

# New insights into the regulation of T cells by $\gamma_c$ family cytokines

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**Abstract** | Common cytokine receptor  $\gamma$ -chain ( $\gamma_c$ ) 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  $\alpha\beta$  T cells,  $\gamma\delta$  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  $\gamma$ -chain ( $\gamma_c$ ) on the X chromosome is mutated.  $\gamma_c$  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.

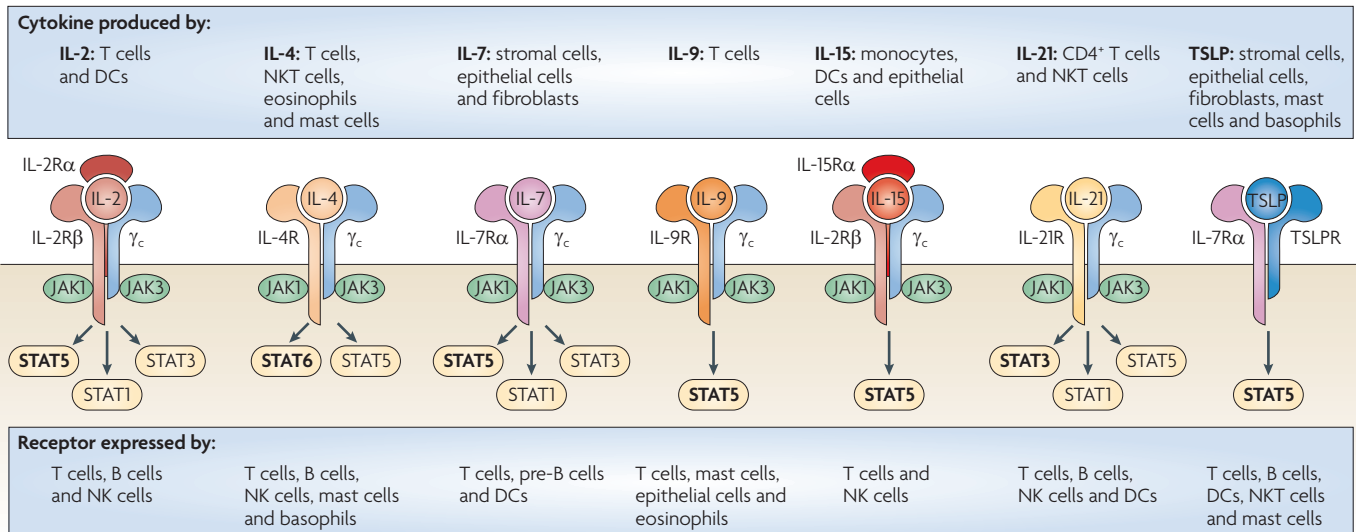
Cytokines are hormones of the immune system that have important functions related to cellular proliferation, differentiation and survival. Type I cytokines have a common structure that contains four  $\alpha$ -helical bundles and they include many interleukins, as well as some growth and haematopoietic factors. One important family of type I cytokines is the common cytokine receptor  $\gamma$ -chain ( $\gamma_c$ ) 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  $\gamma_c$  (also known as IL-2R $\gamma$  and CD132)<sup>1,2</sup>.

$\gamma_c$  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-2R $\alpha$ , IL-2R $\beta$  and  $\gamma_c$ ), which together form the high-affinity IL-2R (FIG. 1), but which in other combinations can bind IL-2 with low affinity (IL-2R $\alpha$  alone) or intermediate affinity (IL-2R $\beta$  and  $\gamma_c$ ). The structures of some of the receptors for members of the  $\gamma_c$  family are known, providing insight into how different cytokines can each interact with  $\gamma_c$ <sup>4</sup>.

The gene encoding  $\gamma_c$  (IL2RG) is mutated in humans with X-linked severe combined immunodeficiency (XSCID)<sup>5</sup>, and these patients lack T cells and natural killer (NK) cells, which indicates that  $\gamma_c$  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  $\gamma_c$  is shared by the receptors for multiple cytokines<sup>1</sup>.

IL-2 is a T cell growth factor, can augment NK cell cytolytic activity and promotes immunoglobulin production by B cells<sup>6</sup>. In addition, it contributes to the development of regulatory T (T<sub>Reg</sub>) cells and therefore peripheral T cell tolerance<sup>7</sup>, as well as regulating the proliferation and apoptosis of activated T cells<sup>8,9</sup>. IL-4 is required for the development and function of T helper 2 (T<sub>H2</sub>) cells and is therefore regarded as the classical T<sub>H2</sub> cell cytokine. IL-4 also has an important role in allergy and immunoglobulin class switching<sup>10</sup>. 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<sup>5</sup>, as well as in patients with SCID caused by mutations in Janus kinase 3 (JAK3)<sup>11,12</sup>, which encodes a signalling molecule downstream of  $\gamma_c$ , or by mutations in IL7RA (also known as CD127)<sup>13</sup> (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<sup>1</sup>. 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<sup>14</sup>. In addition, IL-7 is well known for its potent role as a lymphocyte survival factor<sup>15,16</sup>. IL-9 is produced by a subset of activated CD4<sup>+</sup> T cells<sup>17,18</sup> and it induces the activation of epithelial cells, B cells, eosinophils and mast cells<sup>19</sup> (FIG. 1). Although IL-9 has been shown to function as a T cell growth factor during the late phase of an immune response<sup>20</sup>, its role in T cell biology remains unclear. IL-15 is essential for the development

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**Figure 1 | Receptors for  $\gamma_c$  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  $\gamma_c$ -chain ( $\gamma_c$ ; also known as IL-2R $\gamma$ ) and IL-2R $\beta$ , and the receptors for IL-7 and TSLP share IL-7R $\alpha$ . Of the cytokines shown, only TSLP does not signal through a receptor containing  $\gamma_c$ . There are three classes of IL-2 receptor that bind IL-2 with low affinity (IL-2R $\alpha$  alone), intermediate affinity (IL-2R $\beta$  and  $\gamma_c$ ) and high affinity (IL-2R $\alpha$ , IL-2R $\beta$  and  $\gamma_c$ ); only the high-affinity IL-2 receptor is shown. The receptor for each  $\gamma_c$  family cytokine activates Janus kinase 1 (JAK1) and JAK3, whereas the receptor for TSLP has been reported to not activate any JAK<sup>25,26</sup>. 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.

**Regulatory T cell** (T<sub>Reg</sub> cell). A specialized type of CD4<sup>+</sup> T cell that can suppress the responses of other T cells. T<sub>Reg</sub> cells provide a crucial mechanism for the maintenance of peripheral T cell tolerance. They are characterized by the expression of the  $\alpha$ -chain of the interleukin-2 receptor (IL-2R $\alpha$ ; 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.

of NK cells, and it is the defective IL-15-induced signaling that results in the failure of NK cell development in patients with both XSCID and JAK3-deficient SCID<sup>1</sup>. IL-15 also has an essential role in CD8<sup>+</sup> T cell homeostasis<sup>16</sup>. IL-21 is the most recently described member of the  $\gamma_c$  family<sup>2</sup> 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<sup>+</sup> T cell populations and acting as a pro-apoptotic factor for NK cells and incompletely activated B cells<sup>2</sup>. IL-21 has also been shown to be an essential mediator of the development of type 1 diabetes mellitus<sup>21,22</sup> and systemic lupus erythematosus (SLE)<sup>23</sup> in animal models, and to have potent antitumour actions<sup>2</sup>.

$\gamma_c$  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  $\gamma_c$  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  $\gamma_c$  family but that has overlapping functions with IL-7, known as thymic stromal lymphopoietin (TSLP)<sup>25</sup>. Whereas the IL-7 receptor contains IL-7R $\alpha$  and  $\gamma_c$ , the TSLP receptor consists of IL-7R $\alpha$  and TSLPR (also known as CRLF2), which is closely related to  $\gamma_c$ <sup>26,27</sup> (FIG. 1).

**Direct effects of  $\gamma_c$  family cytokines on T cells**

**Regulation of naive and memory  $\alpha\beta$  T cell homeostasis.**  $\gamma_c$ -deficient mice have a low thymic output of T cells and lymphopaenia, and those T cells that do develop have impaired survival<sup>28</sup>. IL-7 seems to be the most important of the  $\gamma_c$  family cytokines for regulating the homeostasis of naive and memory T cells<sup>29–32</sup> (FIG. 2). In contrast to other  $\gamma_c$  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<sup>16,33</sup>. The availability of IL-7 is regulated by both its production and its consumption by CD4<sup>+</sup> T cells<sup>16,34</sup>. So, decreased numbers of CD4<sup>+</sup> T cells in humans are associated with increased levels of IL-7 (REF. 34).

A distinctive feature of IL-7 compared with the other  $\gamma_c$  family cytokines relates to the expression of its receptor. Whereas expression of most of the cognate receptor chains for  $\gamma_c$  family cytokines is upregulated after T cell receptor (TCR) activation, IL-7R $\alpha$  is expressed by naive and memory resting T cells but its expression is downregulated after TCR activation<sup>29,35</sup> (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-7R $\alpha$  on T cells<sup>35–37</sup>, 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-7R $\alpha$  and are poised to receive

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 <i>IL2RG</i> . 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 <i>Il4<sup>-/-</sup>Il21r<sup>-/-</sup></i> 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 <i>JAK3</i> . 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 <i>in vitro</i> studies	1,146

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

survival signals *in vivo*<sup>37</sup>. Maintaining IL-7R $\alpha$  expression depends, at least in part, on the transcription factor GABP (GA-binding protein)<sup>38</sup>, and GABP and the transcription repressor GFI1 (growth factor independent 1) control the up- and downregulation of IL-7R $\alpha$  expression, respectively<sup>39</sup>.

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*<sup>15,16</sup>. 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<sup>29,30,40,41</sup> (FIG. 2).

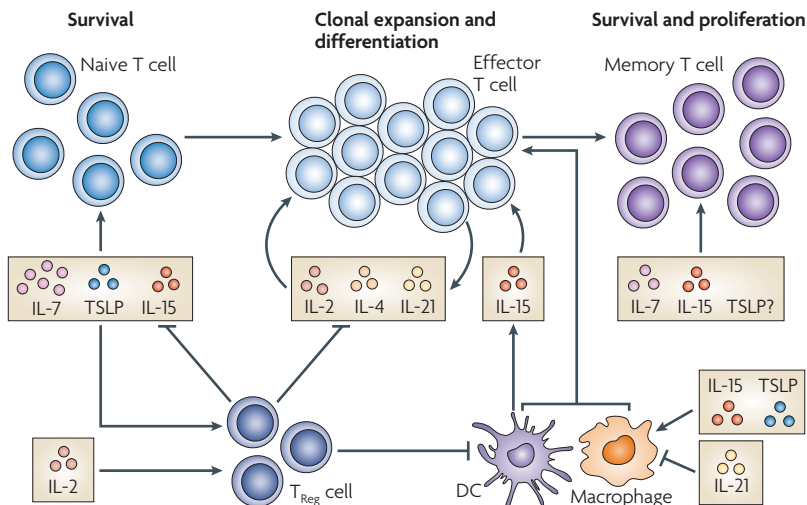
Although *Il7ra<sup>-/-</sup>* and *Il7<sup>-/-</sup>* mice each have markedly decreased numbers of T cells, the absence of IL-7 in *Il7<sup>-/-</sup>* mice can be partially compensated for by increasing levels of TSLP, which can result in the partial restoration of normal T and B cell numbers<sup>42,43</sup>. These observations indicated that TSLP might have a role in T cell homeostasis. Indeed, administration of recombinant TSLP to *Il2rg<sup>-/-</sup>* mice (that is,  $\gamma_c$ -deficient mice) results in a partial increase in the number of CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Consistent with this, restoration of CD4<sup>+</sup> and CD8<sup>+</sup> T cell numbers after irradiation is less efficient in *Tslpr<sup>-/-</sup>* mice than in irradiated wild-type mice<sup>42</sup>. Moreover, TSLP promotes the survival of CD8<sup>+</sup> T cells in both normal and lymphopaenic conditions<sup>44</sup>. Interestingly, whereas IL-7 induces the proliferation (as well as survival) of naive CD8<sup>+</sup> T cells in lymphopaenic mice, TSLP does not affect the proliferation of these cells<sup>44</sup>. 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<sup>+</sup> T cells that express high levels of IL-2R $\beta$  (also known as CD122)<sup>30,45–47</sup>, particularly the IL-2R $\beta^{\text{hi}}$ LY49<sup>+</sup> subset of memory CD8<sup>+</sup> T cells<sup>48</sup>, are the most sensitive to IL-15. Although IL-15 does not have an essential role in the homeostatic proliferation of memory CD4<sup>+</sup> T cells, IL-15 was reported to affect the homeostasis of these cells in the absence of IL-7 (REF. 49). Furthermore, depleting CD8<sup>+</sup> 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<sup>+</sup> T cells<sup>49</sup>. IL-15 is not crucial for the development of naive T cells, but *Il15<sup>-/-</sup>* mice have decreased numbers of naive CD8<sup>+</sup> T cells and these cells have decreased proliferative rates, which probably explains the slower recovery rate of adoptively transferred naive CD8<sup>+</sup> T cells in *Il15<sup>-/-</sup>* mice compared with wild-type mice<sup>40,47,50</sup>. Although memory CD8<sup>+</sup> T cells express high levels of IL-15R $\alpha$ <sup>46</sup> (TABLE 2), their proliferation is greater in response to administration of an IL-15–IL-15R $\alpha$  complex than of purified IL-15 alone<sup>51,52</sup>; in this system, IL-15 that is bound to IL-15R $\alpha$  is presented to cells expressing the other IL-15R subunits, IL-2R $\beta$  and  $\gamma_c$ <sup>53</sup>. Indeed, under physiological conditions, *trans*-presentation of IL-15 by IL-15R $\alpha$  on the surface of other non-T cells is required<sup>54</sup>, 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<sup>+</sup> T cell populations *in vitro*<sup>55</sup>. Whereas IL-21 alone induces the survival of naive but not memory mouse CD8<sup>+</sup> T cells, in the presence of IL-15 and IL-21 combined, the rate of apoptosis in both populations of CD8<sup>+</sup> T cells is markedly decreased and cell proliferation is increased<sup>55</sup>. Similarly, the combination of IL-15 and IL-21 increases antigen-independent proliferation of human naive CD8<sup>+</sup> T cells *in vitro*<sup>56</sup>, the number of CD8<sup>+</sup> T cells producing IL-2 and interferon- $\gamma$  (*IFN* $\gamma$ ) and the cytotoxic activity of these cells after TCR activation<sup>55,56</sup>. Although *Il21r<sup>-/-</sup>* mice have normal numbers of peripheral

**Trans-presentation**

A process by which the  $\alpha$ -chain of the interleukin-15 receptor (IL-15R $\alpha$ ) presents IL-15 in *trans* to other cells expressing a complex (with an intermediate affinity for IL-15) that contains IL-2R $\beta$  and the common cytokine receptor  $\gamma$ -chain ( $\gamma_c$ ), which then transduce a signal.



**Figure 2 | Direct and indirect effects of  $\gamma_c$  family cytokines and TSLP on T cell proliferation, homeostasis and differentiation.** Cytokines of the common cytokine receptor  $\gamma_c$  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<sup>57</sup>, overexpression of IL-21 increases the number of memory  $CD8^+$  T cells<sup>58</sup>; 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  $\gamma_c$  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<sup>59</sup> and it is important for the initiation of  $T_H2$  cell differentiation<sup>60,61</sup>. It is well known that IL-2 can induce the proliferation and survival of TCR-activated human and mouse T cells<sup>6,62</sup> and is required for sustained expansion of T cell populations<sup>8</sup>. 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<sup>63</sup>, 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))<sup>9</sup>. Conversely, IL-2 treatment during the contraction phase of the T cell response results in increased survival and accumulation of T cells<sup>8,63,64</sup>. 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-7R $\alpha$  and upregulate IL-2R $\alpha$ , IL-15R $\alpha$  and IL-2R $\beta$  expression (TABLE 2). It was therefore predicted that IL-7 is not required for the function of activated T cells<sup>29</sup>, and that IL-2 and/or IL-15, the production of which is also increased by activated dendritic cells (DCs)<sup>65–67</sup>, could increase the proliferative rate and/or decrease the contraction of effector T cell populations<sup>64,68,69</sup>. Although a selective population of primed T cells re-expresses IL-7R $\alpha$ <sup>70</sup>, IL-7 signalling is not essential for the formation of functional memory  $CD4^+$  and  $CD8^+$  T cells<sup>71–74</sup>, 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: TSLP expression is increased after TCR activation<sup>44,75</sup> (TABLE 2), TSLP increases the proliferation of TCR-activated  $CD4^+$  T cells *in vitro*<sup>42,75</sup> and TSLP production is increased during the acute phase of an immune response to pathogens and allergens<sup>76</sup>.

**Regulation of  $\gamma\delta$  T cell homeostasis.**  $\gamma\delta$  T cells are a population of T cells that arise from the same precursors as  $\alpha\beta$  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<sup>77,78</sup>. The expression of both  $\gamma_c$  and IL-7R $\alpha$  is essential for normal  $\gamma\delta$  T cell development<sup>78</sup>. Under lymphopaenic conditions,  $\gamma\delta$  T cells undergo MHC-independent homeostatic proliferation that requires IL-7 or IL-15 (REFS 79,80). Although  $\alpha\beta$  and  $\gamma\delta$  T cells express comparable levels of IL-7R $\alpha$  and IL-2R $\beta$ <sup>79</sup>, partial depletion of  $\alpha\beta$  T cells, NK cells or  $\gamma\delta$  T cells themselves significantly increases the homeostatic proliferation of  $\gamma\delta$  T cells, which shows that these cells compete for limited quantities of IL-7 and IL-15 (REFS 79–81). So, the maintenance of  $\gamma\delta$  T cells as well as  $\alpha\beta$  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-2R $\alpha$  (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<sup>7</sup>. Although IL-2 induces the proliferation and clonal expansion of conventional T cells<sup>6,62</sup>, 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<sup>7</sup>. However, the lack of IL-2, IL-2R $\alpha$  or IL-2R $\beta$  does not alter FOXP3 expression or result in a complete loss of  $T_{Reg}$  cells<sup>82–85</sup>. By contrast,  $\gamma_c$ -deficient (*Il2rg*<sup>-/-</sup>) mice and *Jak3*<sup>-/-</sup> mice, in addition to having very low numbers of T cells, are devoid of FOXP3<sup>+</sup>  $T_{Reg}$  cells<sup>83,86</sup>.



Table 2 | Expression of receptors for  $\gamma_c$  family cytokines and TSLP

Receptor chain	Level of expression		
	Naive T cells	Effector T cells	Memory T cells
$\gamma_c$ (CD132)	Intermediate	Intermediate	Intermediate
IL-2R $\alpha$ (CD25)	None	High	None
IL-2R $\beta$ (CD122)	Low	High	High*
IL-4R $\alpha$ (CD124)	None	High	ND
IL-7R $\alpha$ (CD127)	Intermediate	None <sup>†</sup>	High
IL-15R $\alpha$	Low	High	High
IL-21R	Low	High	ND
TSLPR <sup>§</sup>	Low	Intermediate	ND

\*Sustained at a high level on CD8<sup>+</sup> memory T cells. <sup>†</sup>Only a few effector T cells express IL-7R $\alpha$ . <sup>§</sup>The level of TSLPR expression by T cells is shown relative to its expression by dendritic cells.  $\gamma_c$ , common cytokine receptor  $\gamma$ -chain; IL, interleukin; ND, not determined; TSLP, thymic stromal lymphopoietin.

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

Although deficiency of IL-7 or IL-15 (which both activate STAT5) does not alter the number of FOXP3<sup>+</sup> T<sub>Reg</sub> cells<sup>88,94</sup>, 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<sub>Reg</sub> cells than is observed in mice lacking either IL-2 or IL-2R $\alpha$  alone<sup>88,95</sup>. Interestingly, mouse T<sub>Reg</sub> cells express low levels of IL-7R $\alpha$ <sup>94,95</sup>, and in contrast to other subsets of T cells that can re-express IL-7R $\alpha$  after culture *in vitro*, peripheral T<sub>Reg</sub> cells from mice do not upregulate IL-7R $\alpha$  expression after *in vitro* culture<sup>94</sup>. Nevertheless, the low level of IL-7R $\alpha$  that is expressed by mouse T<sub>Reg</sub> 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<sub>Reg</sub> cells<sup>95</sup>. Similarly, most human CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup> T<sub>Reg</sub> cells have lower levels of IL-7R $\alpha$  expression than do CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>-</sup> T cells<sup>96,97</sup>. *Il7ra*<sup>-/-</sup> mice have a marked decrease in the number of T<sub>Reg</sub> cells in lymphoid tissues and decreased suppressive activity compared with *Il7*<sup>-/-</sup> mice<sup>94</sup>. These differences can be explained by the ability of TSLP (which signals through a receptor that contains IL-7R $\alpha$ ) to also mediate the induction of T<sub>Reg</sub> cells<sup>94</sup>. In conclusion, IL-2, IL-7, IL-15 and TSLP all contribute to the development and function of T<sub>Reg</sub> cells.

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

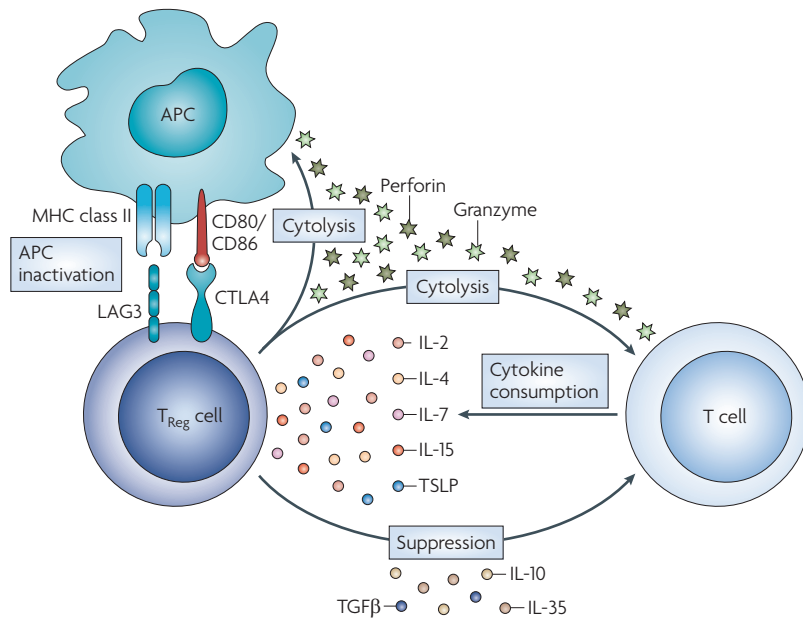
**Indirect effects of  $\gamma_c$  family cytokines on T cells**

*T cell survival and proliferation through DCs.* It is well known that  $\gamma_c$  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  $\gamma_c$  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-2R $\beta$  and  $\gamma_c$ <sup>66,101,102</sup> and upregulate the expression of IL-15R $\alpha$  in response to type I and II IFNs and inducers of nuclear factor- $\kappa$ B (NF- $\kappa$ B) activation, such as ligands for Toll-like receptors (TLRs)<sup>65,66</sup>. Similar signals promote the production of IL-15 by DCs and epithelial cells<sup>65,66</sup>. 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<sup>+</sup> and CD8<sup>+</sup> T cells<sup>65-67,103</sup>. 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<sup>104</sup>. 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 IFN $\alpha$ -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<sup>105</sup>.

Both IL-4 and TSLP are involved in T<sub>H</sub>2 cell responses and have essential roles in allergic diseases<sup>10,25,76</sup>, 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*<sup>148,149</sup>. 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 IFN $\alpha$ <sup>106</sup>. 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<sup>25</sup>. 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 ( $\alpha$ ,  $\beta$  and  $\omega$ ) 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 (IFN $\gamma$ ) 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- $\beta$  (TGF $\beta$ ), interleukin-10 (IL-10) and IL-35 and by the consumption of cytokines of the common cytokine receptor  $\gamma$ -chain ( $\gamma_c$ ) family. Deprivation of  $\gamma_c$  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<sup>25</sup>. 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<sup>107</sup>. 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<sup>108</sup>. 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<sup>109,110</sup>. Because IL-21 is produced by  $CD4^+$  T cells after antigen stimulation<sup>2</sup> 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,  $\gamma_c$  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- $\beta$  (TGF $\beta$ ), 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  $\gamma_c$  family cytokines, thereby resulting in the apoptosis of conventional T cells *in vitro*<sup>98,111</sup>. 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<sup>98</sup>. Note that the mechanisms listed above are not mutually exclusive and that more than one mechanism might be used.

### $\gamma_c$ 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  $\gamma_c$  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  $IFN\gamma$  production and increased IL-12R $\beta$ 2 expression by APCs<sup>112</sup>. Although IL-2 is the earliest detected cytokine to be produced by naive  $CD4^+$  T cells after TCR stimulation<sup>59</sup>, and this cytokine is one of the main products of  $T_H1$  cells<sup>113</sup>, 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<sup>114</sup>, but IL-21 does not affect expression of the  $T_H1$  cell-associated transcription factor T-bet (also known as TBX21) or of IL-12R $\beta$ 2 by mouse  $CD4^+$  T cells<sup>114</sup>. Instead, IL-21 can inhibit  $IFN\gamma$  production by naive  $CD4^+$  T cells that are undergoing  $T_H1$  cell differentiation by repressing expression of the T-box transcription factor Eomesodermin<sup>115</sup>. It is unclear whether this inhibition of  $IFN\gamma$  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  $IFN\gamma$ , T-bet and IL-12R $\beta$ 2 expression<sup>116</sup>, which indicates that, under certain circumstances, IL-21 might promote  $T_H1$  cell differentiation.

***T<sub>H</sub>2 cell differentiation.*** *In vitro* studies have shown that IL-2 and IL-4 are both required for the efficient induction of T<sub>H</sub>2 cells. IL-2 is produced early after the activation of naive CD4<sup>+</sup> T cells and activates STAT5A and STAT5B to promote increased transcription of the *Il4ra* gene, leading to the increased cell surface expression of IL-4R $\alpha$  (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<sup>60</sup>. 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<sub>H</sub>2 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<sub>H</sub>2 cytokine locus *in vivo*, which is consistent with the observation that IL-4 is produced by T<sub>H</sub>2 cells after they express IL-4R $\alpha$ <sup>61</sup>. So, IL-2-induced signalling during T<sub>H</sub>2 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-4R $\alpha$  expression, which indicates that multiple STAT5 activators might be able to prime T cells for T<sub>H</sub>2 cell differentiation<sup>61</sup>. Although IL-21 can also promote STAT5 activation, IL-21-induced signalling does not affect the efficiency of T<sub>H</sub>2 cell differentiation *in vitro*<sup>57</sup>, which is consistent with the fact that IL-21 mainly activates STAT3 rather than STAT5. IL-21R-deficient mice have decreased responses to T<sub>H</sub>2 cell-inducing pathogens; however, it is possible that this results from decreased effects of IL-21 on macrophage activation<sup>117</sup> rather than from direct effects on T<sub>H</sub>2 cells.

**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.

***T<sub>H</sub>17 cell differentiation.*** The differentiation of T<sub>H</sub>17 cells depends in part on TGF $\beta$ , an immunosuppressive cytokine that also has a role in T<sub>Reg</sub> cell differentiation. The presence of either IL-6 or IL-21 during priming with TGF $\beta$  subverts T cell differentiation from the FOXP3-directed T<sub>Reg</sub> cell pathway to the T<sub>H</sub>17 cell pathway through the induction of expression of the orphan nuclear receptor retinoic acid receptor-related orphan receptor- $\gamma$ t (ROR $\gamma$ t; also known as RORC)<sup>118–120</sup>. T<sub>H</sub>17 versus T<sub>Reg</sub> cell differentiation is therefore determined by the presence of IL-6 or IL-21.

IL-2 can promote the development of T<sub>Reg</sub> cells, and it inhibits the differentiation of naive CD4<sup>+</sup> T cells into T<sub>H</sub>17 cells<sup>121,122</sup>. Accordingly, administration of IL-2 to tumour-bearing mice can decrease the number of IL-17-producing cells and increase the number of T<sub>Reg</sub> cells<sup>123</sup>. Correspondingly, *Il2*<sup>-/-</sup> mice have a decrease in the number of T<sub>Reg</sub> cells<sup>84</sup> 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*<sup>-/-</sup> mice<sup>7</sup>. However, *Il17*<sup>-/-</sup>*Il2*<sup>-/-</sup> mice develop systemic autoimmune haemolytic anaemia to the same extent as *Il2*<sup>-/-</sup> mice, which indicates that IL-17-producing cells are not absolutely required for this disease process and that other potentially redundant

cytokines also contribute<sup>124</sup>. Although IL-2 inhibits T<sub>H</sub>17 cell differentiation, it can provide proliferative signals to human T<sub>H</sub>17 cells, as shown by the IL-2-induced *in vitro* proliferation of T<sub>H</sub>17 cells from normal donors and from patients with uveitis or scleritis<sup>125</sup>. Interestingly, the inhibitory effects of IL-2 on the T<sub>H</sub>17 cell lineage can be prevented by IL-1, which indicates that the local cytokine profile controls the IL-17<sup>+</sup> T cell pool<sup>126</sup>.

The role of IL-21 in the differentiation of T<sub>H</sub>17 cells is controversial. *In vitro* experiments have shown that IL-21 is crucial for upregulating IL-23R expression by T<sub>H</sub>17 cells<sup>120</sup>. IL-23, which is produced by APCs, is an important factor in the differentiation and proliferation of T<sub>H</sub>17 cells and therefore in inflammatory diseases, but IL-23R is not expressed by naive CD4<sup>+</sup> T cells. IL-21 therefore promotes the expansion of T<sub>H</sub>17 cell populations by increasing their responsiveness to IL-23. Although T<sub>H</sub>17 cell differentiation is decreased in the absence of IL-21-induced signalling *in vitro*<sup>118–120</sup>, the role of IL-21 in T<sub>H</sub>17 cell development *in vivo* and in T<sub>H</sub>17 cell-mediated autoimmune disease is less clear. Specifically, T<sub>H</sub>17 cell development in the lamina propria of the small intestine can occur in the absence of IL-21-induced signalling<sup>127</sup>. Moreover, although one study reported that the development of experimental autoimmune encephalomyelitis (EAE) was significantly decreased in IL-21-deficient mice<sup>119</sup>, two other studies found no difference in the development of EAE in either IL-21- or IL-21R-deficient mice<sup>128,129</sup>. So, although IL-21 can promote the differentiation of T<sub>H</sub>17 cells, its effects can apparently be compensated for by other cytokines, at least in certain circumstances.

***T<sub>FH</sub> cell differentiation.*** T<sub>FH</sub> cells are a distinct subset of CD4<sup>+</sup> T cells that provide help to B cells in germinal centres during the generation of T cell-dependent antibody responses. T<sub>FH</sub> cells are characterized by the expression of high levels of CXC-chemokine receptor 5 (CXCR5) and the co-stimulatory molecules ICOS and CD40L. T<sub>FH</sub> 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<sub>FH</sub> cells. *Il21*<sup>-/-</sup> mice have defective germinal centre formation as well as decreased numbers of T<sub>FH</sub> cells<sup>131</sup>. Unlike T<sub>H</sub>17 cells, which can also produce high levels of IL-21 (REF. 2), T<sub>FH</sub> cells develop independently of the transcription factor ROR $\gamma$ t and do not produce IL-17 (REF. 132). Although the differentiation of T<sub>FH</sub> cells during a normal T cell-dependent antibody response requires IL-21 production, the excessive differentiation of T<sub>FH</sub> 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<sub>FH</sub> cells in germinal centres in some systemic autoimmune diseases<sup>133</sup>.

***CD8<sup>+</sup> T cell differentiation.*** CD8<sup>+</sup> T cells also undergo differentiation into polarized T cytotoxic 1 (T<sub>C</sub>1), T<sub>C</sub>2 and T<sub>C</sub>17 cell populations, which parallel the CD4<sup>+</sup> T<sub>H</sub>1, T<sub>H</sub>2 and T<sub>H</sub>17 cell populations. One distinction is that naive CD8<sup>+</sup> T cells produce only minimal levels of IL-2 and no IL-21, so that the source of these cytokines during

**Table 3 | Effects of decreased versus increased signalling induced by  $\gamma_c$  family cytokines and TSLP**

Cytokine	Decreased signalling*		Increased signalling†	
	Positive effect	Negative effect	Positive effect	Negative effect
IL-2	Immunosuppression in organ allografts and in models of leukaemia or lymphoma (daclizumab) <sup>§</sup>	Lymphoproliferative disorders and autoimmunity associated with loss of T <sub>Reg</sub> 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 <sup>+</sup> 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 <sub>H</sub> 17 cell differentiation	Anti-cancer agent	Aberrant CD8 <sup>+</sup> 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. <sup>§</sup>Daclizumab (Zenapax; Roche) is a humanized IL-2R $\alpha$ -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<sup>147</sup>.  $\gamma_c$ , common cytokine receptor  $\gamma$ -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<sub>H</sub>17 cell, T helper 17 cell; T<sub>Reg</sub> cell, regulatory T cell; TSLP, thymic stromal lymphopoietin.

an immune response must be from either activated CD4<sup>+</sup> T cells or other cells, such as natural killer T cells (which can produce IL-21 (REF. 134)). In addition to a role for  $\gamma_c$  family cytokines in the expansion of CD8<sup>+</sup> T cell populations, IL-2 and IL-21 have distinct effects on CD8<sup>+</sup> T cell differentiation when they are present during TCR priming. The presence of IL-21 during priming leads to the generation of CD28<sup>hi</sup>CD8<sup>+</sup> T cells that can produce IL-2, potentially overcoming the requirement for IL-2 from CD4<sup>+</sup> T<sub>H</sub> cells<sup>135</sup>. Moreover, whereas priming of tumour-specific CD8<sup>+</sup> T cells *in vitro* in the presence of IL-2 can potentially promote their proliferation and increase their cytolytic activity, priming in the presence of IL-21 was shown to inhibit these processes<sup>136</sup>. However, when these two populations of CD8<sup>+</sup> T cells primed under different conditions were transferred into tumour-bearing mice, the IL-21-primed CD8<sup>+</sup> T cells had greater antitumour immunity and greater secondary clonal expansion and persistence than did the IL-2-primed CD8<sup>+</sup> 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<sup>+</sup> T cells<sup>136</sup>, which indicates that these cytokines might induce epigenetic changes at the time of priming. So, distinct  $\gamma_c$  family cytokines have different effects on CD8<sup>+</sup> 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,  $\gamma_c$  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<sup>+</sup> T cell populations in patients infected with HIV<sup>137,138</sup> and as an anticancer agent, with efficacy in the treatment of some patients with melanoma and renal cell carcinoma<sup>139</sup>. The related cytokine IL-15 holds promise as an adjuvant for vaccines<sup>139</sup>; IL-15 preferentially induces the proliferation of CD8<sup>+</sup> T cells rather than T<sub>Reg</sub> 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<sup>139</sup>. 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<sup>140</sup> and, similarly, the administration of IL-7 to humans induces a selective increase in the number of CD4<sup>+</sup> and CD8<sup>+</sup> T cells but does not affect the number of T<sub>Reg</sub> cells<sup>32,141</sup>.

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  $\beta$ -islet cells.

tumours, and it is now in Phase II clinical trials for the treatment of humans with cancer<sup>2,142</sup>. 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<sup>-/-</sup>* background<sup>21</sup>, and similarly, manifestations of SLE no longer develop when BXSB-*Yaa* mice are crossed to the *Il21r<sup>-/-</sup>* background<sup>23</sup>. 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<sup>25,76</sup> 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<sup>143–145</sup>. These studies collectively underscore a range of potential therapeutic uses for  $\gamma_c$  family cytokines and TSLP.

Concluding remarks and future directions

The  $\gamma_c$  family cytokines have central roles in the regulation of a range of immunological processes. The sharing of  $\gamma_c$  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  $\gamma_c$ . 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-4Ra, but decreases the expression of IL-7Ra). 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|IFN $\gamma$ |IFN $\gamma$ |IL-2|IL-2R $\alpha$ |IL-2R $\beta$ |IL-2R $\gamma$ |IL-4|IL-4R $\alpha$ |IL-7|IL7RA|IL-9|IL-12R $\beta$ 2|IL-15|IL-15R $\alpha$ |IL-21|JAK3|MCL1|STAT3|STAT5A|STAT5B|STAT6|T-bet|TGF $\beta$ |TSLP|TSLPR  
 OMIM: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>  
 IL-7RA-deficient SCID|JAK3-deficient SCID|XCID

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