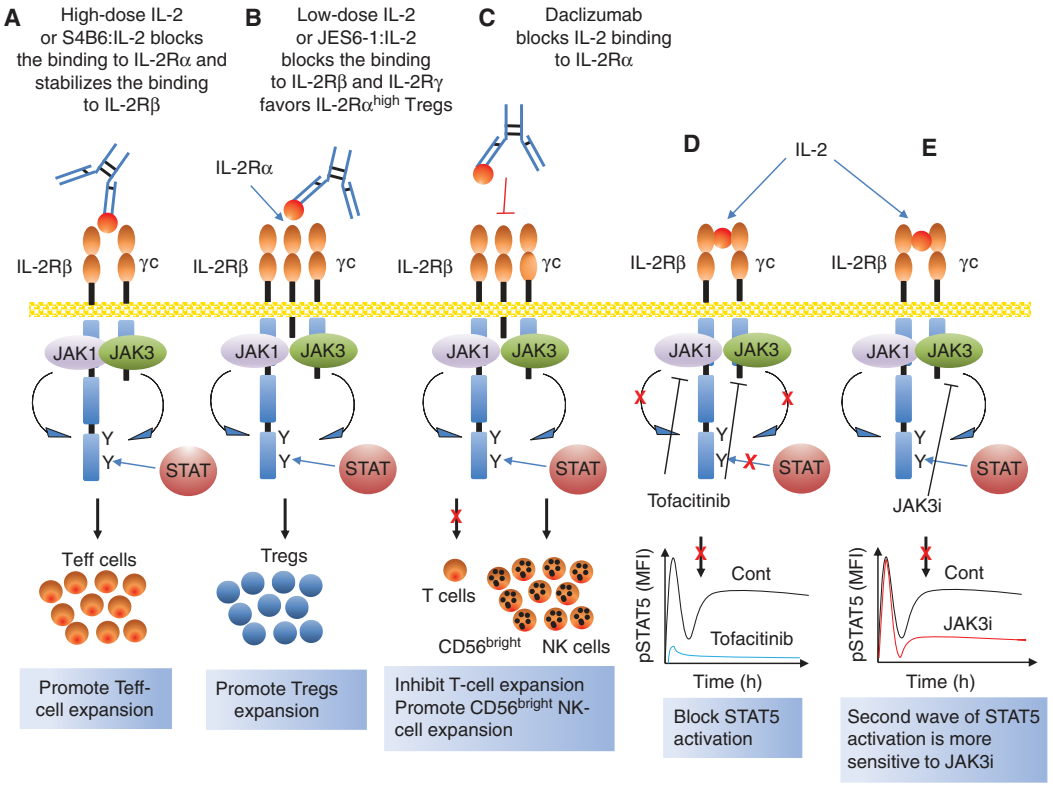

Figure 5. Modulation of interleukin (IL)-2 signaling by antibodies or Janus kinase (JAK) inhibitors. (*A*) High-dose IL-2 or IL-2 complexed with anti-IL-2 antibody S4B6 preferentially promotes the expansion of effector T cells to enhance the immune response, whereas (*B*) low-dose IL-2 or IL-2 complexed with anti-IL-2 antibody JES6-1 preferentially expands Treg cells to suppress the immune response. (*C*) The humanized anti-IL-2Rα antibody, daclizumab, can block IL-2 binding to IL-2Rα to favor the expansion of $CD56^{bright}$ natural killer (NK) cells while diminishing T-cell expansion. (*D*) The JAK inhibitor, tofacitinib, can potently inhibit signal transducers and activators of transcription (STAT) activation by γ chain (γc) family cytokines because of its inhibitory effect on JAK3 and JAK1, whereas (*E*) JAK3i more efficiently inhibits JAK3 and blocks the second wave of STAT5 activation and proliferation of $CD4^+$ T cells stimulated with IL-2.

can selectively mimic either high-dose or low-dose IL-2 treatment. The IL-2–JES6-1 complexes, like low-dose IL-2, can expand Treg and the IL-2–S4B6 complexes, similar to high-dose IL-2, can expand Teff cells (Fig. 5) (Boyman et al. 2006). The reason for the differential effects of these two anti-IL-2 antibodies has been elucidated by structural and biochemical studies (Spangler et al. 2015). JES6-1–IL-2 complexes sterically block the interaction of IL-2 with IL-2Rβ and γc and lower the affinity of IL-2–IL-2Rα interaction to favor $IL\text{-}2R\alpha^{high}$ cells, including Treg cells. In contrast, S4B6–IL-2 complexes sterically block the interaction of IL-2 with IL-2Rα, resulting in increased affinity and stability of IL-2–IL-2Rβ interaction to favor the expansion of $IL\text{-}2R\alpha^{low}$ T cells (Spangler et al. 2015).

To extend these mouse studies into human cancer immunotherapy clinical trials, a monoclonal antihuman IL-2 antibody, NARA1, has been used. NARA1 binds IL-2Rα with high affinity, therefore blocking the interaction of IL-2 with IL-2Rα (Arenas-Ramirez et al. 2016). In vivo administration of IL-2–NARA1 complexes into mice preferentially expands $CD8^+$ T, $CD44^{hi}CD8^+$ T, and NK cells over $CD25^+$ $CD4^+$ T cells, resulting in superior antimela-

noma $CD8^+$ T-cell responses than those achieved with high-dose IL-2. In another study, adoptive transfer of tumor-reactive $CD8^+$ T cells treated with IL-2–anti-IL-2 complexes, but not IL-15-soluble IL-15Rα complexes, showed sustained antitumor immunity (Su et al. 2015); this is attributed to a vigorous and sustained expansion of IL-2–anti-IL-2 complex-treated cells in vivo versus a poor and transient expansion of IL-15-soluble IL-15Rα-treated cells. The sustained expression of high-level IL-2Rα on these tumor-reactive $CD8^+$ T cells is caused by IL-2Rα's ability to sustain IL-2 signaling by recycling IL-2 to the cell surface. Consistent with this finding and the critical role of IL-15 in maintaining memory $CD8^+$ T cells in vivo, membrane-bound chimeric IL-15 on CD19-specific chimeric antigen receptor $(CAR)^+$ T cells can maintain long-lived $CD45RO^-CCR7^+CD95^+$ T cells in vivo; these cells most resemble T-memory stem cells and show potent antitumor activity for established $CD19^+$ leukemias (Hurton et al. 2016). STAT5 activated by IL-15 plays a role in maintaining these cells in vivo even after tumor clearance.

The detailed analyses of the IL-2–IL-2 receptor complexes also led to the creation of IL-2 molecules that can differentially act on different T-cell populations by changing the binding affinity of IL-2 with one of the IL-2 receptor chains (Fig. 6). For example, "super-2" (also known as H9) is more potent than WT IL-2 based on its augmented affinity for IL-2Rβ, where it no longer requires the presence of IL-2Rα to mediate STAT5 activation (Levin et al. 2012). H9 more potently expands cytotoxic T cells than Treg cells and shows less-severe VLS

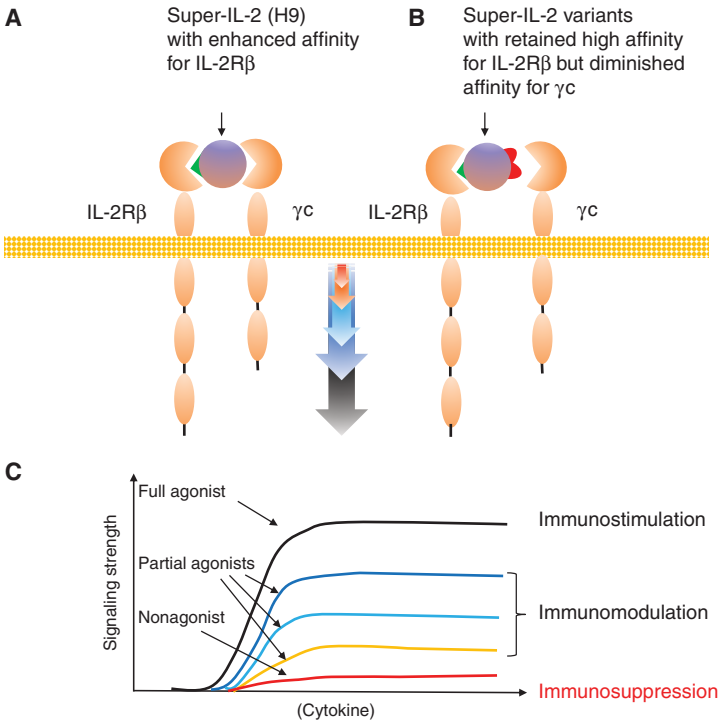

Figure 6. An interleukin (IL)-2 superkine and IL-2 partial agonists. (*A*) An IL-2 superkine (super-IL-2, H9) (green triangle) shows enhanced affinity for IL-2Rβ and more potent activity. (*B*) By retaining the high-affinity binding for IL-2Rβ of H9 (in green) but by changing additional amino acids (in red) on H9 to reduce the affinity for γc, a number of partial agonists with different potencies for activating IL-2 signaling pathways were created as well as a nonagonist (H9-RETR) that could potently inhibit the actions of both IL-2 and IL-15. (*C*) Schematic of full, partial, and nonagonists of IL-2. (Based on Fig. 1A in Mitra et al. 2015.)

as assessed by pulmonary edema in mice than WT IL-2. A number of H9 variants were also generated, which retain high-affinity binding for IL-2Rβ but have altered binding affinity for γc, thereby outcompeting endogenous IL-2 and IL-15 and showing distinct activities on different T cells (Fig. 6) (Mitra et al. 2015). As such, these molecules are partial agonists, and indeed represent the first partial agonists for a type I cytokine. Interestingly, H9-RET, which contains three amino acid substitutions at the IL-2–γc interface, can promote the proliferation of preactivated but not freshly isolated $CD8^+$ T cells; whereas H9-RETR, with four amino acid substitutions at the interface, only minimally activates STAT5 and does not promote T-cell proliferation. However, H9-RETR can potently antagonize IL-2 or IL-15 activity—if anything—more potently than blocking antibodies to IL-2Rα or IL-2Rβ and similar to the combination of such agents, so that it inhibits IL-2-induced NK cytolytic activity, prolongs survival in a mouse GVHD model, and inhibits spontaneous proliferation of malignant cells from patients with the chronic/smoldering form adult T-cell leukemia (Mitra et al. 2015).

Engineered IL-4 superkines have also been generated. A type I IL-4 receptor–selected IL-4 superkine shows a much higher binding affinity for IL-2Rγ chain and is 3- to 10-fold more potent than WT IL-4 to activate STAT6 phosphorylation and cytokine production, whereas a variant selected with high affinity to IL-13Rα1 more potently induces differentiation of monocyte-derived DCs (Junttila et al. 2012). Dupilumab (developed by Regeneron Pharmaceuticals and Sanofi) is a fully humanized IgG4 monoclonal antibody to IL-4Rα that inhibits signaling by both IL-4 and IL-13 and has been approved by the FDA for treating adult patients with moderate-to-severe atopic dermatitis (Chang and Nadeau 2017; Shirley 2017b). Collectively, these results show that using monoclonal antibodies, engineered cytokines, and potentially small molecules are ways to fine-tune cytokine signal strength and selectively promote certain functions of immune cells. Such molecules represent next-generation approaches to treat infectious, allergic, and autoimmune disorders, and cancer.

Given the key roles of JAKs in mediating cytokine signaling, including by γc family cytokines, a number of JAK inhibitors have been developed to suppress cytokine-mediated inflammation. Because of their potent immunosuppressive activity, these JAK inhibitors have been tested in clinical trials for autoimmune disorders, including psoriasis, diabetic nephropathy, atopic dermatitis, myelofibrosis, juvenile idiopathic arthritis (JIA), RA, SLE, and IBD (Winthrop 2017). Among them, tofacitinib preferentially inhibits JAK1 and JAK3 and to a lesser extent JAK2 (Changelian et al. 2003; Meyer et al. 2010) and was approved by the FDA for treating RA and is being tested in a phase III trial for psoriasis and UC and in a phase I trial for JIA (Winthrop 2017). In a large cohort phase III trial, tofacitinib showed promising efficacy as an induction and maintenance therapy for patients with moderate-to-severe UC (Sandborn et al. 2017).

Thus, a wide variety of approaches to more efficiently modulate γc family cytokine signals have been and are being developed, which hopefully will further enhance the treatment of patients with various immune disorders and cancers. For example, high-dose IL-2 and super IL-2 (H9) can potently promote Teff-cell expansion and function to treat malignancies; low-dose IL-2 and H9 agonist variants preferentially expand Treg cells to better treat autoimmune disorders like T1D; the humanized anti-IL-2Rα antibody, daclizumab, can block IL-2 binding to IL-2Rα to inhibit T-cell expansion while serving to expand $CD56^{bright}$ NK cells because of enhanced availability of IL-2; and the H9-RETR variant can block IL-2 and IL-15 binding to IL-2Rβ, thus suppressing the growth of chronic/smoldering acute T-cell leukemia ex vivo. In mice, anti-IL-2 antibody S4B6 complexed with IL-2 mimics the action of high-dose IL-2, whereas anti-IL-2 antibody JES6-1 complexed with IL-2 mimics the action of low-dose IL-2. Moreover, in addition to tofacitinib, which can inhibit JAK1 and JAK2 in addition to JAK3, more specific JAK3 inhibitors have been developed but have not yet been evaluated clinically. Moreover, it is possible that specific inhibitors for STAT proteins may also be useful immunosuppressants.

CONCLUSIONS

In this review, we have discussed the roles of γc family cytokines, including their biological actions, mechanisms of signaling and gene regulation, and the therapeutic applications and potential of administering or blocking the actions of these cytokines. The study of this system has had profound impact, from elucidating the basis of human inherited immunodeficiency, spawning new medications (e.g., IL-2 and JAK inhibitors), and providing the basis for the first human gene therapy (for XSCID), as well as providing tremendous insight into the molecular basis of gene regulation and cell differentiation. Future mechanistic studies will be invaluable for greater understanding of the basic science of these cytokines as well as evolving new therapeutic approaches to a range of diseases. Furthermore, the approaches used for modulation of IL-2 signals and the lessons learned may be broadly applicable to other γc family cytokines as well as other cytokines and growth factors, with implications for scientific investigation and potentially for therapeutic advances as well.

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