New insights into the regulation of T cells by γ_c family cytokines

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Abstract | Common cytokine receptor γ-chain (γ_c) family cytokines have crucial roles in the development, proliferation, survival and differentiation of multiple cell lineages of both the innate and adaptive immune systems. In this Review, we focus on our current understanding of the distinct and overlapping effects of interleukin-2 (IL-2), IL-7, IL-9, IL-15 and IL-21, as well as the IL-7-related cytokine thymic stromal lymphopoietin (TSLP), on the survival and proliferation of conventional αβ T cells, γδ T cells and regulatory T cells. This knowledge potentially allows for the therapeutic manipulation of immune responses for the treatment of cancer, autoimmunity, allergic diseases and immunodeficiency, as well as for vaccine development.

X-linked severe combined immunodeficiency (XSCID). A recessive, inherited disease in which the gene encoding the common cytokine receptor γ-chain (γ_c) on the X chromosome is mutated. γ_c is an essential component of six cytokine receptors and its mutation results in a profound immunodeficiency that accounts for approximately half of all cases of SCID and is characterized by an absence of T cells and natural killer cells. Patients with XSCID have a normal number of B cells but these are non-functional.

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Cytokines are hormones of the immune system that have important functions related to cellular proliferation, differentiation and survival. Type I cytokines have a common structure that contains four α-helical bundles and they include many interleukins, as well as some growth and haematopoietic factors. One important family of type I cytokines is the common cytokine receptor γ-chain (γ_c) family, which consists of interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15 and IL-21 (FIG. 1), and is so named because the receptors for these cytokines share γ_c (also known as IL-2Rγ and CD132)[1,2].

γ_c was first discovered as a component of the receptor for IL-2 (REF. 3), which is the prototypical member of this family. The IL-2 receptor (IL-2R) consists of three chains (IL-2Rα, IL-2Rβ and γ_c), which together form the high-affinity IL-2R (FIG. 1), but which in other combinations can bind IL-2 with low affinity (IL-2Rα alone) or intermediate affinity (IL-2Rβ and γ_c). The structures of some of the receptors for members of the γ_c family are known, providing insight into how different cytokines can each interact with γ_c[4].

The gene encoding γ_c (*IL2RG*) is mutated in humans with X-linked severe combined immunodeficiency (XSCID)[5], and these patients lack T cells and natural killer (NK) cells, which indicates that γ_c is crucial for the development of these cells. The finding that the immune defects in patients with XSCID are much more severe than those of humans or mice lacking IL-2, in which the development of T and NK cells is normal, led to the hypothesis and subsequent confirmation that γ_c is shared by the receptors for multiple cytokines[1].

IL-2 is a T cell growth factor, can augment NK cell cytolytic activity and promotes immunoglobulin production by B cells[6]. In addition, it contributes to the development of regulatory T (T_{Reg}) cells and therefore peripheral T cell tolerance[7], as well as regulating the proliferation and apoptosis of activated T cells[8,9]. IL-4 is required for the development and function of T helper 2 (T_H2) cells and is therefore regarded as the classical T_H2 cell cytokine. IL-4 also has an important role in allergy and immunoglobulin class switching[10]. IL-7 has a central role in the development of T cells in both humans and mice. Indeed, defective IL-7-induced signalling is responsible for the effects on T cell development that are observed in patients with XSCID[5], as well as in patients with SCID caused by mutations in Janus kinase 3 (*JAK3*)[11,12], which encodes a signalling molecule downstream of γ_c, or by mutations in *IL7RA* (also known as CD127)[13] (TABLE 1). Interestingly, IL-7 is also required for the development of B cells in mice but it is not necessary for B cell development in humans; B cells develop normally in patients with XSCID (*IL2RG* mutation), JAK3-deficient SCID and IL-7RA-deficient SCID[1]. However, in an *in vitro* model, IL-7 can promote the development of human B cells from adult bone marrow haematopoietic stem cells (HSCs), although not from cord blood HSCs[14]. In addition, IL-7 is well known for its potent role as a lymphocyte survival factor[15,16]. IL-9 is produced by a subset of activated $CD4^+$ T cells[17,18] and it induces the activation of epithelial cells, B cells, eosinophils and mast cells[19] (FIG. 1). Although IL-9 has been shown to function as a T cell growth factor during the late phase of an immune response[20], its role in T cell biology remains unclear. IL-15 is essential for the development

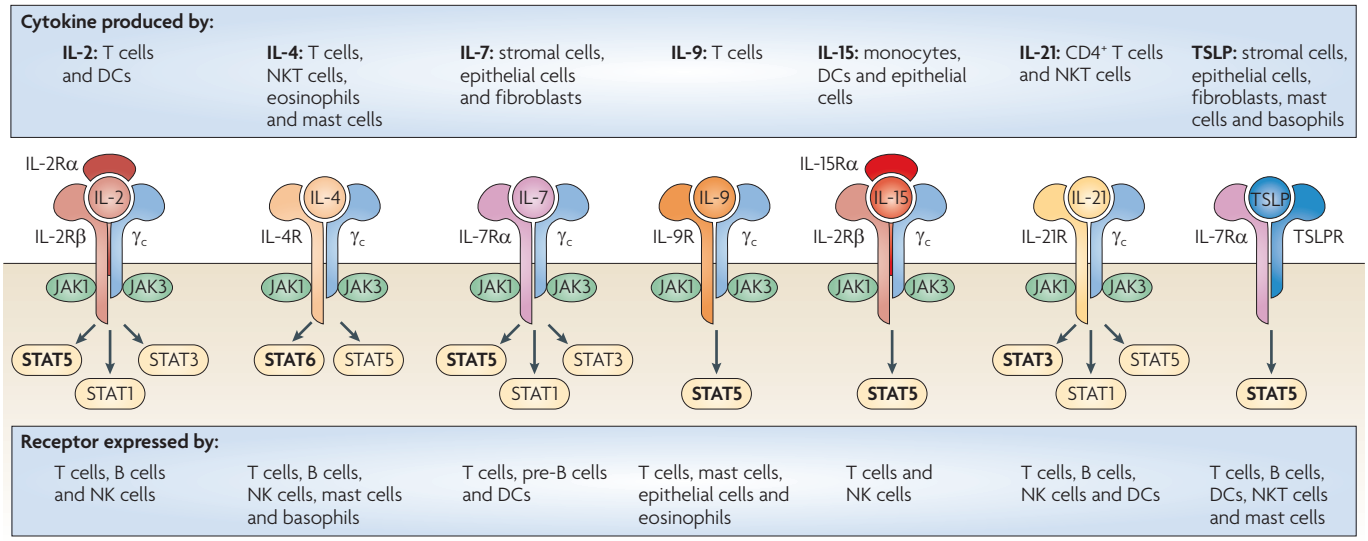

Figure 1 | **Receptors for γ_c family cytokines and TSLP.** Shown are the receptors for interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, IL-21 and thymic stromal lymphopoietin (TSLP). IL-2 and IL-15 are the only two of these cytokines to have three receptor chains. The receptors for these two cytokines share the common cytokine receptor γ-chain (γ_c; also known as IL-2Rγ) and IL-2Rβ, and the receptors for IL-7 and TSLP share IL-7Rα. Of the cytokines shown, only TSLP does not signal through a receptor containing γ_c. There are three classes of IL-2 receptor that bind IL-2 with low affinity (IL-2Rα alone), intermediate affinity (IL-2Rβ and γ_c) and high affinity (IL-2Rα, IL-2Rβ and γ_c); only the high-affinity IL-2 receptor is shown. The receptor for each γ_c family cytokine activates Janus kinase 1 (JAK1) and JAK3, whereas the receptor for TSLP has been reported to not activate any JAK[25,26]. The main signal transducer and activator of transcription (STAT) proteins that are activated by these cytokine receptors are shown in bold. STAT5 refers to both STAT5A and STAT5B. DC, dendritic cell; NK cell, natural killer cell; NKT cell, natural killer T cell.

of NK cells, and it is the defective IL-15-induced signalling that results in the failure of NK cell development in patients with both XSCID and JAK3-deficient SCID[1]. IL-15 also has an essential role in $CD8^+$ T cell homeostasis[16]. IL-21 is the most recently described member of the γ_c family[2] and it has broad actions that include promoting the terminal differentiation of B cells to plasma cells, cooperating with IL-7 or IL-15 to drive the expansion of $CD8^+$ T cell populations and acting as a pro-apoptotic factor for NK cells and incompletely activated B cells[2]. IL-21 has also been shown to be an essential mediator of the development of type 1 diabetes mellitus[21,22] and systemic lupus erythematosus (SLE)[23] in animal models, and to have potent antitumour actions[2].

γ_c family cytokines all signal through the JAK–STAT (signal transducer and activator of transcription) pathway. Interestingly, IL-2, IL-7, IL-9 and IL-15 mainly activate STAT5A and STAT5B (together referred to here as STAT5), whereas IL-4 generally activates STAT6 and IL-21 mainly activates STAT3 (REF. 24) (FIG. 1). The activation of different STAT proteins could help to explain the different effects of these cytokines.

As mentioned above, some of the γ_c family cytokines broadly contribute to lymphocyte homeostasis, which is the main focus of this Review. We also discuss another cytokine that is not a member of the γ_c family but that has overlapping functions with IL-7, known as thymic stromal lymphopoietin (TSLP)[25]. Whereas the IL-7 receptor contains IL-7Rα and γ_c, the TSLP receptor consists of IL-7Rα and TSLPR (also known as CRLF2), which is closely related to γ_c[26,27] (FIG. 1).

Direct effects of γ_c family cytokines on T cells

Regulation of naive and memory αβ T cell homeostasis. γ_c-deficient mice have a low thymic output of T cells and lymphopaenia, and those T cells that do develop have impaired survival[28]. IL-7 seems to be the most important of the γ_c family cytokines for regulating the homeostasis of naive and memory T cells[29–32] (FIG. 2). In contrast to other γ_c family cytokines, the levels of which increase after immune cell activation, IL-7 is constitutively produced by stromal and epithelial cells in the bone marrow and thymus and by fibroblastic reticular cells in the T cell zones of secondary lymphoid organs[16,33]. The availability of IL-7 is regulated by both its production and its consumption by $CD4^+$ T cells[16,34]. So, decreased numbers of $CD4^+$ T cells in humans are associated with increased levels of IL-7 (REF. 34).

A distinctive feature of IL-7 compared with the other γ_c family cytokines relates to the expression of its receptor. Whereas expression of most of the cognate receptor chains for γ_c family cytokines is upregulated after T cell receptor (TCR) activation, IL-7Rα is expressed by naive and memory resting T cells but its expression is downregulated after TCR activation[29,35] (TABLE 2). This indicates that IL-7 mainly mediates its effects on naive and memory T cells rather than on activated T cells (see below). IL-2, IL-7 and other pro-survival cytokines can transiently decrease the expression of IL-7Rα on T cells[35–37], decreasing their responsiveness to IL-7 and also decreasing IL-7 consumption, thereby increasing the availability of IL-7 for other cells that express high levels of IL-7Rα and are poised to receive

Regulatory T cell
(T_{Reg} cell). A specialized type of $CD4^+$ T cell that can suppress the responses of other T cells. T_{Reg} cells provide a crucial mechanism for the maintenance of peripheral T cell tolerance. They are characterized by the expression of the α-chain of the interleukin-2 receptor (IL-2Rα; also known as CD25) and the transcription factor forkhead box P3 (FOXP3).

Plasma cell
A non-dividing, terminally differentiated, immunoglobulin-secreting cell of the B cell lineage.

Systemic lupus erythematosus
(SLE). An autoimmune disease in which autoantibodies that are specific for DNA, RNA or proteins associated with nucleic acids form immune complexes that damage small blood vessels, especially in the kidneys. Patients with SLE generally have abnormal B and T cell function.

Table 1 | **The basis of defects in severe combined immunodeficiency (SCID)**

Form of SCID	Lineage abnormalities	Causes of defects	Refs
XSCID	T and NK cells absent; B cells present but non-functional	The disease results from mutations in *IL2RG*. Decreased T cell development is due to defective IL-7-induced signalling. Lack of NK cell development is the result of defective IL-15-induced signalling. Functional B cell abnormalities are due to a lack of T cell help and defects in IL-4- and IL-21-induced signalling, as indicated by the pan-hypogammaglobulinaemia found in *Il4*$^{-/-}$*Il21r*$^{-/-}$mice, which is associated with germinal centre abnormalities in these mice	1,5, 57
JAK3-deficient SCID	T and NK cells absent; B cells present but non-functional	The disease results from mutations in *JAK3*. Abnormalities are due to the same reasons as in XSCID	11,12
IL-7RA-deficient SCID	T cells absent; in humans, B cells are present but in IL-7R-deficient mice, B cells are absent	The disease results from defective IL-7-induced signalling with a possible partial contribution from TSLP. Humans with IL-7 deficiency have not been reported. Mice with IL-7R deficiency have a more severe T cell phenotype than mice with IL-7 deficiency	13, 42,43
IL-2RB-deficient SCID	NK cells absent; T and B cells present	The disease seems to result from defective IL-15-induced signalling, based on the phenotype of IL-15-, IL-15RA- or IL-2RB-deficient mice, patients with IL-2RB-deficient SCID and *in vitro* studies	1,146

IL, interleukin; *JAK3*, Janus kinase 3; NK cell, natural killer cell; TSLP, thymic stromal lymphopoietin.

survival signals *in vivo*[37]. Maintaining IL-7Rα expression depends, at least in part, on the transcription factor GABP (GA-binding protein)[38], and GABP and the transcription repressor GFI1 (growth factor independent 1) control the up- and downregulation of IL-7Rα expression, respectively[39].

IL-7 uses at least two different mechanisms to support T cell homeostasis. First, it promotes T cell survival by activating the pro-survival phosphoinositide 3-kinase (PI3K)–AKT signalling pathway and by increasing the expression of survival factors such as B cell lymphoma 2 (BCL-2) and myeloid cell leukaemia sequence 1 (MCL1), whereas it inhibits the expression of the pro-apoptotic factors BAX and BAD[15,16]. Second, IL-7 induces the proliferation of naive and memory T cells in lymphopaenic conditions and of memory T cells, but not naive T cells, under normal physiological conditions[29,30,40,41] (FIG. 2).

Although *Il7ra*$^{-/-}$ and *Il7*$^{-/-}$ mice each have markedly decreased numbers of T cells, the absence of IL-7 in *Il7*$^{-/-}$ mice can be partially compensated for by increasing levels of TSLP, which can result in the partial restoration of normal T and B cell numbers[42,43]. These observations indicated that TSLP might have a role in T cell homeostasis. Indeed, administration of recombinant TSLP to *Il2rg*$^{-/-}$ mice (that is, γ_c-deficient mice) results in a partial increase in the number of CD4$^+$ and CD8$^+$ T cells. Consistent with this, restoration of CD4$^+$ and CD8$^+$ T cell numbers after irradiation is less efficient in *Tslpr*$^{-/-}$ mice than in irradiated wild-type mice[42]. Moreover, TSLP promotes the survival of CD8$^+$ T cells in both normal and lymphopaenic conditions[44]. Interestingly, whereas IL-7 induces the proliferation (as well as survival) of naive CD8$^+$ T cells in lymphopaenic mice, TSLP does not affect the proliferation of these cells[44]. A possible explanation for this observation is that IL-7, but not TSLP, can activate JAK3 and is a more potent activator of STAT5 (REFS 25,26).

IL-15 is another important homeostatic cytokine and memory CD8$^+$ T cells that express high levels of IL-2Rβ (also known as CD122)[30,45–47], particularly the IL-2Rβ^{hi}LY49$^+$ subset of memory CD8$^+$ T cells[48], are the most sensitive to IL-15. Although IL-15 does not have an essential role in the homeostatic proliferation of memory CD4$^+$ T cells, IL-15 was reported to affect the homeostasis of these cells in the absence of IL-7 (REF. 49). Furthermore, depleting CD8$^+$ T cells and NK cells, which are the main consumers of IL-15, results in a greater availability of IL-15 and increases the homeostatic proliferation of memory CD4$^+$ T cells[49]. IL-15 is not crucial for the development of naive T cells, but *Il15*$^{-/-}$ mice have decreased numbers of naive CD8$^+$ T cells and these cells have decreased proliferative rates, which probably explains the slower recovery rate of adoptively transferred naive CD8$^+$ T cells in *Il15*$^{-/-}$ mice compared with wild-type mice[40,47,50]. Although memory CD8$^+$ T cells express high levels of IL-15Rα[46] (TABLE 2), their proliferation is greater in response to administration of an IL-15–IL-15Rα complex than of purified IL-15 alone[51,52]; in this system, IL-15 that is bound to IL-15Rα is presented to cells expressing the other IL-15R subunits, IL-2Rβ and γ_c[53]. Indeed, under physiological conditions, *trans*-presentation of IL-15 by IL-15Rα on the surface of other non-T cells is required[54], underscoring the importance of this mode of signalling for IL-15.

IL-7 and IL-15 can also function cooperatively with IL-21 to expand CD8$^+$ T cell populations *in vitro*[55]. Whereas IL-21 alone induces the survival of naive but not memory mouse CD8$^+$ T cells, in the presence of IL-15 and IL-21 combined, the rate of apoptosis in both populations of CD8$^+$ T cells is markedly decreased and cell proliferation is increased[55]. Similarly, the combination of IL-15 and IL-21 increases antigen-independent proliferation of human naive CD8$^+$ T cells *in vitro*[56], the number of CD8$^+$ T cells producing IL-2 and interferon-γ (IFNγ) and the cytotoxic activity of these cells after TCR activation[55,56]. Although *Il21r*$^{-/-}$ mice have normal numbers of peripheral

Trans-presentation
A process by which the α-chain of the interleukin-15 receptor (IL-15Rα) presents IL-15 in *trans* to other cells expressing a complex (with an intermediate affinity for IL-15) that contains IL-2Rβ and the common cytokine receptor γ-chain (γ_c), which then transduce a signal.

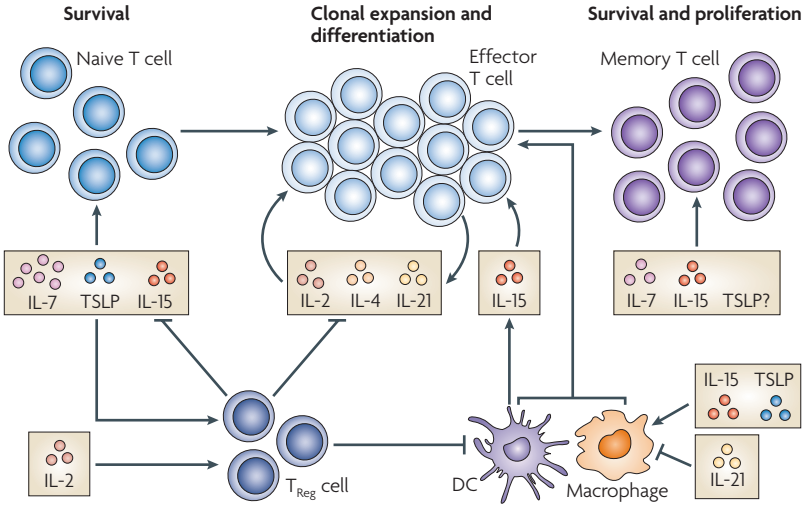

Figure 2 | **Direct and indirect effects of γ_c family cytokines and TSLP on T cell proliferation, homeostasis and differentiation.** Cytokines of the common cytokine receptor γ-chain (γ_c) family can directly influence the survival, activation, proliferation and differentiation of T cells (top half of the figure), as well as indirectly affecting these processes through effects on dendritic cells (DCs), macrophages and regulatory T (T_{Reg}) cells (bottom half of the figure). Although interleukin-15 (IL-15) is a crucial factor for memory $CD8^+$ T cell homeostasis, it is also responsible for the recovery of naive $CD8^+$ T cells in lymphopaenic conditions. In the absence of IL-7, IL-15 has important effects on the homeostasis of memory $CD4^+$ T cells. Both IL-7 and thymic stromal lymphopoietin (TSLP) are important for the survival of naive T cells, with IL-7 having the greater role. The effect of TSLP on memory T cells has not been evaluated. IL-2, IL-4 and IL-21 are produced by activated T cells and have essential roles in T cell differentiation. In addition, IL-2 and IL-15 can increase the proliferation of T cells after antigen stimulation.

$CD8^+$ T cells[57], overexpression of IL-21 increases the number of memory $CD8^+$ T cells[58]; it is unclear whether this is an effect of IL-21 alone or the result of synergistic actions of IL-21 with constitutively produced IL-7 or IL-15. Together, these data underscore the wide range of actions of various γ_c family cytokines, in particular IL-7 and IL-15, in naive and memory T cell homeostasis.

Proliferation and survival of effector T cells. IL-2 is perhaps the earliest cytokine to be secreted by T cells after TCR stimulation[59] and it is important for the initiation of T_H2 cell differentiation[60,61]. It is well known that IL-2 can induce the proliferation and survival of TCR-activated human and mouse T cells[6,62] and is required for sustained expansion of T cell populations[8]. Although administration of supra-physiological levels of IL-2 to mice infected with lymphocytic choriomeningitis virus during the expansion phase of the antiviral T cell response unexpectedly decreases the number of antigen-specific $CD4^+$ T cells[63], this might reflect the ability of IL-2 to induce apoptosis of T cells that have been recently activated through their TCR (known as activation-induced cell death (AICD))[9]. Conversely, IL-2 treatment during the contraction phase of the T cell response results in increased survival and accumulation of T cells[8,63,64]. Overall, the role of IL-2 is multi-faceted owing to its complex effects on driving T cell proliferation, promoting the clonal expansion of T_{Reg} cells (see later) and mediating AICD.

Activation-induced cell death
(AICD). A process in which activated T cells re-stimulated through their T cell receptor undergo cell death after engagement of cell death receptors, such as CD95 or the tumour necrosis factor receptor, or after exposure to reactive oxygen species.

The role of IL-7 and IL-15 in the expansion of effector and memory T cell populations has been widely studied. Immediately after TCR activation, most T cells downregulate IL-7Rα and upregulate IL-2Rα, IL-15Rα and IL-2Rβ expression (TABLE 2). It was therefore predicted that IL-7 is not required for the function of activated T cells[29], and that IL-2 and/or IL-15, the production of which is also increased by activated dendritic cells (DCs)[65–67], could increase the proliferative rate and/or decrease the contraction of effector T cell populations[64,68,69]. Although a selective population of primed T cells re-expresses IL-7Rα[70], IL-7 signalling is not essential for the formation of functional memory $CD4^+$ and $CD8^+$ T cells[71–74], which could indicate potentially redundant functions of TSLP and IL-7 or instead the important actions of other cytokines. Several findings support a possible role for TSLP in the expansion of effector and memory T cell populations: TSLPR expression is increased after TCR activation[44,75] (TABLE 2), TSLP increases the proliferation of TCR-activated $CD4^+$ T cells *in vitro*[42,75] and TSLP production is increased during the acute phase of an immune response to pathogens and allergens[76].

Regulation of γδ T cell homeostasis. γδ T cells are a population of T cells that arise from the same precursors as αβ T cells in the thymus. They migrate to the periphery, mostly to epithelial tissues, and have broad immunological actions, which include the production of cytokines and chemokines, cytolytic activity in response to pathogens, regulation of the viability and proliferation of keratinocytes, induction of macrophage and DC responses and presentation of antigen to T cells[77,78]. The expression of both γ_c and IL-7Rα is essential for normal γδ T cell development[78]. Under lymphopaenic conditions, γδ T cells undergo MHC-independent homeostatic proliferation that requires IL-7 or IL-15 (REFS 79,80). Although αβ and γδ T cells express comparable levels of IL-7Rα and IL-2Rβ[79], partial depletion of αβ T cells, NK cells or γδ T cells themselves significantly increases the homeostatic proliferation of γδ T cells, which shows that these cells compete for limited quantities of IL-7 and IL-15 (REFS 79–81). So, the maintenance of γδ T cells as well as αβ T cells is regulated by IL-7 and IL-15.

Maintenance of T_{Reg} cells. T_{Reg} cells are a subset of $CD4^+$ T cells that were defined in part by their constitutive expression of IL-2Rα (also known as CD25) and the T_{Reg} cell-specific transcription factor forkhead box P3 (FOXP3), which controls the development and function of these cells[7]. Although IL-2 induces the proliferation and clonal expansion of conventional T cells[6,62], IL-2 also mediates immune tolerance at least in part through its regulation of T_{Reg} cells. IL-2 deficiency is characterized by a decrease in the number and function of T_{Reg} cells and, accordingly, leads to lymphoproliferation and autoimmunity[7]. However, the lack of IL-2, IL-2Rα or IL-2Rβ does not alter FOXP3 expression or result in a complete loss of T_{Reg} cells[82–85]. By contrast, γ_c-deficient (*Il2rg*$^{-/-}$) mice and *Jak3*$^{-/-}$ mice, in addition to having very low numbers of T cells, are devoid of $FOXP3^+$ T_{Reg} cells[83,86].

Table 2 | **Expression of receptors for γ_c family cytokines and TSLP**

Receptor chain	Level of expression		
	Naive T cells	*Effector T cells*	*Memory T cells*
γ_c (CD132)	Intermediate	Intermediate	Intermediate
IL-2Rα (CD25)	None	High	None
IL-2Rβ (CD122)	Low	High	High*
IL-4Rα (CD124)	None	High	ND
IL-7Rα (CD127)	Intermediate	None‡	High
IL-15Rα	Low	High	High
IL-21R	Low	High	ND
TSLPR§	Low	Intermediate	ND

*Sustained at a high level on $CD8^+$ memory T cells. ‡Only a few effector T cells express IL-7Rα. §The level of TSLPR expression by T cells is shown relative to its expression by dendritic cells. γ_c, common cytokine receptor γ-chain; IL, interleukin; ND, not determined; TSLP, thymic stromal lymphopoietin.

STAT5 seems to be crucial for the development of T_{Reg} cells and its activation is sufficient to increase the number of $CD4^+CD25^+$ T_{Reg} cells even in the absence of IL-2 production[87] or when there is defective IL-2-induced signalling[88]. In addition, deletion of *Stat5a* and *Stat5b* genes in mice is characterized by a marked decrease in the number of T_{Reg} cells in the thymus and in the periphery[86]. Correspondingly, a patient with a missense mutation in the *STAT5B* gene had a decreased number of $CD4^+CD25^{hi}$ T cells and these cells had a marked decrease in the level of expression of FOXP3 and impaired suppressive activity[89]. These findings confirm earlier observations indicating that STAT5A and STAT5B are crucial factors for signal transduction downstream of IL-2R[90–93] and suggest that other γ_c family cytokines, such as IL-7 and IL-15, that also activate STAT5 might contribute to T_{Reg} cell development and maintenance.

Although deficiency of IL-7 or IL-15 (which both activate STAT5) does not alter the number of $FOXP3^+$ T_{Reg} cells[88,94], the absence of IL-7- or IL-15-induced signalling in combination with disrupted IL-2R signalling results in a greater decrease in the number of T_{Reg} cells than is observed in mice lacking either IL-2 or IL-2Rα alone[88,95]. Interestingly, mouse T_{Reg} cells express low levels of IL-7Rα[94,95], and in contrast to other subsets of T cells that can re-express IL-7Rα after culture *in vitro*, peripheral T_{Reg} cells from mice do not upregulate IL-7Rα expression after *in vitro* culture[94]. Nevertheless, the low level of IL-7Rα that is expressed by mouse T_{Reg} cells seems to be functional, as IL-7, even in the absence of IL-2-induced signalling, can mediate the survival, although not the proliferation, of mouse T_{Reg} cells[95]. Similarly, most human $CD4^+CD25^+FOXP3^+$ T_{Reg} cells have lower levels of IL-7Rα expression than do $CD4^+CD25^+FOXP3^-$ T cells[96,97]. *Il7ra*$^{-/-}$ mice have a marked decrease in the number of T_{Reg} cells in lymphoid tissues and decreased suppressive activity compared with *Il7*$^{-/-}$ mice[94]. These differences can be explained by the ability of TSLP (which signals through a receptor that contains IL-7Rα) to also mediate the induction of T_{Reg} cells[94]. In conclusion, IL-2, IL-7, IL-15 and TSLP all contribute to the development and function of T_{Reg} cells.

Although IL-2, IL-4, IL-7, IL-15 and IL-21 can promote the survival of T_{Reg} cells and rescue them from apoptosis *in vitro*, only IL-2 induces their proliferation and clonal expansion[98]. Consistent with this, the peripheral homeostasis of T_{Reg} cells *in vivo* is more dependent on IL-2 than on the other γ_c family cytokines[7], and neutralizing IL-2 in mice not only decreases the number of T_{Reg} cells in the thymus but also prevents their clonal expansion in lymph nodes[99]. Correspondingly, IL-2 therapy during immune reconstitution after chemotherapy markedly increases the size of the T_{Reg} cell compartment[100].

Indirect effects of γ_c family cytokines on T cells

T cell survival and proliferation through DCs. It is well known that γ_c family cytokines have pleiotropic effects on the immune system and that they can stimulate various populations of cells in addition to T cells, which in turn affect T cell homeostasis. For example, DCs are key players in the activation of an adaptive immune response, and γ_c family and related cytokines, the expression of which is induced by pathogens, can activate (for example, IL-15 or TSLP) or inhibit (for example, IL-7 or IL-21) the function of DCs (FIG. 2).

DCs constitutively express IL-2Rβ and γ_c[66,101,102] and upregulate the expression of IL-15Rα in response to type I and II IFNs and inducers of nuclear factor-κB (NF-κB) activation, such as ligands for Toll-like receptors (TLRs)[65,66]. Similar signals promote the production of IL-15 by DCs and epithelial cells[65,66]. Therefore, IL-15 has both paracrine and autocrine actions on DCs that result in the increased survival of mature DCs, the upregulation of expression of co-stimulatory molecules and the increased presentation of antigen by DCs to $CD4^+$ and $CD8^+$ T cells[65–67,103]. DCs from aged mice produce less IL-15 than do those from young mice, and the functional defects of DCs from aged mice can be reversed by IL-15 treatment[104]. So, the decrease in IL-15 production by DCs with age might be a factor that contributes to decreased immunity to pathogens in the elderly. Moreover, infection of humans with hepatitis C virus decreases IFNα-mediated IL-15 production by DCs and therefore decreases the maturation of functional DCs, which has been suggested to be a possible mechanism for the poor T cell-mediated immunity against this virus[105].

Both IL-4 and TSLP are involved in T_H2 cell responses and have essential roles in allergic diseases[10,25,76]; however, their effects on DCs differ. IL-4 is a survival factor for DCs and, in combination with granulocyte/macrophage colony-stimulating factor, promotes the differentiation of DCs from mouse bone marrow progenitor cells and from human monocytes *in vitro*[148,149]. DCs pre-cultured in the presence of IL-4 express a relatively low level of MHC and co-stimulatory molecules, which is indicative of an immature phenotype, and these cells respond poorly to IFNα[106]. Unlike IL-4, TSLP is not required for DC differentiation, but (as shown by *in vitro* experiments) it promotes the activation of DCs and their upregulation of expression of MHC class II and co-stimulatory molecules, including CD80, CD86 and OX40L[25]. Human DCs

Type I and type II IFNs
Interferons (IFNs) are proteins with potent antiviral activity that are of particular importance during the early response to pathogens. Type I (or viral) IFNs comprise families (α, β and ω) of homologous proteins that interact with a common two-chain receptor (consisting of IFNAR1 and IFNAR2). Type II (or immune) IFN is represented by a single protein (IFNγ) that interacts with a different two-chain receptor (consisting of IFNGR1 and IFNGR2).

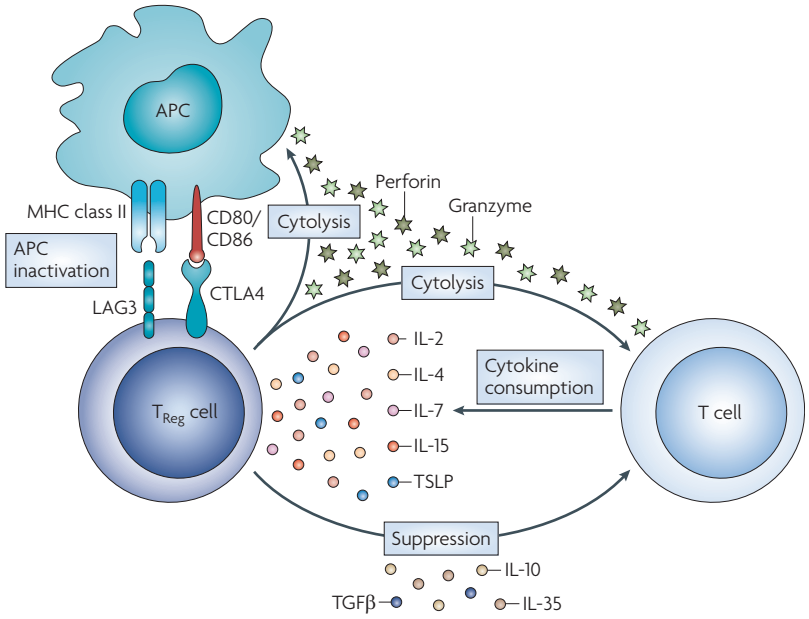

Figure 3 | **Mechanisms of T cell regulation by T_{Reg} cells.** Regulatory T (T_{Reg}) cells use several mechanisms to suppress the activation and proliferation of conventional T cells. T_{Reg} cells modulate the functions of antigen-presenting cells (APCs) by inhibiting their maturation and blocking the cell surface expression of MHC molecules and co-stimulatory molecules (CD80 and CD86), thereby attenuating interactions between APCs and T cells. T_{Reg} cells might have cytolytic effects on target T cells, as well as on APCs, through the secretion of granzymes and perforin. T_{Reg} cells suppress the activation and proliferation of T cells through the secretion of inhibitory cytokines, such as transforming growth factor-β (TGFβ), interleukin-10 (IL-10) and IL-35 and by the consumption of cytokines of the common cytokine receptor γ-chain (γ_c) family. Deprivation of γ_c family cytokines induces the expression of pro-apoptotic proteins by conventional T cells and increases their apoptotic rate. CTLA4, cytotoxic T lymphocyte antigen 4; LAG3, lymphocyte activation gene 3; TSLP, thymic stromal lymphopoietin.

that are stimulated with TSLP support naive $CD4^+$ T cell homeostasis and induce robust proliferation and differentiation of human $CD4^+$ T cells into inflammatory T_H2 cells[25]. In mice, TSLP has an important role in intestinal immunity by inhibiting the lipopolysaccharide-induced production of IL-12 by DCs and thereby decreasing the number of $IFN\gamma^+CD4^+$ T cells that are generated[107]. Interestingly, IL-7 maintains the immature phenotype of DCs and can downregulate MHC class II expression by mature mouse DCs, which correlates with decreased homeostatic proliferation of $CD4^+$ T cells[108]. IL-21 is not required for DC differentiation, but pre-treatment of DCs with IL-21 inhibits their maturation in response to TLR stimuli, thereby suppressing DC functions, such as antigen presentation and cytokine and chemokine secretion[109,110]. Because IL-21 is produced by $CD4^+$ T cells after antigen stimulation[2] and IL-21-primed DCs have inhibitory effects on T cell responses, the production of IL-21 by T cells could activate a DC-mediated negative feedback loop.

Conventional T cell homeostasis through T_{Reg} cells. As discussed above, γ_c family cytokines have an important role in the development and maintenance of T_{Reg} cells. In turn, T_{Reg} cells inhibit the proliferation of autoreactive T cells, thereby preventing autoimmunity, and suppress the response of conventional T cells to foreign and self-antigens. Several mechanisms have been proposed to explain how T_{Reg} cells mediate this suppression (FIG. 3), which include: the inhibition of responder T cells by producing suppressive cytokines such as transforming growth factor-β (TGFβ), IL-10 and IL-35; the inactivation of antigen-presenting cells (APCs) through expression of the inhibitory molecules cytotoxic T lymphocyte antigen 4 (CTLA4) and lymphocyte activation gene 3 (LAG3); the killing of target cells through cytolytic activity; and the consumption of pro-survival γ_c family cytokines, thereby resulting in the apoptosis of conventional T cells *in vitro*[98,111]. Although it is not yet clear whether the cytokine-deprivation mechanism occurs *in vivo,* T_{Reg} cells can induce cytokine-dependent apoptosis of conventional $CD4^+$ T cells in mice[98]. Note that the mechanisms listed above are not mutually exclusive and that more than one mechanism might be used.

γ_c family cytokines and T cell differentiation

Naive T cells can differentiate during a primary antigen response into several distinct polarized subsets, such as T_H1, T_H2, T_H17 and T follicular helper (T_{FH}) cells. These subsets produce discrete sets of cytokines and chemokines to allow responses to different classes of pathogen. Four γ_c family cytokines are among the main cytokines that are produced by these polarized cells: T_H1 cells produce IL-2, T_H2 cells produce IL-4 and IL-9, and T_H17 and T_{FH} cells, as well as T_H1 and T_H2 cells, produce IL-21. These cytokines act on other target cells to direct immune responses, but IL-2, IL-4 and IL-21 also have important roles in the early development of $CD4^+$ T cell subsets.

T_H1 cell differentiation. T_H1 cell differentiation depends mainly on APC-derived IL-12, which leads to IFNγ production and increased IL-12Rβ2 expression by APCs[112]. Although IL-2 is the earliest detected cytokine to be produced by naive $CD4^+$ T cells after TCR stimulation[59], and this cytokine is one of the main products of T_H1 cells[113], it is not clear whether IL-2-induced signalling contributes to early commitment to the T_H1 cell lineage. IL-21 was reported to be a T_H2-type cytokine that had inhibitory effects on T_H1 cells[114], but IL-21 does not affect expression of the T_H1 cell-associated transcription factor T-bet (also known as TBX21) or of IL-12Rβ2 by mouse $CD4^+$ T cells[114]. Instead, IL-21 can inhibit IFNγ production by naive $CD4^+$ T cells that are undergoing T_H1 cell differentiation by repressing expression of the T-box transcription factor Eomesodermin[115]. It is unclear whether this inhibition of IFNγ production by IL-21 has a role in modulating T_H1 cell responses *in vivo* as opposed to promoting the differentiation of T_H17 cells (see below). Interestingly, in human peripheral blood T cells stimulated through the TCR, IL-21 actually induces IFNγ, T-bet and IL-12Rβ2 expression[116], which indicates that, under certain circumstances, IL-21 might promote T_H1 cell differentiation.

T_H2 cell differentiation. *In vitro* studies have shown that IL-2 and IL-4 are both required for the efficient induction of T_H2 cells. IL-2 is produced early after the activation of naive $CD4^+$ T cells and activates STAT5A and STAT5B to promote increased transcription of the *Il4ra* gene, leading to the increased cell surface expression of IL-4Rα (also known as CD124) and subsequent increased responsiveness to IL-4 (REF. 61). IL-2 also induces binding of STAT5 to consensus binding sites located within DNase I hypersensitivity sites in the *Il4* locus, thereby promoting increased accessibility of this locus to the formation of transcriptional complexes[60]. A genome-wide *in vivo* analysis showed that IL-2, through its effects on STAT5, activates not only the *Il4ra* locus but also the entire T_H2 cytokine locus, which includes *Sept8, Kif3a, Il4, Il13, Rad50, Il15* and *Irf1*. Interestingly, this analysis showed that STAT5A and STAT5B bind first at the *Il4ra* locus and then at the T_H2 cytokine locus *in vivo*, which is consistent with the observation that IL-4 is produced by T_H2 cells after they express IL-4Rα[61]. So, IL-2-induced signalling during T_H2 cell differentiation results in both increased production of IL-4 and increased responsiveness to IL-4, leading to stabilization of this lineage. Other cytokines that can activate STAT5, including IL-7 and IL-15, were also shown to induce IL-4Rα expression, which indicates that multiple STAT5 activators might be able to prime T cells for T_H2 cell differentiation[61]. Although IL-21 can also promote STAT5 activation, IL-21-induced signalling does not affect the efficiency of T_H2 cell differentiation *in vitro*[57], which is consistent with the fact that IL-21 mainly activates STAT3 rather than STAT5. IL-21R-deficient mice have decreased responses to T_H2 cell-inducing pathogens; however, it is possible that this results from decreased effects of IL-21 on macrophage activation[117] rather than from direct effects on T_H2 cells.

T_H17 cell differentiation. The differentiation of T_H17 cells depends in part on TGFβ, an immunosuppressive cytokine that also has a role in T_{Reg} cell differentiation. The presence of either IL-6 or IL-21 during priming with TGFβ subverts T cell differentiation from the FOXP3-directed T_{Reg} cell pathway to the T_H17 cell pathway through the induction of expression of the orphan nuclear receptor retinoic acid receptor-related orphan receptor-γt (RORγt; also known as RORC)[118–120]. T_H17 versus T_{Reg} cell differentiation is therefore determined by the presence of IL-6 or IL-21.

IL-2 can promote the development of T_{Reg} cells, and it inhibits the differentiation of naive $CD4^+$ T cells into T_H17 cells[121,122]. Accordingly, administration of IL-2 to tumour-bearing mice can decrease the number of IL-17-producing cells and increase the number of T_{Reg} cells[123]. Correspondingly, *Il2*$^{-/-}$ mice have a decrease in the number of T_{Reg} cells[84] and an increase in the production of IL-17 (REF. 121), which indicates that IL-17-producing cells might contribute to the autoimmune disease that develops in *Il2*$^{-/-}$ mice[7]. However, *Il17*$^{-/-}$*Il2*$^{-/-}$ mice develop systemic autoimmune haemolytic anaemia to the same extent as *Il2*$^{-/-}$ mice, which indicates that IL-17-producing cells are not absolutely required for this disease process and that other potentially redundant cytokines also contribute[124]. Although IL-2 inhibits T_H17 cell differentiation, it can provide proliferative signals to human T_H17 cells, as shown by the IL-2-induced *in vitro* proliferation of T_H17 cells from normal donors and from patients with uveitis or scleritis[125]. Interestingly, the inhibitory effects of IL-2 on the T_H17 cell lineage can be prevented by IL-1, which indicates that the local cytokine profile controls the IL-17$^+$ T cell pool[126].

The role of IL-21 in the differentiation of T_H17 cells is controversial. *In vitro* experiments have shown that IL-21 is crucial for upregulating IL-23R expression by T_H17 cells[120]. IL-23, which is produced by APCs, is an important factor in the differentiation and proliferation of T_H17 cells and therefore in inflammatory diseases, but IL-23R is not expressed by naive $CD4^+$ T cells. IL-21 therefore promotes the expansion of T_H17 cell populations by increasing their responsiveness to IL-23. Although T_H17 cell differentiation is decreased in the absence of IL-21-induced signalling *in vitro*[118–120], the role of IL-21 in T_H17 cell development *in vivo* and in T_H17 cell-mediated autoimmune disease is less clear. Specifically, T_H17 cell development in the lamina propria of the small intestine can occur in the absence of IL-21-induced signalling[127]. Moreover, although one study reported that the development of experimental autoimmune encephalomyelitis (EAE) was significantly decreased in IL-21-deficient mice[119], two other studies found no difference in the development of EAE in either IL-21- or IL-21R-deficient mice[128,129]. So, although IL-21 can promote the differentiation of T_H17 cells, its effects can apparently be compensated for by other cytokines, at least in certain circumstances.

T_{FH} cell differentiation. T_{FH} cells are a distinct subset of $CD4^+$ T cells that provide help to B cells in germinal centres during the generation of T cell-dependent antibody responses. T_{FH} cells are characterized by the expression of high levels of CXC-chemokine receptor 5 (CXCR5) and the co-stimulatory molecules ICOS and CD40L. T_{FH} cells produce high levels of IL-21 (REF. 130), which can act on B cells in germinal centres and as an autocrine factor for T_{FH} cells. *Il21*$^{-/-}$ mice have defective germinal centre formation as well as decreased numbers of T_{FH} cells[131]. Unlike T_H17 cells, which can also produce high levels of IL-21 (REF. 2), T_{FH} cells develop independently of the transcription factor RORγt and do not produce IL-17 (REF. 132). Although the differentiation of T_{FH} cells during a normal T cell-dependent antibody response requires IL-21 production, the excessive differentiation of T_{FH} cells that accompanies systemic autoimmunity in sanroque mice is independent of IL-21, which indicates that there are alternative mechanisms for the maintenance and/or proliferation of T_{FH} cells in germinal centres in some systemic autoimmune diseases[133].

$CD8^+$ T cell differentiation. $CD8^+$ T cells also undergo differentiation into polarized T cytotoxic 1 (T_C1), T_C2 and T_C17 cell populations, which parallel the $CD4^+$ T_H1, T_H2 and T_H17 cell populations. One distinction is that naive $CD8^+$ T cells produce only minimal levels of IL-2 and no IL-21, so that the source of these cytokines during

DNAse I hypersensitivity sites
Sites of nuclease sensitivity when nuclei from cells are exposed to limiting concentrations of DNase I. The digested regions of DNA correspond to sites of open DNA, which might be transcription factor-binding sites or areas of altered nucleosome conformation.

Lamina propria
The layer of mucosal tissue directly under the mucosal epithelial cell surface of the gastrointestinal tract, in which effector immune cells for mucosal immunity reside.

Experimental autoimmune encephalomyelitis
(EAE). An experimental model of multiple sclerosis that is induced by immunization of susceptible animals with myelin-derived antigens, such as myelin basic protein, proteolipid protein or myelin oligodendrocyte glycoprotein.

Germinal centres
These structures, which are found in peripheral lymphoid tissues (for example, the spleen or lymph nodes), are sites of B cell proliferation and selection for clones that produce antigen-specific antibodies of higher affinity.

Sanroque mice
An autoimmune strain of mice that carries a loss-of-function mutation in the gene *roquin* (also known as *Rc3h1*). These mice have a T cell-mediated systemic lupus erythematosus-like syndrome and severe autoimmune diabetes when on a susceptible genetic background.

Table 3 | Effects of decreased versus increased signalling induced by γ_c family cytokines and TSLP

Cytokine	Decreased signalling*		Increased signalling‡	
	Positive effect	*Negative effect*	*Positive effect*	*Negative effect*
IL-2	Immunosupression in organ allografts and in models of leukaemia or lymphoma (daclizumab)§	Lymphoproliferative disorders and autoimmunity associated with loss of T_{Reg} cells	Anti-cancer and immunodeficiency (HIV) treatment associated with increased number of NK cells and increased NK and LAK cell activity	Capillary leak syndrome
IL-4	Decreased asthma symptoms and resistance to leishmaniasis	Defect in immunoglobulin class switching, resulting in no IgE production and failure to protect against helminth infection	None	Allergy, atopic dermatitis, airway inflammation and pro-fibrotic effect
IL-7	None	SCID associated with a defect in T cell homeostasis	Immunodeficiency treatment	Lymphomas, dermatitis and chronic colitis
IL-9	Decreased asthma symptoms and impaired goblet cell hyperplasia	None	None	Airway inflammation
IL-15	None	Decreased innate immunity associated with loss of NK cells, and defective homeostasis of memory $CD8^+$ T cells	Adjuvant with viral vaccine, anti-cancer and immunodeficiency treatment	Lymphomas
IL-21	Prevention of autoimmune diseases (such as EAE, SLE and type 1 diabetes mellitus)	Defect in B cell maturation, with decreased IgG1 and IgG3 production and pan-hypogammaglobulinaemia; defect in T_H17 cell differentiation	Anti-cancer agent	Aberrant $CD8^+$ T cell homeostasis and autoimmunity
TSLP	Prevention of the development of allergic lung inflammation	Possible relationship to Crohn's disease	Increased lymphoid cellularity	Atopic dermatitis, airway inflammation and inflammatory arthritis

Results obtained using *knock out mice or blocking or neutralization of receptors or cytokines, or ‡overexpression or administration of cytokines. §Daclizumab (Zenapax; Roche) is a humanized IL-2Rα-specific blocking antibody that prevents binding of IL-2 to the high-affinity IL-2 receptor complex that is expressed by leukaemia or lymphoma cells and allograft-activated cytotoxic T lymphocytes[147]. γ_c, common cytokine receptor γ-chain; EAE, experimental autoimmune encephalomyelitis; IL, interleukin; LAK cell, lymphokine-activated killer cell; NK cell, natural killer cell; SCID, severe combined immunodeficiency; SLE, systemic lupus erythematosus; T_H17 cell, T helper 17 cell; T_{Reg} cell, regulatory T cell; TSLP, thymic stromal lymphpoietin.

an immune response must be from either activated $CD4^+$ T cells or other cells, such as natural killer T cells (which can produce IL-21 (REF. 134)). In addition to a role for γ_c family cytokines in the expansion of $CD8^+$ T cell populations, IL-2 and IL-21 have distinct effects on $CD8^+$ T cell differentiation when they are present during TCR priming. The presence of IL-21 during priming leads to the generation of $CD28^{hi}CD8^+$ T cells that can produce IL-2, potentially overcoming the requirement for IL-2 from $CD4^+$ T_H cells[135]. Moreover, whereas priming of tumour-specific $CD8^+$ T cells *in vitro* in the presence of IL-2 can potently promote their proliferation and increase their cytolytic activity, priming in the presence of IL-21 was shown to inhibit these processes[136]. However, when these two populations of $CD8^+$ T cells primed under different conditions were transferred into tumour-bearing mice, the IL-21-primed $CD8^+$ T cells had greater antitumour immunity and greater secondary clonal expansion and persistence than did the IL-2-primed $CD8^+$ T cells. These differences, which persisted *in vivo* in the absence of further cytokine stimulation, were associated with distinctive and persistent gene expression profiles in IL-2- versus IL-21-primed $CD8^+$ T cells[136], which indicates that these cytokines might induce epigenetic changes at the time of priming. So, distinct γ_c family cytokines have different effects on $CD8^+$ T cell differentiation, with particularly marked diversity between IL-2 and IL-21 in priming for antitumour effects.

Therapeutic implications

As is evident from the information presented above, γ_c family cytokines and TSLP have crucial roles in regulating numerous activities of immune cells, which have been harnessed to modulate immune responses for therapeutic purposes (TABLE 3). IL-2 is already used in the clinic to expand and maintain $CD4^+$ T cell populations in patients infected with HIV[137,138] and as an anticancer agent, with efficacy in the treatment of some patients with melanoma and renal cell carcinoma[139]. The related cytokine IL-15 holds promise as an adjuvant for vaccines[139]; IL-15 preferentially induces the proliferation of $CD8^+$ T cells rather than T_{Reg} cells and therefore, in contrast to IL-2, is not expected to induce increased tolerance, and IL-15 has stronger effects than IL-2 on the activity of NK cells and cytotoxic T lymphocytes[139]. IL-7 and TSLP are other potential agents that might be used to increase the number of T cells in individuals with inherited or acquired immunodeficiency (TABLE 3). Indeed, the treatment of SIV-infected primates with IL-7 was shown to increase the number of circulating naive and memory T cells[140] and, similarly, the administration of IL-7 to humans induces a selective increase in the number of $CD4^+$ and $CD8^+$ T cells but does not affect the number of T_{Reg} cells[32,141].

IL-21 could also have substantial clinical potential (TABLE 3); its potent antitumour effects have been described in animal models with large established

Non-obese diabetic (NOD) mice
NOD mice spontaneously develop type 1 diabetes mellitus as a result of autoreactive T cell-mediated destruction of pancreatic β-islet cells.

tumours, and it is now in Phase II clinical trials for the treatment of humans with cancer[2,142]. In addition, blocking IL-21 might prove valuable in treating autoimmune diseases. In this regard, diabetes does not develop in the non-obese diabetic (NOD) mouse model of type 1 diabetes mellitus when the animals are crossed to the *Il21r*$^{-/-}$ background[21], and similarly, manifestations of SLE no longer develop when BXSB-*Yaa* mice are crossed to the *Il21r*$^{-/-}$ background[23]. These studies underscore the potential role of IL-21 in autoimmunity and indicate that interfering with the action of IL-21 might have therapeutic potential for several autoimmune disorders. Finally, the IL-7-related cytokine TSLP seems to have a role in the development of atopic dermatitis and asthma[25,76] and perhaps also other allergic diseases. Blocking TSLP with a soluble TSLPR-specific antibody has been shown to protect against the development of pulmonary allergic inflammation in a mouse model[143–145]. These studies collectively underscore a range of potential therapeutic uses for γ_c family cytokines and TSLP.

Concluding remarks and future directions

The γ_c family cytokines have central roles in the regulation of a range of immunological processes. The sharing of γ_c between the receptors for members of this family could be a mechanism for inducing overlapping actions but it could also be a basis for the ability of this family of cytokines to compete with each other for the recruitment of γ_c. In addition, these cytokines can affect signalling by other members of the family by altering the expression of their receptors, creating a system of intricate cross-regulation (for example, IL-2 increases the expression of its own receptor and IL-4Rα, but decreases the expression of IL-7Rα). The actions of these cytokines have clear clinical relevance, and increasing or decreasing their effects has implications for the treatment of cancer, autoimmunity, allergy and immunodeficiency. Future efforts will be directed not only towards further elucidation of the basic biology of these cytokines, including aspects of gene regulation and signalling, but also towards achieving therapeutic benefits in a range of pathological states.

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Competing interests statement
The authors declare competing financial interests: see web version for details.

DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
BAD | BAX | BCL-2 | FOXP3 | IFNα | IFNγ | IL-2 | IL-2Rα | IL-2Rβ | IL-2Rγ | IL-4 | IL-4Rα | IL-7 | *IL7RA* | IL-9 | IL-12Rβ2 | IL-15 | IL-15Rα | IL-21 | *JAK3* | MCL1 | STAT3 | STAT5A | STAT5B | STAT6 | T-bet | TGFβ | TSLP | TSLPR
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
IL-7RA-deficient SCID | JAK3-deficient SCID | XSCID

FURTHER INFORMATION

Warren Leonard's homepage: http://public.nhlbi.nih.gov/Staff/Home/UserInputForPerson.aspx?LabId=lmi&OID=952&source=external

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