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Cytokines of the γ_c family control CD4+ T cell differentiation and function

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Abstract

Naive $CD4^+$ T cells undergo massive proliferation and differentiation into at least four distinct helper T cell subsets after recognition of foreign antigen–derived peptides presented by dendritic cells. Each helper T cell subset expresses a distinct set of genes that encode unique transcription factor(s), as well as hallmark cytokines. The cytokine environment created by activated $CD4^+$ T cells, dendritic cells and/or other cell types during the course of differentiation is a major determinant for the helper T cell fate. This Review focuses on the role of cytokines of the common γ-chain (γ_c) family in the determination of the effector helper T cell phenotype that naive $CD4^+$ T cells adopt after being activated and in the function of these helper T cells.

Cytokines regulate a variety of cellular responses, including proliferation, differentiation and survival. Among the several different classes of cytokines, type I cytokines have a particularly important role. Type I cytokines have a four α-helix bundle structure and bind transmembrane proteins whose extracellular regions contain a hematopoietin receptor domain. This evolutionarily conserved, 200–amino acid region derived from a tandem of two ancestral fibronectin-like domains has four conserved cysteine residues in the amino-terminal segment and a tryptophan-serine doublet near the carboxy-terminal end[1]. Although they were first defined as cytokines, the type I cytokines also include hematopoietic factors and endocrine hormones. Their receptors belong to the type I cytokine receptor superfamily.

An important subfamily of the type I cytokines are those that use the common γ-chain (γ_c) to generate signaling receptor complexes. These include interleukin 2 (IL-2), IL-4, IL-7, IL-9, IL-15 and IL-21 (ref. 2). In addition, the cytokines IL-13 and TSLP are closely related to IL-4 and IL-7, respectively, and, although they do not use γ_c, they use an alternative chain (IL-13Rα1 for IL-13, and TSLPR for TSLP) that may have comparable features. In general, the receptor chain that binds the cytokine with high affinity is designated the α-chain (for example, IL-4Rα); the IL-2 receptor (IL-2R) and IL-15R complexes are exceptions to this rule. IL-2R consists of three subunits: the IL-2 receptor β-chain (IL-2Rβ (CD122)), which is the analog of the α-chains in other receptor complexes; the common γ-chain (γ_c (CD132)); and a third chain (IL-2Rα (CD25)) that is not a member of the structural family of type I

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cytokine receptors. IL-2Rα alone binds IL-2, although it does so with low affinity and no signaling ability. An intermediate-affinity IL-2R complex is composed of IL-2Rβ and γ_c, and all three subunits form the high-affinity IL-2R complex, which has both a rapid on rate and a slow off rate[3]. The IL-15R complex is similar to the IL-2R complex, with IL-2Rβ and γ_c but with the IL-15Rαhomolog of IL-2Rα. The IL-15R system, although structurally homologous to the IL-2R system, is unique in that not all the receptor subunits are necessarily expressed on the same cells. IL-15 may be captured by cells that express an IL-15Rα chain and then may be presented *in trans* (that is, as an IL-15-IL-15Rα complex) to neighboring cells that express IL-2Rβ and γ_c chains, which leads to IL-15-mediated immune responses[4].

Each of the receptors for the γ_c family of cytokines transduces signals through the kinases Jak1 and Jak3, but different members of the family activate different transcription factors of the STAT family[2]. IL-2, IL-7, IL-9 and IL-15 activate mainly STAT5 (both STAT5A and STAT5B); IL-4 activates STAT6 and, to a lesser extent, STAT5; and IL-21 activates mainly STAT3. In this Review, we will discuss the role of cytokines of the γ_c family in the fate of peripheral $CD4^+$ T cells during their differentiation into effector helper T cells after exposure to their cognate antigens and in their function. We emphasize results from mouse systems, recognizing that although the principles of helper T cell differentiation in mice and humans are similar, there are some differences in detail[5].

T cells originate in the thymus and undergo a process of selection in which cells able to bind complexes of self peptide and major histocompatibility complex (MHC) with some threshold affinity are rescued from apoptosis (positive selection), whereas cells with high affinity for self peptide–MHC complexes are eliminated (negative selection). Cytokines of the γ_c family have a crucial role in this selection process; excellent reviews of this topic have been published elsewhere[6–8].

When naive $CD4^+$ T cells recognize foreign antigen–derived peptides presented in the context of MHC class II on dendritic cells (DCs) in the periphery, these cells undergo a process that includes massive proliferation and differentiation into distinct helper T cell subsets. There is still considerable uncertainty about the number of these subsets, the precursor-product relationships among them and their ability to convert from one to another. At least four different subsets of helper T cells (T_H1, T_H2, T_H17 and regulatory T cells (T_{reg} cells)) have been studied in great detail. Each expresses a distinct set of regulatory transcription factors, including what is sometimes designated a ‘master regulator’, as well as hallmark cytokines. Indeed, the cytokine environment created by activated $CD4^+$ T cells themselves, by ‘partner’ DCs and/or by other cell types during the course of differentiation is one of the key determinants for the differentiation into distinct helper T cell subsets[9].

T_H1 differentiation: the role of IL-2

The master regulatory factor T-bet has a central role in T_H1 differentiation. In developing T_H1 cells, IL-2-driven activation of STAT5 controls the binding of T-bet to the conserved noncoding sequence CNS-1 in the promoter of the gene (*Ifng*) encoding interferon-γ (IFN-γ) and thereby regulates IFN-γ production and the positive feedback process through which

T_H1 differentiation proceeds[10]. In addition, IL-2 regulates induction of the IL-12Rβ2 subunit of the IL-12 receptor, an event critical to the completion of T_H1 differentiation because of the central role of IL-12 in both the induction of T-bet and the production of IFN-γ[11]. This IL-2 effect also depends on STAT5 activation[12]. There is a still unresolved controversy about whether the induction of T-bet expression requires the IL-2–STAT5 pathway[10,12]. The key cytokines involved in T_H1 differentiation are IFN-γ and IL-12, with the latter being a type I cytokine that does not use γ_c.

T_H2 differentiation: the role of IL-2 and IL-4

In vitro T_H2 differentiation requires stimulation via the T cell antigen receptor (TCR) and IL-4-mediated activation of STAT6, which jointly induce the expression of GATA-3, a T_H2 master regulatory transcription factor[13]. However, the very first report on *in vitro* T_H2 differentiation pointed out the requirement for both IL-4 and IL-2 for optimal T_H2 development[14]. Although the role of IL-2 in T_H2 differentiation was unclear at that time, subsequent studies have indicated a central role for IL-2 in T_H2 differentiation. Neutralization of endogenous IL-2 results in the failure of naive $CD4^+$ T cells to undergo T_H2 development without affecting their proliferation. In such experiments, the 'differentiation' and 'proliferation and survival' functions of IL-2 can be distinguished because IL-4, a key component of *in vitro* T_H2 differentiation, can provide the second two functions in place of IL-2 but cannot provide its differentiation function[15]. Indeed, ectopic expression of constitutively active STAT5A in activated $CD4^+$ T cells leads to robust T_H2 differentiation even when IL-4 activity is blocked and exogenous IL-12 is provided[16]. STAT5 binds to DNase I–hypersensitivity site II in the second intron of *Il4* (Fig. 1), although the importance of this second intron site relative to that of other potential STAT5-binding sites in the larger *Il4* genetic region has not been established. Thus, the IL-2–STAT5 pathway may function to maintain the *Il4* locus in an open configuration so that transcription factors required for T_H2 differentiation gain access to their binding sites.

IL-2 also upregulates IL-4RαC expression on activated $CD4^+$ T cells in a STAT5-dependent manner, which enhances the capacity of IL-4 to induce signals in developing T_H2 cells. The activation of STAT5 by IL-2 results in the binding of STAT5 to the IFN-γ-activated motif GAS3 in the *Il4ra* locus during the early stage of T_H2 differentiation[17] (Fig. 1). It should be noted that IL-4 itself also upregulates IL-4Rα expression, so the relative importance of IL-2 and IL-4 in enhancing the sensitivity of the developing $CD4^+$ T cells to IL-4 almost certainly depends on the timing of the availability of these cytokines during the T_H2 differentiation process.

In vivo, differentiation of $CD4^+$ T cells down the T_H2 pathway may proceed through either IL-4-dependent routes or IL-4-independent routes. Identification of the sources of IL-4 that initiate IL-4-dependent T_H2 differentiation *in vivo* has been of great interest for many years; among the cell types that have been considered are memory T_H2 cells, natural killer T cells, mast cells, basophils, eosinophils and the naive $CD4^+$ T cells themselves[18]. It has been reported that basophils serve as T_H2-inducing professional antigen-presenting cells *in vivo*, given their ability to express functional MHC class II molecules and to produce a large amount of IL-4 (refs. 19–21). However, the methodology used to establish such a function

for basophils involves depletion of these cells through the use of a monoclonal antibody to the FcεRI receptor for immunoglobulin E. It has been shown that this antibody results in the depletion of not only basophils but also a population of 'inflammatory' DCs expressing Fc∈RI that induce mainly T_H2 differentiation[22]. Furthermore, in another mouse model of depletion of basophils selectively *in vivo* in the offspring of the crossing of mice that express Cre recombinase in basophils (Basoph8 mice) with mice expressing diphtheria toxin α-chain from the ubiquitous *Rosa26* locus (Rosa-DTα mice), the absence of basophils does not affect the ability of $CD4^+$ T cells to produce IL-4 after infection with *Schistosoma mansoni*[23]. Whether basophils are dispensable for all aspects of T_H2 differentiation remains to be established.

A second main determinant of T_H2 differentiation is the strength of signals generated by engagement of the TCR. *In vivo* immunization with a low concentration of antigen favors antibody production over delayed-type hypersensitivity[24]. T_H1 differentiation is favored when agonist peptides are used for immunization, whereas altered peptide ligands, which interact with the TCR with lower affinity, favor T_H2 differentiation[25]. Indeed, in a wide variety of mutant mice in which TCR signals are partially impaired, T_H2 differentiation is favored[26–28]. *In vitro* differentiation of cells stimulated with low and high concentrations of peptide has shown that naive $CD4^+$ T cells that receive weak TCR signals increase their expression of GATA-3 in an IL-4-independent manner at ~14–24 hours after activation, whereas cells that receive strong TCR-mediated signals do not[29] (Fig. 2). The NF-κB1–Bcl-3 complex, the Notch-CSL pathway and the Wnt–β-catenin–TCF-1 pathway have each been proposed to serve a critical role in TCR-driven GATA-3 expression[30–34]. However, gain or loss of function of these pathways, which are the modalities used to study the role of these molecules in this process, may lead to either abnormal thymic development or poor T cell proliferation and survival, even if T cell development seems phenotypically normal[35–37]. Therefore, it is conceivable that the impairment of both GATA-3 expression and subsequent T_H2 differentiation may not be due to the direct regulation of GATA-3 expression by these pathways but may instead be secondary to either abnormal development or insufficient activation of $CD4^+$ T cells derived from donors in which the genes encoding these molecules have been manipulated.

Naive $CD4^+$ T cells that have received strong TCR signals not only fail to upregulate TCR-driven expression of GATA-3 but also do not activate STAT5 in response to IL-2 endogenously produced by activated $CD4^+$ T cells themselves, at least during the first 24 hours after stimulation. This defect in both GATA-3 induction and STAT5 activation through the action of the kinase Erk pathway results in a failure to produce IL-4 or to undergo subsequent T_H2 differentiation[29] (Fig. 2). The physiological relevance of the TCR signal strength–mediated regulation of *in vivo* T_H1 differentiation versus T_H2 differentiation has been an open question. However, two studies have shown that omega-1, a T2 RNase derived from *S. mansoni* egg antigen, acts on DCs to suppress IL-12 production and to diminish the intensity of TCR-mediated signals that naive $CD4^+$ T cells receive, which indicates that manipulation of DC function may result in weak TCR signals even if the antigen amount is not limiting and thus favor *in vivo* T_H2 differentiation[38,39].

Indeed, although IL-4 is essential for the differentiation of naive $CD4^+$ T cells into T_H2 cells *in vitro*[14,40], its requirement for *in vivo* T_H2 differentiation has been a matter of intense debate, given the fact that mice deficient in either IL-4 or STAT6 show normal T_H2 differentiation *in vivo* in response to infection with *Nippostrongylus brasilienis* or *Trichuris muris*[41,42]. In contrast, the deletion of *Gata3* specifically in activated T cells results in the failure to undergo T_H2 differentiation and instead results in the appearance of IFN-γ-producing $CD4^+$ T cells after infection with *N. brasilienis*[43], which indicates an indispensable role for GATA-3 in T_H2 development *in vivo*. Future investigations should focus on clarifying the mechanisms by which helminth infection regulates the induction of GATA-3 and suppression of transcription factors for differentiation into other helper T cell subsets during the early stages of the activation of naive $CD4^+$ T cells. It will also be of particular interest to identify helminth-derived substances similar to *S. mansoni* egg antigen–derived omega-1 that may be responsible for lowering TCR-mediated signals.

T_{reg} cell development and function: role of IL-2, IL-7 and IL-15

Most thymocytes that express TCRs that recognize self peptide in the context of MHC molecules with very low or high affinity are eliminated by failure of positive selection or by negative selection in the thymus, respectively. However, some cells with high-affinity TCRs escape the negative selection process and thus are potentially able to mediate destructive autoimmunity. To prevent such autoreactive T cells from being activated in the periphery, the immune system has evolved several means, one of which involves T_{reg} cells, a specialized subset of $CD4^+$ T cells with high expression of CD25 and the master regulatory transcription factor Foxp3 (ref. 44).

Similar to autoreactive T cells, thymus-derived T_{reg} cells, often called 'natural T_{reg} cells' (nT_{reg} cells), express a TCR with higher affinity for self peptide–MHC than that of TCRs on the bulk of conventional $CD4^+$ T cells, which indicates that nT_{reg} cells escape clonal deletion by negative selection during thymic development[45]. It has been proposed that there are two steps in the development of nT_{reg} cells, as follows: a fraction of immature $CD4^+$ single-positive thymocytes with self-reactive TCRs of sufficiently high affinity gives rise to $Foxp3^-CD25^+$ T_{reg} precursor cells that then give rise to cells that express Foxp3 in response to cytokines of the γ_c family without further activation through the TCR[46]. Indeed, mice deficient in IL-2, CD25 or IL-2Rβ have 50% fewer $Foxp3^+$ thymocytes as wild-type mice have[47–49]. Although the loss of IL-7 or IL-15 alone does not perturb the generation of thymic $Foxp3^+$ cells, the combined elimination of IL-2, IL-7 and IL-15 leads to complete abrogation of $Foxp3^+$ thymocytes, which indicates a substantial role for IL-2 and compensatory roles for IL-7 and IL-15 in nT_{reg} cell development[50,51].

Whether transforming growth factor (TGF-β) is required for the thymic development of nT_{reg} cells remains controversial[52,53]. However, TGF-β is essential for the differentiation of peripheral naive $CD4^+$ T cells into $Foxp3^+$ cells with regulatory ability, called 'induced T_{reg} cells' (iT_{reg} cells)[54]. IL-2 is required for TGF-β-mediated iT_{reg} cell differentiation *in vitro*[55]. Interestingly, the vitamin A metabolite retinoic acid promotes TGF-β-mediated induction of Foxp3 expression in $CD4^+$ T cells *in vitro* independently of the IL-2–STAT5 pathway[56]. Moreover, retinoic acid derived from $CD103^+$ DCs in the mesenteric lymph nodes and the

lamina propria of the small intestine has an essential role in the conversion of naive $CD4^+$ T cells into $Foxp3^+$ T cells with suppressive activity[57–59]. However, the proposal of a role for retinoic acid in generating iT_{reg} cells in the gut has been challenged by the observation that retinoic acid does not act as a cofactor for TGF-β-mediated induction of Foxp3 but is required for optimal activation of the TCR-proximal signaling cascades in $CD4^+$ T cells[60].

How nT_{reg} cells suppress the immune responses of conventional T cells has been of great interest. It has been shown that nT_{reg} cells abrogate the induction of *Il2* mRNA expression in $CD4^+CD25^-$ responder cells *in vitro* without affecting the initial activation of responder T cells, and that nT_{reg} cells require IL-2 for their ability to block *Il2* transcription in the target T cells[61]. Given that nT_{reg} cells do not produce IL-2 in response to stimulation via the TCR, the source of IL-2 required for nT_{reg} cells to demonstrate suppressor activity may well be the conventional $CD4^+$ T cells that will be the eventual targets of the activated T_{reg} cells. Interestingly, detailed kinetic analysis by IL-2-capture assay has shown that nT_{reg} cells do not begin to suppress IL-2 production by $CD4^+CD25^-$ responder cells until 6 hours of coculture, so nT_{reg} cells can receive IL-2 signals until then to activate their suppressor function[62]. However, that model has been challenged by the observation that under certain circumstances, nT_{reg} cells do not abolish IL-2 production by $CD4^+CD25^-$ responder cells but instead compete for IL-2 and for other cytokines that are essential for T cell survival *in vivo*, which leads to apoptosis of the responders owing to cytokine deprivation[63]. Overexpression of the antiapoptotic protein Bcl-2 or loss of the proapoptotic protein Bim in $CD4^+CD25^-$ responder cells renders these cells resistant to nT_{reg} cell–mediated suppression[61]. Further investigation of these contradictory findings in terms of ‘abrogated IL-2 production’ versus ‘cytokine deprivation’ will provide better understanding of the mechanism through which nT_{reg} cells suppress the immunological responses of $CD4^+CD25^-$ T cells.

Generation of T_H17 and follicular helper T cells: role of IL-21

T_H17 cells are important in protection from bacterial and fungal infection and in the development of autoimmunity. It has been proposed that the following three steps control the differentiation of naive $CD4^+$ T cells into T_H17 cells: differentiation induced by TGF-β and IL-6; IL-21-driven amplification; and IL-23-mediated stabilization[64,65]. During the differentiation step, TGF-β and IL-6 in combination with stimulation via the TCR cause naive $CD4^+$ T cells to express IL-23R and to induce the T_H 17 master regulatory transcription factor RORγt, and to produce IL-17A, IL-17F and IL-21 (refs. 66–69). Induction of IL-21 production depends on IL-6-driven activation of STAT3 and stimulation via the inducible costimulator ICOS[70,71]. During the amplification step, IL-21 acts together with TGF-β to further upregulate IL-17 production and IL-23R expression in a STAT3-dependent manner. Genetic loss of either IL-21 or its receptor IL-21R results in less T_H17 differentiation both *in vitro* and *in vivo*[70,72,73]. If mice are depleted of T_{reg} cells by treatment with antibody to CD25 before immunization, IL-21 is able to induce T_H17 responses *in vivo* even in the absence of IL-6, although to a lesser degree than if IL-6 is available. The cellular source of IL-21 in this setting remains unclear[72]. Thus, IL-21 seems to have an important role in the positive feedback regulation of T_H17 differentiation through its activation of STAT3. However, that conclusion has been challenged by a study reporting that mice

deficient in either IL-21 or IL-21R are still able to mount T_H17 responses *in vivo*, which indicates a dispensable role for IL-21 in T_H17 differentiation when proinflammatory cytokines such as IL-6, IL-1 and TNF are abundantly available[74].

Follicular helper T cells (T_{FH} cells) promote T cell–dependent humoral immune responses by providing T cell help to B cells and thereby promote the formation of germinal centers, affinity maturation of antibody-secreting B cells and long-lived antibody responses[75]. T_{FH} cells express the transcriptional repressor Bcl-6 as their master regulator[76–78] and the CXC chemokine receptor CXCR5 (refs. 79,80) and have high expression of the costimulatory molecules ICOS[79,80], PD-1 (ref. 81) and BTLA[82], as well as the signaling adaptor molecule SAP[83], but downregulate their expression of the transcription factor Blimp-1 (ref. 77). It is still a point of considerable controversy whether T_{FH} cells originate directly from naive $CD4^+$ T cells as a distinct subset, similar to T_H1, T_H2, T_H17 and iT_{reg} cells, or whether T_{FH} cells emerge from $CD4^+$ T cells that have adopted a T_H1, T_H2 or T_H17 cell fate. One key issue about the acquisition of T_{FH} identity is clarification of the timing and mechanism by which responding $CD4^+$ T cells acquire expression of Bcl-6 and CXCR5. CXCR5 expression is essential for the migration of activated $CD4^+$ T cells to the follicles, where they interact with B cells that express the same cognate peptide presented by DCs to undergo maturation into functional T_{FH} cells.

Mice with T cell-specific deletion of *Stat3* have a much lower frequency of $CD4^+CXCR5^+$ cells that arise *in vivo* in response to immunization with keyhole limpet hemocyanin in complete Freund's adjuvant, a phenotype that resembles that seen in deficiency in IL-6 or IL-21 (ref. 84). In contrast, mice deficient in IL-6 or IL-21 generate T_{FH} cells normally after infection with lymphocytic choriomeningitis virus (LCMV), which indicates a redundant role for these cytokines in the development of T_{FH} cells[85]. Although the combined absence of IL-6 and IL-21 results in a failure to secrete antigen-specific immunoglobulin G after infection with LCMV, such mice have only slightly less generation of T_{FH} cells than that of their wild-type counterparts[86]. As the dependence of LCMV-generated T_{FH} cells on STAT3 has not been determined, it is uncertain whether IL-6 and IL-21 may be replaced by another activator of STAT3 in this case or whether a STAT3-independent pathway exists for the generation of T_{FH} cells.

T_H17 and T_{FH} differentiation: role of IL-2

The IL-2–STAT5 pathway has been demonstrated to block T_H17 differentiation. When IL-2 is exogenously provided to T_H17-polarizing cultures, the generation of IL-17-producing cells is impaired, whereas there is an increase in the frequency of $Foxp3^+$ cells[87]. Naive $CD4^+$ T cells from mice of the OT-II strain (with transgenic expression of an MHC class II–restricted, ovalbumin-specific TCR) that are deficient in recombination-activating gene 1 and are on the scurfy background, which lack functional Foxp3, still fail to undergo T_H17 differentiation under T_H17-polarizing conditions in the presence of exogenous IL-2 (ref. 88). STAT5 competes with STAT3 for binding to multiple sites in the *Il17a-Il17f* locus; binding of STAT5 to these sites is associated with repressive epigenetic marks across the *Il17a* promoter region and enhancer elements[88], which suggests a mechanism through which IL-2 directly represses T_H17 differentiation (Fig. 3).

Two days after infection with LCMV, T cells from SMARTA mice (which have transgenic expression of a TCR specific for LCMV glycoprotein) $CD4^+$ develop into the following two subpopulations: $CD25^{hi}$ cells, which have high expression of Blimp-1 and undergo a program of differentiation into effector T cells (T_{eff} cells); and $CD25^{int}$ cells, which express Bcl-6 and CXCR5 and undergo differentiation into T_{FH} cells[89]. The failure of $CD25^{hi}$ cells to become T_{FH} cells suggests an inhibitory role for *in vivo* IL-2-generated signals in the development of T_{FH} cells. In addition, the IL-2–STAT5 pathway blocks the generation of T_{FH} cells by inducing Blimp-1, which results in the suppression of Bcl-6 expression[90–93] (Fig. 4). Interestingly, the crucial role of the IL-2–STAT5 pathway in the fate 'decisions' to develop into either T_{eff} cells or T_{FH} cells through regulation of the expression of the two mutually exclusive transcriptional regulators Blimp-1 and Bcl-6 resembles that observed for the differentiation of iT_{reg} cells and T_H17 cells, in which Foxp3 and RORγt reciprocally regulate each other (Figs. 3 and 4).

In addition to the mutual regulation of helper T cell differentiation as a result of the induction of distinctive transcription factors, TCR signal strength is also a key element in determining fate 'decisions' to develop into iT_{reg} cells or T_H17 cells, as well as T_{eff} cells or T_{FH} cells. If naive $CD4^+$ T cells receive weak TCR signals, they do not differentiate into T_H17 cells and express Foxp3 instead, even though they are exposed to T_H17-inducing cytokines[94–96]. Furthermore, the generation and function of T_{FH} cells depends on the strength of the binding of the TCR to a foreign peptide–MHC class II complex[97]. Notably, strong TCR signals transiently inhibit IL-2-driven activation of STAT5, despite abundant production of IL-2 by activated $CD4^+$ T cells, which thereby blocks T_H2 development[29,98]. Thus, it is conceivable that the generation of T_H17 cells and T_{FH} cells may require strong TCR signals to block the IL-2–STAT5 pathway so that the inhibitory effects of IL-2 can be abrogated (Figs. 3 and 4). Clarifying the molecular basis that underlies TCR signal strength–mediated control of the IL-2–STAT5 pathway may provide better understanding of the delicate balance between helper T cell subset fates that are reciprocally regulated.

Concluding remarks

Cytokines of the γ_c family have crucial roles in the fate 'decisions' of naive $CD4^+$ T cells to differentiate into distinct helper T cell subsets and in the function of these effector helper T cells. We have emphasized here the roles of cytokines of the γ_c family in this process through the activation of STAT proteins and the genes targeted by activated STAT proteins, particularly the so-called master regulatory transcription factors. Cytokines of the γ_c family signal through other signaling pathways as well, including activation of the metabolic checkpoint kinase mTOR. The two mTOR pathways, mTORC1 and mTORC2, have a unique function in influencing the fate of cells developing into distinct helper T cell subsets[99,100]. Whether these differences can be accounted for by the action of the cytokines that determine the 'choice' of helper T cell phenotype is not yet clear but is an important area for continued study.

Comprehensive analysis of the cytokine dependence of *in vivo* helper T cell differentiation as well as the regulation of the change in phenotype of differentiated cells ('plasticity') is of great potential importance because this may provide opportunities for the development of

drugs that can ensure that appropriate responses are mounted to given challenges and, possibly, to alter ‘inappropriate’ responses.

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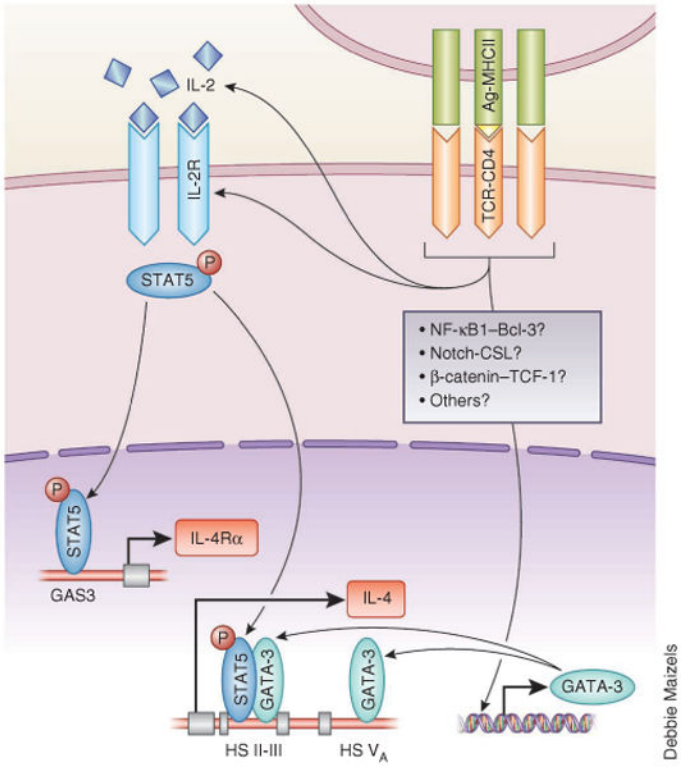

Figure 1.

A model for early T_H2 differentiation. The recognition of an antigen–MHC class II complex (Ag-MHCII) by the TCR on a naive $CD4^+$ T cell leads to the upregulation of GATA-3 expression independently of IL-4 during the early stages of T_H2 differentiation. The NF-ºB1-Bcl-3 complex, the Notch-CSL pathway and the Wnt–β-catenin–TCF-1 pathway have been each proposed to have a critical role in TCR-driven GATA-3 expression. GATA-3 binds to several sites on loci encoding T_H2 cytokines, ncluding DNase I–hypersensitivity sites II and III (HS II-III) and site V (HS V_A) in the *Il4* locus. Stimulation via the TCR also induces the production of IL-2 and expression of the IL-2R complex, which results in the activation of STAT5. Activated STAT5 binds to DNase I–hypersensitivity sites II and III, which act together with GATA-3 to induce small amounts of early IL-4 production, and also binds to the IFN-γ-activated GAS3 motif in the *Il4ra* locus to upregulate IL-4Rα expression.

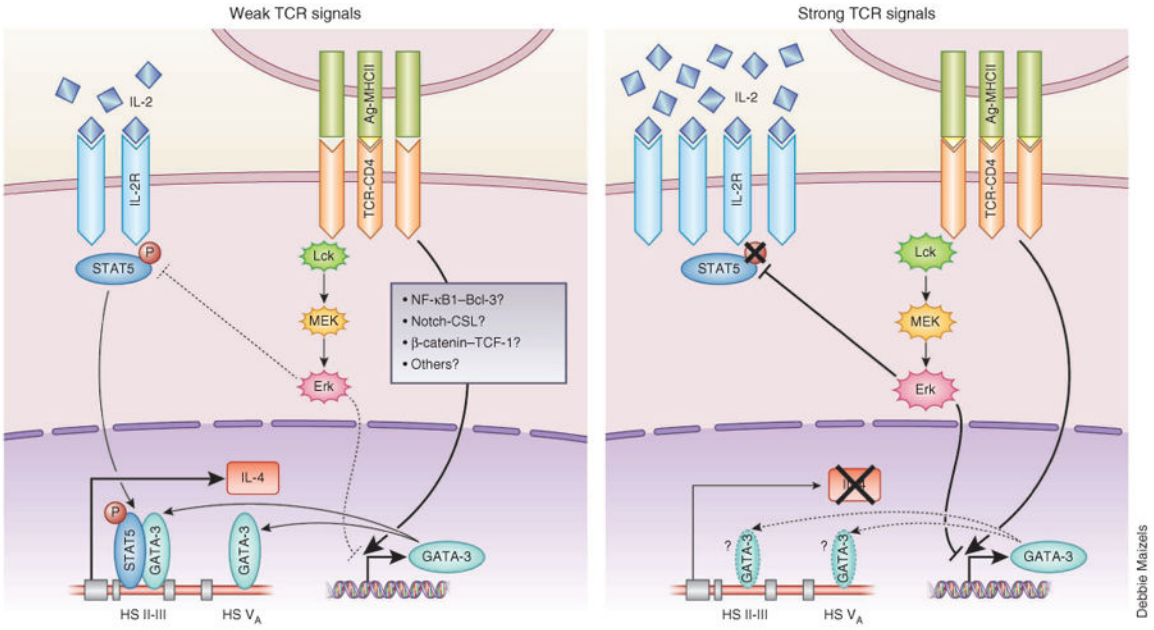

Figure 2.

A model for the regulation of early T_H2 differentiation by TCR signal strength. When naive $CD4^+$ T cells receive strong TCR signals (right), prolonged and intense activation of the Erk pathway results in not only the failure to upregulate TCR-driven early expression of GATA-3 but also transient inhibition of IL-2-mediated activation of STAT5, at least during the first 24 hours after stimulation, despite the abundant IL-2 production and IL-2R expression. This defect in both GATA-3 upregulation and STAT5 activation leads to a lack of both early production of IL-4 and subsequent T_H2 differentiation. In contrast, when naive $CD4^+$ T cells receive weak TCR signals (left), the degree of activation of the Erk pathway is not strong enough to suppress TCR-driven early expression of GATA-3 or to block STAT5 activation in response to small amounts of IL-2, which allows T cells to generate early production of IL-4 and to undergo subsequent T_H2 differentiation.

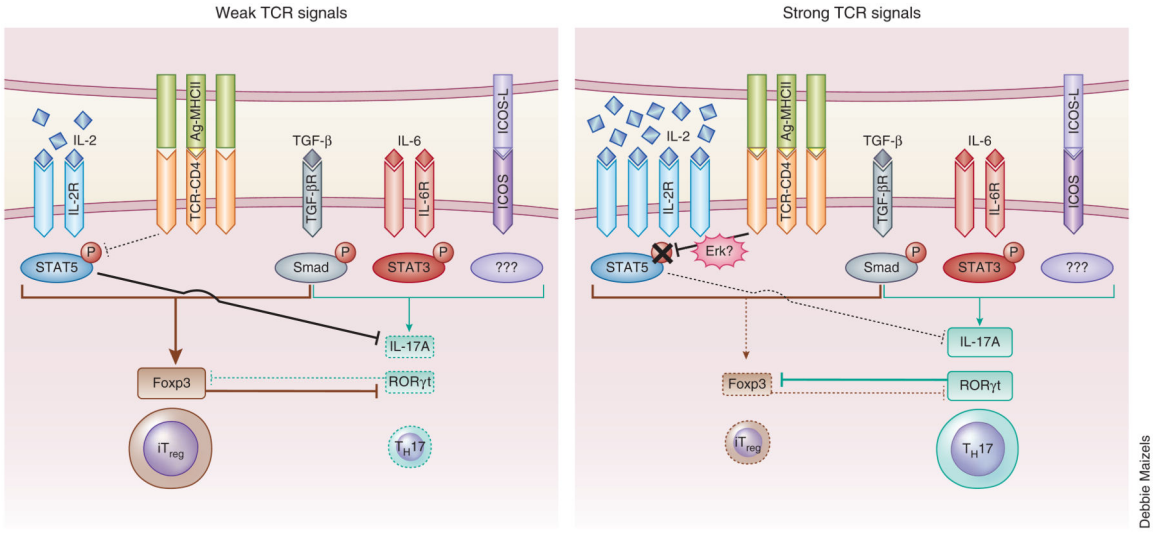

Figure 3.

A model for early determination of iT_{reg} fate versus T_H17 fate controlled by TCR signal strength. During early T_H17 differentiation phase, naive $CD4^+$ T cells require a combination of the cytokines IL-6 and TGF-β and costimulation (including ICOS), as well as strong TCR signals, to induce the expression of RORγt and T_H17 cytokines (right). When naive $CD4^+$ T cells receive weak TCR signals under T_H17-polarizing conditions, the differentiation of Foxp3-expressing iT_{reg} cells is favored (left). Although weak TCR signals induce only small amounts of IL-2 production and IL-2R expression, IL-2-mediated STAT5 activation blocks IL-17A production and induces Foxp3 expression, which suppresses the induction of RORγt and thereby favors iT_{reg} differentiation. In contrast, despite abundant IL-2 production and IL-2R expression, transient inhibition of STAT5 activation by strong TCR signals leads to the failure to induce Foxp3 but allows expression of genes encoding RORγt and T_H17 cytokines and thereby favors T_H17 differentiation. Smad, signal-transducer protein(s) downstream of the receptor for TGF-β (TGF-βR).

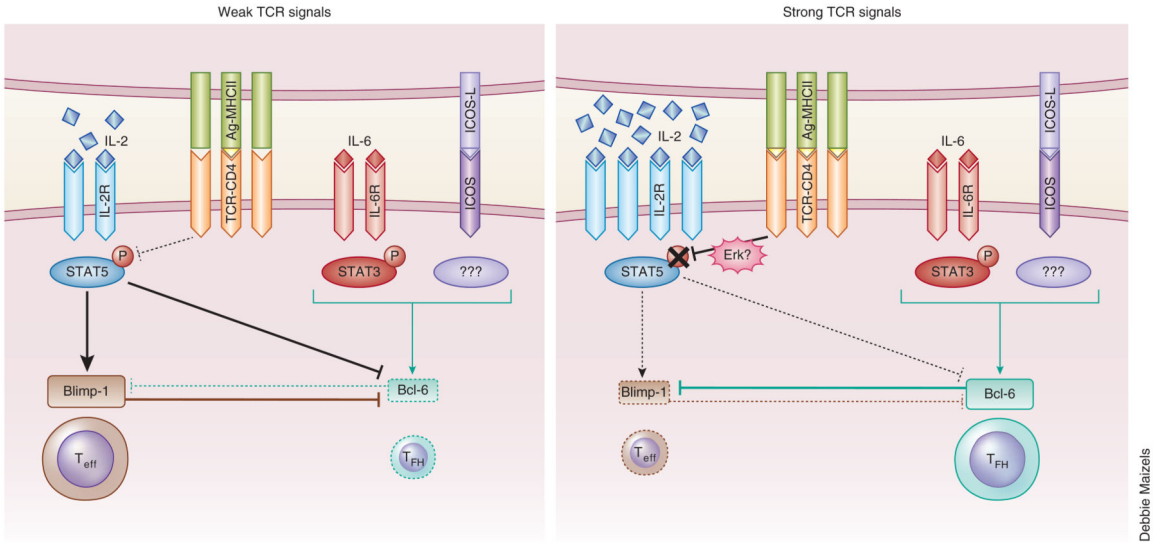

Figure 4.

A model for early determination of T_{eff} cell fate versus T_{FH} cell fate controlled by TCR signal strength. During the early phase of differentiation into the T_{FH} cell subset, naive $CD4^+$ T cells require the cytokine IL-6 and costimulation (including ICOS), as well as strong TCR signals, to induce the expression of Bcl-6 (right). Although strong TCR signals induce abundant production of IL-2 and expression of the IL-2R complex, transient inhibition of STAT5 activation, presumably through the action of the Erk pathway, leads to the failure to express Blimp-1 and allows Bcl-6 expression induced by IL-6 and stimulation via ICOS and thereby results in differentiation into the T_{FH} cell subset. In contrast, T cells that have received weak TCR signals under T_{FH} cell–polarizing conditions can activate STAT5 in response to small amounts of IL-2, which induces Blimp-1 expression and suppresses Bcl-6 expression and thereby results in 'preferential' differentiation into the T_{eff} cell subset (left).