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From IL-2 to IL-37: the expanding spectrum of anti-inflammatory cytokines

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Abstract

Feedback regulatory circuits provided by regulatory T cells (T_{reg} cells) and suppressive cytokines are an intrinsic part of the immune system, along with effector functions. Here we discuss some of the regulatory cytokines that have evolved to permit tolerance to components of self as well as the eradication of pathogens with minimal collateral damage to the host. Interleukin 2 (IL-2), IL-10 and transforming growth factor-β (TGF-β) are well characterized, whereas IL-27, IL-35 and IL-37 represent newcomers to the spectrum of anti-inflammatory cytokines. We also emphasize how information accumulated through *in vitro* as well as *in vivo* studies of genetically engineered mice can help in the understanding and treatment of human diseases.

The immune system protects humans from myriad invaders in the form of parasites, viruses, bacteria, fungi, germinating pollen grains and so on. However, it is critical to distinguish between friend and foe to maintain homeostasis and prevent host damage. The microbes that live in symbiosis with humans and that, among their many roles, permit humans to digest food, produce vitamins, regulate the development of the immune system and prevent the growth of pathogenic microbes can be classified as 'friends'[1–5]. Mammals have a sophisticated immune system that does the tricky job of rejecting the harmful non-self and tolerating microbial friends without reacting to its own constituents. This is a fine line to walk. Incapacitation of the immune system through genetic mutation and exposure to radiation or chemotherapy, among other factors, can lead to life-threatening infections. Lack of regulation, on the contrary, leads to inflammation and autoimmunity.

To accomplish the task noted above, the immune system relies on effector immune responses tailored to eradicate particular pathogens, as well as feedback regulatory circuits provided by regulatory T cells (T_{reg} cells) and suppressive cytokines. The original observations that led to the identification of innate and adaptive immunity did not cover the concept of counter-regulation. It took half a century to show that the immune system can be actively and specifically silenced or made tolerant. Deciphering the mechanisms that lead to immune tolerance has been an arduous journey because of their diversity and complexity. This includes the deletion of autoreactive T cells in the thymus (the so-called 'central tolerance') and dominant mechanisms of peripheral tolerance in which suppressive or regulatory T cells, 'instructed' by tolerogenic dendritic cells (DCs)[6–8], prevent or limit the activation of autoreactive T cells.

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The concept of regulatory or suppressor T cells is now firmly established[9–11]. Three main types of $CD4^+$ T_{reg} cells can be distinguished. Two express the transcription factor Foxp3, which can be induced naturally in the thymus (natural T_{reg} cells) or in the periphery (inducible T_{reg} cells). The third type, the Tr1 cells, do not express Foxp3 but secrete interleukin 10 (IL-10) and transforming growth factor-β (TGF-β) in response to antigenic stimulation[12–14]. $Foxp3^+$ T cells have a critical role in the maintenance of self-tolerance, as demonstrated in patients with IPEX syndrome ('immune dysregulation polyendocrinopathy enteropathy, X-linked'). These patients, who have mutations in the gene encoding Foxp3, suffer from a combination of organ-specific autoimmune diseases[15–17]. The $Foxp3^+$ T cell population is composed of subsets that can be distinguished on the basis of their expression of cell-surface markers[18–20], and they control effector cells such as those of the helper T cell subsets T_H1, T_H2 and T_H17 through the expression or activation of specific helper T cell–associated transcription factors. Expression of the chemokine receptors CCR6, CXCR3, CCR4 and CCR10 allows the separation of human $Foxp3^+$ T_{reg} cells into four independent cell populations[21]. Human blood T_{reg} cells have also been divided into two subsets based on their expression of CD45RA (a marker of naive cells) and Foxp3. Thus, $CD45RA^+Foxp3^{lo}$ cells include naive or resting T_{reg} cells, whereas $CD45RA^-Foxp3^{hi}$ cells include effector or activated T_{reg} cells. $CD45RA^-Foxp3^{lo}$ cells are not T_{reg} cells[22].

It took considerable effort to establish how T_{reg} cells suppress immune responses. Several mechanisms have been identified that contribute to their suppressive functions (Fig. 1). These include both cell contact– and cell factor-dependent mechanisms, such as the production of IL-10; the production and surface expression of TGF-β; the production of IL-35; the release of cytolytic molecules such as granzyme and perforin; the consumption of IL-2 through high density of cell-surface CD25 (the α-chain of the IL-2 receptor), which 'weans' effector T cells from IL-2; and the degradation of ATP through ectonucleotidases; and expression of the inhibitory receptor CTLA-4, which outcompetes the costimulatory receptor CD28 on effector cells for access to the costimulatory molecules CD80 and CD86 on antigen- presenting cells[23–26]. Many studies have reported alterations in the frequency and/or function of T_{reg} cells in systemic autoimmune diseases[27]. We will not discuss the strategies that have been proposed for the adoptive transfer of T_{reg} cells into transplant patients or patients suffering from autoimmunity[28,29]. Instead, this Review will describe some of the regulatory cytokines that are involved in the generation of immunotolerance and protection of the host during immune responses that are induced to eradicate invading pathogens. Much can also be learned from certain pathogens and from malignancies, as they exploit unique mechanisms of host tolerance to evade the immune attack. Clearly, rational understanding of these mechanisms will have a considerable effect on medicine, as it may lead to the development of targeted therapies that will complement the present approaches. These approaches include monoclonal antibodies that antagonize proinflammatory cytokines, chemical agents that block cytokine signaling pathways, deletion of specific cell populations or blockade of costimulation[30].

More specifically, here we will discuss six regulatory cytokines and classify them into two distinct groups on the basis of the extent of the present knowledge. For IL-2, IL-10 and TGF-β, the old triad of anti-inflammatory cytokines, we extract those salient features that distinguish them from each other. We also summarize the known key features of the newcomers IL-27, IL-35 and IL-37. We emphasize how information accumulated through *in vitro* as well as *in vivo* studies of genetically engineered mice can help in the understanding and treatment of human disease.

IL-2

IL-2 was discovered 30 years ago through its ability to induce the *in vitro* growth of activated T cells[31]. It might be predicted that IL-2 deficiency would lead to immunodeficiency. However, contrary to the expectations at the time, IL-2-deletion in mice does not result in grossly abnormal or impaired lymphocyte development. Instead, such mice die prematurely from invasion of nonlymphoid organs by activated T cells, associated with autoimmune anemia and inflammatory bowel disease[32,33]. The conundrum was resolved with the discovery of T_{reg} cells that have high expression of CD25 and thereby consume IL-2 (ref. 34).

Patients with mutations in *FOXP3* and at least one patient with a *CD25* mutation developed severe autoimmune multiorgan involvement, which indicates the importance of IL-2 and Foxp3 for T_{reg} cell function in humans[16,17,35]. Studies of mice of the nonobese diabetic strain have shown that susceptibility to diabetes is associated with lower expression of IL-2 (refs. 36–39). In fact, IL-2 is critical for the maintenance of T_{reg} cells in the periphery, and neutralization of IL-2 results in autoimmunity[40]. Conversely, administration of a low dose of IL-2 to mice of the nonobese diabetic strain prevents the development of diabetes and can even induce remission of established disease[41,42]. IL-2 seems to prevent diabetes by inducing a repertoire of islet-reactive $CD4^+Foxp3^+$ T_{reg} cells that suppress low-avidity islet-reactive effector cells, which thus escape negative selection in the thymus[43].

IL-2 also controls inflammation by inhibiting T_H17 differentiation. It does so by interfering with IL-6-dependent signaling events[44], including downregulation of expression of the IL-6 receptor and replacement of the transcription factor STAT3 with STAT5 on target DNA-binding sites in genes required for T_H17 differentiation[44,45]. Indeed, *Il2*$^{-/-}$ mice have higher concentrations of IL-17 in the serum[44]. The differentiation of T_H17 cells is facilitated by the specific expression of Aiolos, a member of the Ikaros family of transcription factors that directly silences the *Il2* locus[46]. Actually, the consumption of IL-2 by $Foxp3^+$ T_{reg} cells facilitates the differentiation of T_H17 cells *in vitro* and *in vivo*[47,48]. Thus, administration of IL-2 should be considered for inhibiting IL-17-dependent inflammatory processes.

IL-2 also affects the development of follicular helper T cells (T_{FH} cells), a subset of T cells that control humoral immune responses[49–52]. T_{FH} cells are characterized by the production of IL-21 and the expression of CXCR5, which allows the localization of these cells to developing germinal centers, where they help B cells undergo isotype switching and somatic mutations[52]. Human $CXCR5^+CD4^+$ T cells can be divided into three subsets according to chemokine-receptor expression. These subsets can be altered in systemic autoimmunity, such as dermatomyositis. Administration of IL-2 to mice infected with influenza virus results in a considerable decrease in the titers of influenza virus–specific immunoglobulin G1 (IgG1). This decrease is associated with a decrease in germinal-center formation and in the number of influenza virus–specific plasma cells. As discussed above for T_H17 cells, the inhibitory effect of IL-2 on the development of T_{FH} cells is indirect, as IL-2 interferes with commitment to the T_{FH} lineage without affecting already differentiated T_{FH} cells[53–55].

Thus, by increasing the number of T_{reg} cells and decreasing the number of T_H17 and T_{FH} cells, IL-2 can prevent the uncontrolled expansion of immune responses and limit overall inflammation. These findings have important therapeutic implications. Although high-dose IL-2 is an approved therapy for metastatic cancer, its clinical value has proven limited, possibly because of the population expansion of T_{reg} cells rather than that of tumor-specific effector cytotoxic T lymphocytes[56]. In keeping with the regulatory properties of IL-2, two exciting early proof-of-concept studies have demonstrated that the administration of low-

dose IL-2 can diminish inflammation and ameliorate disease in patients suffering from chronic graft-versus-host disease or hepatitis C virus–related vasculitis[57,58].

IL-10

Initially described as a product of T_H2 cells that inhibits the function of T_H1 cells, IL-10 is now recognized to be produced by almost every type of cell of the immune system, including most lymphocyte populations and cells of the innate immune system, such as antigen-presenting cells (DCs and macrophages) and granulocytes[59–61]. IL-10 is the best-characterized member of a family that includes IL-19, IL-20, IL-22, IL-24 and IL-26 (ref. 62). At least four viruses 'highjack' the gene encoding IL-10 to evade the host immune response.

IL-10 limits the immune response during infection and thus prevents immune system–mediated damage to the host[63]. There are several layers of regulation of IL-10 expression[64]. Enhancement or silencing of transcription of the gene encoding IL-10 depends first on chromatin structure and then on accessibility to a set of transcription factors. The next level of regulation is provided by post-transcriptional mechanisms, which might explain why different cells ultimately produce different amounts of IL-10 and for different durations[48,65].

In mice, IL-10 deficiency leads to colitis after colonization by particular microorganisms[66,67], which suggests an important role for IL-10 in the control of intestinal homeostasis. This is further evident in humans, as mutation in the genes encoding either IL-10 gene or its two receptor components results in an autosomal recessive disease characterized by early-onset severe inflammatory bowel disease[68,69].

IL-10 acts at various stages of the immune response in a coordinated way that efficiently restrains the inflammatory process. IL-10 affects many important functions of monocytes, macrophages and DCs, from phagocytosis to the production of cytokines to the expression of costimulators and the processing and presentation of antigens. IL-10 inhibits the production of proinflammatory cytokines and chemokines by DCs, macrophages and monocytes. It also inhibits the expression of major histocompatibility complex and costimulatory molecules. In addition, it activates a protolerogenic pathway in DCs through the upregulation of the IL-1 receptor IL-1RA, TGF-β, the inhibitory immunoglobulin-like transcript receptors and major histocompatibility complex class III molecules such as HLA-G[70]. That in turn may contribute to the induction of IL-10, providing an autocrine loop for reinforcement of immunoregulation. In response to IL-10, DCs can induce the generation of IL-10 from many T cell subsets[70], which further reinforces immunotolerance and/or immunoregulation.

The anti-inflammatory effects of IL-10 are not mediated solely through effects on DCs and macrophages[71]. IL-10 also directly acts on proinflammatory T_H17 cells and 'T_H1 plus T_H17' cells (positive for IL-17A and interferon-γ) cells, which have high expression of a functional IL-10 receptor[72]. IL-10 blocks the proliferation of T_H17 cells *in vivo*, which holds promise for the treatment of established colitis[72,73]. IL-10 also has a direct effect on $CD4^+Foxp3^+$ T_{reg} cells *in vivo* by promoting their survival[74] and contributes to the function of $Foxp3^+$ T_{reg} cells, as mice with T_{reg} cell–specific ablation of IL-10 develop inflammatory bowel disease. However, such mice do not develop systemic autoimmunity, which suggests that IL-10 production by $Foxp3^+$ T_{reg} cells is necessary for the control of immune responses at environmental interfaces[75]. In humans, IL-10 has a potent effect on the growth and differentiation of B cells[76,77]. IL-10 is a switch factor for IgG1 and IgG3 and, in combination with TGF-β, for IgA1 and IgA2 (an isotype found in humans but not in mice), which are associated with mucosal protection. Overall, whereas IL-10 may function in the

gut to restrain inflammatory and immune processes (and thus disease), IL-10 also functions to eradicate or control infection by mucosal pathogens and commensal bacteria.

A wide variety of diseases seem to be associated with overproduction of IL-10, including autoimmune diseases such as systemic lupus erythematosus, cancers such as melanoma and infectious diseases such as leishmaniasis and possibly tuberculosis[60]. IL-10 has been administered to a large number of patients suffering from various diseases. Early phase I and II studies showed trends toward efficacy for systemically administered IL-10 in both psoriasis and Crohn's disease, results that have not been confirmed in larger blinded studies[60]. It remains possible that the induction of IL-10 at the right site and at the right time, or its targeted delivery, might help control inflammatory pathologies. Targeting of a microbial antigen to the asialoglycoprotein receptor on the surface of human DCs through a fusion protein of antibody to DC asialoglycoprotein receptor and antigen elicits IL-10 production by DCs[78]. That in turn 'instructs' both naive and memory antigen-specific T cells to secrete IL-10 and develop IL-10-dependent immunosuppressive properties. However, antagonists to IL-10 might prove useful for the treatment of chronic infectious diseases and cancer[60].

TGF-β

TGF-β belongs to a family of molecules with many roles in a variety of cell types. So far, more than 40 members of this family are known. These proteins have a dimeric structure and cluster in several subfamilies. The TGF-β subfamily includes six isoforms, three of which are expressed in mammals[79–82]. Of those, TGF-β1 is involved in embryogenesis and has the most prominent role in the immune system by controlling several aspects of inflammatory responses, T cell differentiation, B cell isotype switching and tolerance (Fig. 2).

The pivotal role of TGF-β in immune tolerance was identified in TGF-β1-deficient mice, which develop an early and fatal multifocal inflammatory disease that is prevented by depletion of either $CD4^+$ or $CD8^+$ T cells[83]. Indeed, most tissues have high expression of the gene encoding TGF-β, and TGF-β seems to have a role in immune homeostasis[84]. That contrasts with other anti-inflammatory cytokines such as IL-10, whose expression is minimal in unstimulated tissues and seems to require triggering by commensal or pathogenic flora. Unlike the disease of IL-10-deficient mice, the inflammatory disease in TGF-β-deficient mice starts early in life, before major challenge with microbes. The systemic inflammation might actually be due to T cell autoreactivity, as demonstrated through genetic studies, most particularly of mice with T cell–specific deficiency in the TGF-β receptor TGF-βRII. Thus, TGF-β signaling is indispensable for limiting T cell responses to self in the periphery and thereby has a critical role in steady-state immunotolerance or homeostasis.

TGF-β is essential for the induction of Foxp3 in naive $CD4^+$ T cells[85,86] and does so in synergy with retinoic acid[87–89]. Notably, TGF-β and retinoic acid are produced by the $CD103^+$ DCs of the small intestine, which are inducers of T_{reg} cells. TGF-β further induces the differentiation of naive T cells into pathogenic T_H17 cells[90,91] while inhibiting the generation of T_H1 and T_H2 cells[92]. The gut shows enrichment for $Foxp3^+$ T_{reg} cells and T_H17 cells, and the balance between these two populations is tightly controlled[93]. In this context, TGF-β is an important switch factor for IgA, the 'mucosal' isotype, and mice with genetically altered TGF-β signaling lack IgA[94,95]. *In vitro* studies of human cells have further confirmed the role of TGF-β in isotype switching to both IgA1 and IgA2, an activity enhanced by IL-10 and IL-21 (ref. 96).

TGF-β is initially produced as an inactive protein complex that undergoes a multistep maturation process. It is translated as a dimeric pre-pro-TGF-β, which is cleaved to yield the

latent TGF-β (LTGF-β) complex composed of homodimeric LAP (latency-associated peptide) that wraps around homodimeric mature TGF-β[97]. Proteolytic cleavage allows the generation of three different forms of TGF-β: the small latent form (LTGF-β) composed of TGF-β bound to LAP; a large soluble latent form that consists of LTGF-β covalently linked to latent TGF-β-binding protein; and a membrane latent form composed of LTGF-β associated with the membrane protein GARP (LRRC32)[98]. All three forms require further proteolytic processing to free the active TGF-β component.

The activation of TGF-β proceeds through the degradation of LAP or its conformational alteration. Plasmin, matrix metalloproteinases and thrombospondin-1 participate in proteolytic activation of TGF-β. Integrins $\alpha_V\beta_6$ and $\alpha_V\beta_8$ activate TGF-β through different mechanisms after binding to the LAP Arg-Gly-Asp motif. The phenotype of mice with DC-specific $\alpha_V\beta_8$ deficiency is similar to that of mice with T cell–specific deletion of TGF-β[99]. Both naive T cells and T_{reg} cells produce latent TGF-β after encountering antigen-loaded DCs. The $\alpha_V\beta_8$ on DCs then activates latent TGF-β, which results in the release of active soluble TGF-β into the microenvironment. Thus, targeting $\alpha_V\beta_8$ in DCs might prove useful for the modulation of TGF-β function. Indeed, parasites and bacteria[100,101] have learned how to exploit the TGF-β signaling pathway to suppress immune responses by inducing Foxp3 in naive T cells. Studies of TGF-βRII-deficient T cells have suggested that TGF-β contributes to T cell tolerance by enhancing T_{reg} cell function and inhibiting effector T cells. Thus, in the absence of TGF-β signaling in T cells, $CD4^+$ T_{reg} cells progressively disappear from the periphery[102,103].

Alterations in specific components of the TGF-β signaling pathway may contribute to a broad range of pathologies, such as cardiovascular and developmental diseases, fibrosis and cancer. Antagonists to the TGF-β pathway are being developed for the treatment of bone diseases, fibrosis and cancer. Hopefully, these antagonists will prove to be safe enough for the targeted manipulation of the TGF-β signaling pathways in the context of autoimmunity and inflammation.

The new triad: IL-27, IL-35 and IL-37

The IL-12 family includes four heterodimeric molecules, IL-12, IL-23, IL-27 and IL-35, which are composed of shared α-chains and β-chains (Fig. 3). Whereas IL-12 and IL-23 have proinflammatory properties, IL-27 and IL-35 have anti-inflammatory properties. IL-12 and IL-23 share the β-chain p40 (IL-12β), whereas IL-27 and IL-35 share the β-chain EBI3. IL-12 and IL-35 share the α-chain p35, whereas IL-23 and IL-27 have unique α-chains[104]. IL-12 and IL-23 are disulfide-linked heterodimers that are secreted efficiently, whereas IL-27 and IL-35 lack the disulfide linkage and are secreted in small amounts. Whereas IL-35 is produced mainly by T_{reg} cells, the secretion of IL-12, IL-23 and IL-27 by myeloid cells such as macrophages and DCs is dependent on the set of IRF transcription factors that are activated after contact with specific pathogen–associated molecular patterns[105].

IL-27

IL-27 is composed of p28 (IL-30) and EBI3 subunits[106]. It is produced mainly by macrophages and DCs. Initially, IL-27 was described as a T_H1-promoting factor, but subsequent studies have demonstrated its anti-inflammatory roles. In particular, mice deficient in the receptor for IL-27 that are infected with *Leishmania* die from excessive immune responses[107,108]. IL-27 converts activated, inflammatory $CD4^+$ T cells into IL-10-producing T_H1 or Tr1 cells[109,110]. IL-27 upregulates expression of the transcription factor AhR in T cells. After activation, AhR acts in synergy with the transcription factor c-Maf and allows the activation of *Il10* and *Il21*, which results in the generation of Tr1 cells[111]. IL-27 also prevents the development of T_H2 cells and T_H17 cells in various inflammatory

settings[110]. Studies of human visceral leishmaniasis have concluded that IL-27 is associated with responses in which T cells produce effector cytokines and IL-10 (ref. 112). Such findings suggest that 'turning on' IL-27 may be considered as a treatment for inflammatory diseases. However, IL-27 also suppresses the production of IL-2, which might hamper the growth of T_{reg} cells[113], thereby resulting in the induction of colitis in mice[114]. Thus additional studies are needed to determine how the ability of IL-27 to induce IL-10 counteracts the ability of IL-27 to limit T_{reg} cell populations. Manipulation of the AhR pathway might represent an alternative approach for altering IL-27 signaling for the treatment of inflammatory disorders.

When it acts alone, the IL-27 subunit p28 (IL-30) seems to act as a natural antagonist of signaling via the signal-transducing receptor gp130 (ref. 115). In this scenario, IL-30 blocks signaling mediated by IL-6, IL-11 and IL-27, including IL-6-dependent T_H17 responses. Overexpression of IL-30 in mice causes defective thymus-dependent B cell responses due to an inability to form germinal centers. IL-30 can prevent hepatotoxicity mediated by IL-12, interferon-γ and concana-valin A[116]. Clearly, additional studies are needed for full understanding of the physiological and pathogenic roles of IL-30.

IL-35

IL-35 was identified as an additional anti-inflammatory and immuno-suppressive cytokine only 5 years ago[117]. Like IL-27, IL-35 is a member of the IL-12 family. IL-35 heterodimers are composed of EBI3 and the IL-12p35 subunit. There is still relatively limited knowledge of this molecule, and it has been provided mostly by studies of mice. IL-35 is not constitutively expressed in tissues[84] and is produced mainly by T_{reg} cells[118]. The gene encoding IL-35 is also transcribed by vascular endothelial cells, smooth muscle cells and monocytes after activation with proinflammatory cytokines and lipopolysaccharide[84]. IL-35 induces the transformation of $CD4^+$ effector T cells into T_{reg} cells that in turn express IL-35 but lack expression of Foxp3, TGF-β and IL-10 ($iT_{reg}35$ cells)[119]. The $iT_{reg}35$ cells generated *in vitro* can prevent and revert the development of autoimmunity in various mouse models. These include the systemic autoimmunity of *Foxp3*$^{-/-}$ mice, peptide-induced experimental autoimmune encephalitis and inflammatory bowel disease induced by $CD45RB^+CD4^+$ T cells in mice deficient in recombination-activating gene 1 (ref. 119). Conversely, *in vitro*–generated $iT_{reg}35$ cells accelerate the development of B16 melanoma and prevent the generation of antitumor $CD8^+$ T cell responses. T cells that secrete IL-35 and have suppressive functions can be induced in the intestines of mice infected with the intestinal parasite *Trichuris muris* and in the tumor beds of melanoma and colorectal adenocarcinoma.

Ectopic expression of IL-35 in pancreatic beta cells prevents auto-immune diabetes[120], and IL-35 protects against collagen-induced arthritis[121]. In humans, $iT_{reg}35$ cells can be induced by exposure to virus-infected DCs *in vitro* in a manner dependent on CD274 (the ligand for the immunoinhibitory receptor PD-1 (PD-L1)) and CD169 (sialoadhesin)[122]. A burst of information about IL-35 should arrive in the coming years, given its potent suppressive functions.

IL-37

The IL-1 family of cytokines encompasses 11 proteins that share a similar β-barrel structure. Some members of this family are well characterized. IL-1α (IL-1F1), IL-1β (IL-1F2) and IL-18 (IL-1F4) are very important in the initiation of the inflammatory reaction and in driving T_H1 and T_H17 inflammatory responses. In contrast, IL-1 receptor antagonist (IL-1RA or IL-1F3) and the receptor antagonist that binds to the receptor IL-1Rrp2 (IL-36Ra or IL-1F5) diminish inflammation by blocking the binding of the agonist receptor

ligands. The biological role of IL-37 (IL-1F7) is just starting to be elucidated[123]. It is transcribed as five different splice variants (IL-1F7a–IL-1F7e). IL-1F7b is the largest isoform, as it is encoded by five of the six exons spanning the gene encoding IL-37. Like IL-1 and IL-18, IL-37 is produced as a precursor that must be cleaved by caspase-1 to be activated[124].

Studies of mouse models that express human IL-37 have concluded that this cytokine downregulates inflammation[125]. Mice with transgenic expression of human IL-37 are less susceptible than are wild-type mice to lipopolysaccharide-induced shock and to dextran sulfate–induced colitis[126,127]. The effect is IL-10 independent, as antibody blockade of the IL-10 receptor does not reverse IL-37-mediated protection. Bone marrow–transfer studies have indicated that IL-37 originates from hematopoietic cells. Transgenic mice have lower serum and tissue concentrations of proinflammatory cytokines and have less DC activation. Expression of IL-37 in macrophages or epithelial cells dampens the secretion of proinflammatory cytokines, whereas human blood cells in which the gene encoding IL-37 has been silenced have higher expression of these cytokines. Transient expression of IL-37 in the liver of mice protects them from concanavalin A– induced hepatitis. IL-37 has thus emerged as a natural suppressor of innate inflammatory responses. These exciting early findings will undoubtedly fuel a greater interest in this unusual member of the IL-1 family.

The way forward

The past decade has witnessed the successful treatment of human autoimmune and inflammatory diseases through the targeting of inflammatory cytokines (such as TNF, IL-1, IL-6 and IL-23) or costimulatory molecules (such as CTLA-4–Ig). Still, many of these diseases remain refractory to such approaches. Cytokine modulation to reinstate self-tolerance might need to be established in the early phases of disease, before irreversible tissue damage develops[128].

Greater understanding of the equilibrium between the various effector T cell and suppressor or regulatory T cell pathways will permit the design of more holistic therapeutic interventions. The delivery of cytokines with key roles in these regulatory pathways holds great potential. Given the complexity of these pathways, however, it might be naive to believe that their systemic administration will permit clinicians to control autoimmunity and inflammation. Targeted delivery of IL-2 or IL-10 (ref. 129) to inflammatory sites and targeted activation of latent TGF-β through the local induction of integrins in the relevant sites have already been proposed. Whether targeted induction of IL-27, IL-35 or IL-37 would result in therapeutic benefit remains to be further explored. Undoubtedly, understanding of the relevance of these pathways in specific disease pathogenesis remains a priority. Biomarkers will need to be identified for monitoring responses as well for focusing these approaches to the right disease and/or the right group of patients with individual diseases. Alternatively, for those diseases for which autoantigens have been identified, such as type I diabetes and multiple sclerosis, designing ‘vaccines’ that will specifically elicit tolerance to the autoantigens represents a clear path for development. Existing studies have shown that targeting antigens to DCs in the absence of costimulation can induce antigen-specific tolerance[130–132]. Certainly, better understanding of the anti- inflammatory cytokine network will bring a renewed approach to the treatment of inflammatory diseases.

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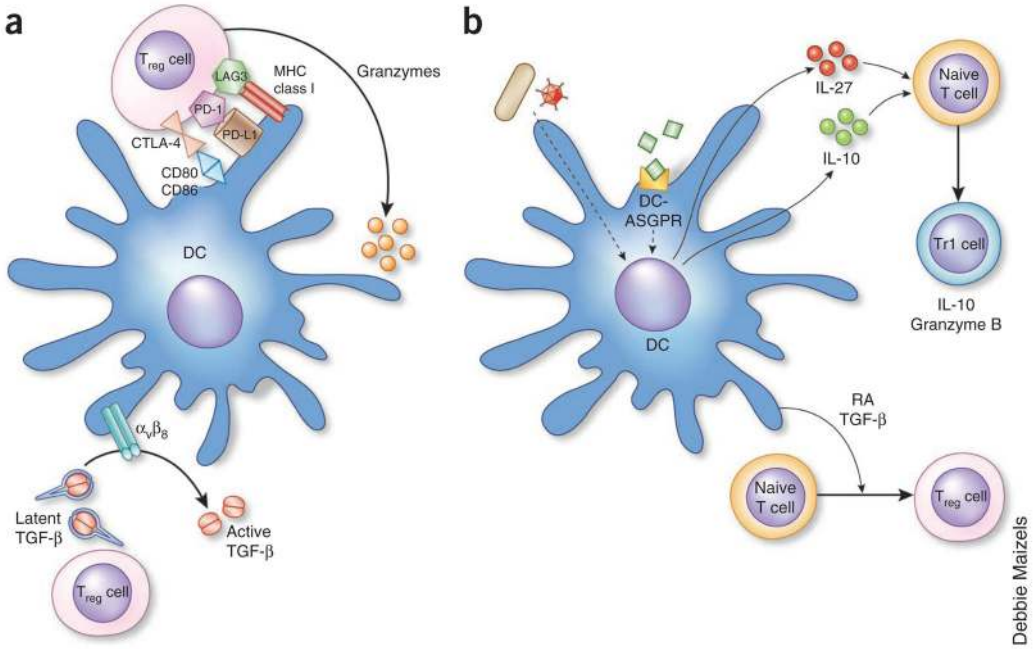

Figure 1.

The dialog between T_{reg} cells and DCs. (**a**) T_{reg} cells can inhibit the priming of effector T cells by preventing DC maturation through cell surface signaling by CTLA-4, PD-1 or LAG3 or by killing DCs through the secretion of granzymeps. After being stimulated by DCs, T cells can secrete latent TGF-β, which is activated by $\alpha_V\beta_8$ expressed on the surface of DCs. The activated TGF-β can now signal DCs and other cell types. (**b**) DCs can induce the differentiation of T_{reg} cells. DCs activated by microbes or by ligation of certain surface molecules such as DC asialoglycoprotein receptor (DC-ASGPR) secrete either IL-27 or IL-10, which induce T cells to produce IL-10 (Tr1 cell). A subset of DCs secrete retinoic acid (RA) and TGF-β, which induce the differentiation of T cells into T_{reg} cells. MHC, major histocompatibility complex.

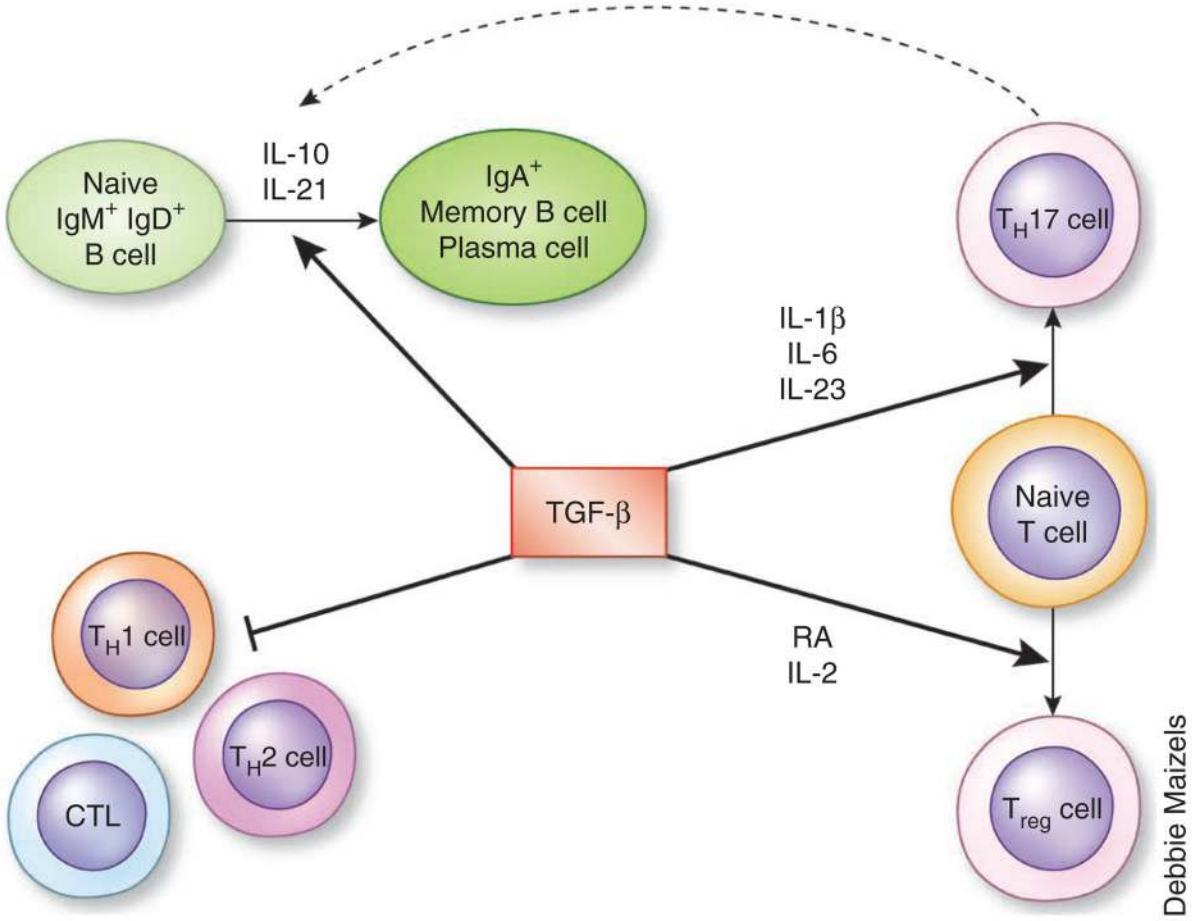

Figure 2.

The dual roles of TGF-β in tolerance and immunity. TGF-β inhibits T_H1 cells, T_H2 cells and cytotoxic T lymphocytes (CTL), whereas it induces, in combination with other cytokines, the differentiation of T_{reg} cells and T_H17 cells. TGF-β together with IL-10 or IL-21 induces CD40-activated B cells to switch into IgA^+ B cells, possibly with the help of T_H17 cells[52].

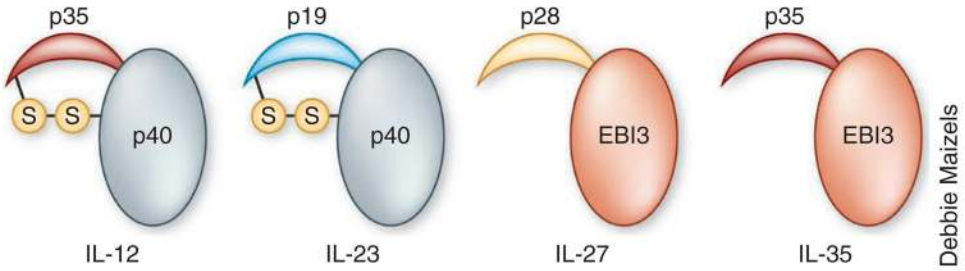

Figure 3.
Members of the IL-12 family. IL-12 and IL-23 share the β-chain p40 (IL-12β), whereas IL-27 and IL-35 share the β-chain EBI3. IL-12 and IL-35 share the p35 α-chain, whereas IL-23 and IL-27 have unique α-chains. IL-12 and IL-23 are disulfide-linked heterodimers, whereas IL-27 and IL-35 lack the disulfide linkage.