

IL-2- and CD25-dependent immunoregulatory mechanisms in the homeostasis of T-cell subsets

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IL-2 plays a pivotal role in regulating the adaptive immune system by controlling the survival and proliferation of regulatory T (Treg) cells, which are required for the maintenance of immune tolerance. Moreover, IL-2 is implicated in the differentiation and homeostasis of effector T-cell subsets, including T_H1, T_H2, T_H17, and memory CD8⁺ T cells. The IL-2 receptor is composed of 3 distinct subunits, namely the α (CD25), β (CD122), and γ (γ c) chains. Of crucial importance for the delivery of IL-2 signals to Treg cells is the expression of CD25, which, along with CD122 and γ c, confers high affinity binding to IL-2. Notably, recent findings suggest a novel role for CD25, whereby CD25 molecules on Treg cells and possibly other cells are capable of influencing T-cell homeostasis by means of IL-2 deprivation. This review explores these findings and integrates them into our current understanding of T-cell homeostasis. (J Allergy Clin Immunol 2009;123:758-62.)

Key words: IL-2, CD25, T-cell homeostasis, CD8 T cell, regulatory T cell, T_H1, T_H2, T_H17, cytokine deprivation

IL-2 is a 15-kd cytokine composed of 4 short α -helices and is essentially produced by activated CD4⁺ T cells, although activated CD8⁺ T cells, natural killer (NK) cells, and NK T cells, as well as dendritic cells (DCs) on stimulation with microbial compounds, have also been reported to be capable of secreting IL-2 in smaller amounts.^{1,2} IL-2 can act both in an autocrine and paracrine fashion by binding to the IL-2 receptor (IL-2R). The remarkable degree of conservation of functionally important residues observed between the mouse and human *IL2* genes underlines the importance of this cytokine and is highlighted by the fact that human IL-2 is at least as potent as mouse IL-2 in murine models.

Three distinct receptor chains have been identified as components of the IL-2R^{1,3}: the common γ chain (γ c) or CD132, which is shared by the common γ chain cytokine family, comprising IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; the β chain or CD122, which is shared by both IL-2R and the IL-15 receptor; and the α chain or CD25. Only CD122 and γ c have large intracellular domains and are involved in signal transduction through the Janus kinase/signal transducer and activator of transcription, phosphoinositide 3-

Abbreviations used

DC: Dendritic cell
FoxP3: Forkhead box P3
IL-2R: IL-2 receptor
NK: Natural killer
TCR: T-cell receptor
Treg: Regulatory T cell

kinase, and mitogen-activated protein kinase pathways. Two functional receptor forms have been described²: the dimeric low-affinity receptor (dissociation constant [K_d] $\approx 10^{-9}$ mol/L), which is composed solely of CD122 and γ c, and the trimeric high-affinity receptor (K_d $\approx 10^{-11}$ mol/L), which is composed of CD25, CD122, and γ c. The dimeric low-affinity receptor is found at low levels on naive CD4⁺ T cells, at intermediate levels on naive CD8⁺ T cells and memory CD4⁺ T cells, and at high levels on memory CD8⁺ T cells and NK cells (Table I).^{1,4-9} In contrast, the trimeric high-affinity receptor is essentially expressed on forkhead box P3 (FoxP3)-positive CD4⁺CD25⁺ regulatory T (Treg) cells and activated T cells, although lower levels of CD25 have also been detected on other immune cells, including pre-B cells, thymocytes, and NK cells, as well as on certain nonimmune cell lines.¹ IL-2 is believed to initially bind CD25 and CD122 and subsequently to recruit the γ c component to form a stable quaternary structure, which is rapidly internalized. CD25 is then recycled to the cell surface, whereas the other components of the receptor and IL-2 are degraded rapidly in the lysosome compartment.¹⁰

IL-2 was first identified as a T-cell growth factor as early as 1976. Initial *in vitro* work in the 1980s suggested that IL-2 was required for T-cell proliferation and induction of effector functions. This property of IL-2 eventually led to the use of high-dose IL-2 in the treatment of patients with metastatic melanoma and metastatic renal cell carcinoma.² This model of IL-2 being a potent stimulatory factor remained widely accepted for more than a decade. However, purification and cloning of the cytokine and individual receptor subunits led, in the early 1990s, to the generation of IL-2 and IL-2R knockout mice, which surprisingly exhibited marked lymphoproliferation and severe autoimmunity rather than the expected immunodeficiency.^{1,2} Subsequent studies linked the observed autoimmune disorder to a defect or lack of IL-2-dependent FoxP3⁺CD4⁺CD25⁺ Treg cells, thus highlighting the key role of this subset in maintaining immune tolerance. The IL-2/IL-2R knockout mouse models also highlighted a key function for IL-2 signals in primary and especially secondary T-cell responses. Here we review the role of IL-2 in the generation, function, and homeostasis of different T-cell subsets.

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TABLE I. Surface expression of IL-2R subunits α (CD25), β (CD122), and γc on selected immune and nonimmune cells

Cell type	CD25	CD122	γc
Pre-B cell	+	—*	+
Mature B cell	—	—	+
Thymocytes			
DN1	—	(+) [†]	+
DN2	+	(+) [†]	+
DN3	+	(+) [†]	+
DN4	—	(+) [†]	+
Mature T cell			
Naive	—	+	+
Effector	+ [‡]	+	+
Memory	—	+	+
Treg cell	+	+	+
NK cell	—	+	+
DC	+/- [§]	—	+
Endothelial cell	+	?	?
Fibroblast	+	+	(+) [¶]

DN, Double-negative (CD4⁻CD8⁻) thymocytes; ?, has not been determined yet.*Pre-B cells are generally believed not to express CD122[†]; however, one report describes CD122 expression on pre/pro-B cells from fetal liver.⁶[†]For double-negative thymocytes, there exist contradictory reports regarding CD122 expression.^{1,7}[‡]CD25 is expressed transiently on these cells.[§]Certain activated DC subsets have been shown to express CD25 on their surface.^{8,9}^{||}Our unpublished results.[¶]Fibroblasts have been reported to express CD25 and CD122; however, it remains unclear whether γc is expressed.^{4,5}

CD8⁺ T CELLS

On activation through signals delivered by the T-cell receptor (TCR) and costimulatory molecules, CD8⁺ T cells upregulate CD25 and CD122 and become highly IL-2 sensitive. This was a well-known fact by the time IL-2^{-/-} and IL-2R^{-/-} mice became available, and thus the primary response was extensively investigated in these murine models. Interestingly, most studies examining directly primary responses in these knockout animals concluded that IL-2 signaling was not required to generate protective immunity, although in the absence of IL-2/IL-2R, proliferation kinetics, absolute numbers, and effector functions of CD8⁺ T cells were reported to be suboptimal (Fig 1). A shortcoming of these studies is the severe autoimmunity observed in IL-2^{-/-} and IL-2R^{-/-} mice, which might curtail certain aspects of the immune response.¹ Therefore other investigators opted for TCR-transgenic or bone marrow chimeric mouse models. These latter findings essentially confirmed that IL-2 or its receptor were dispensable to achieve efficient primary immune responses, although maximal responses were only obtained in the presence of IL-2 signaling.

By using the above-mentioned bone marrow chimeras, it has recently been shown that secondary responses of CD8⁺ T cells of CD25^{-/-} origin were severely impaired, whereas the generation of memory CD8⁺ T cells after primary expansion and contraction remained largely unaffected in the absence of high-affinity IL-2R expression.^{11,12} The defect in secondary responses was linked to a lack of IL-2 signaling during the priming phase and could be overcome by injecting IL-2/anti-IL-2 mAb complexes.¹³ This was further supported by the finding showing that memory CD8⁺ T cells were only arising from effector populations capable of IL-2 production.¹⁴ Moreover, for human memory CD8⁺ T cells, capacity to produce IL-2 on restimulation *in vitro* identified a long-lived

memory cell population associated with control of viremia during chronic viral infection.¹⁵ As for T-cell contraction, administration of exogenous IL-2 during this phase had a generally beneficial effect on CD8⁺ T-cell survival and generation of memory cells.¹⁶

Once the pool of resting memory CD8⁺ T cells has been formed, homeostasis of these cells is regulated by survival signals through contact with IL-7 and IL-15 and is TCR independent.¹⁷ However, high levels of CD122 on the cell surface renders memory CD8⁺ T cells highly susceptible to IL-2 signals. It is therefore possible to induce vigorous proliferation of memory CD8⁺ T cells in the presence of a strong exogenous IL-2 signal, such as IL-2/anti-IL-2 mAb complexes.¹³

Similarly to memory cells, homeostatic proliferation of naive CD8⁺ T cells does not require IL-2 but is essentially driven by TCR and IL-7 signaling.¹⁷ However, a strong IL-2 stimulus can also induce proliferation of naive CD8⁺ T cells and their differentiation into memory CD8⁺ T cells. This can be achieved by using highly stimulatory IL-2/anti-IL-2 mAb complexes *in vivo* or alternatively by adoptively transferring naive CD8⁺ T cells to CD25^{-/-} or CD122^{-/-} mice, which exhibit high levels of IL-2 because of their inability to use the cytokine.^{18,19}

T_H1 AND T_H2 CELLS

CD4⁺ T_H cells coordinate immune responses by producing a range of cytokines and are divided into different effector cell subsets based on the functional profiles and cytokines produced. T_H1 cells typically produce large amounts of IFN- γ and IL-2, and other proinflammatory cytokines, such as TNF- α , induce immune responses against intracellular pathogens and have been associated with organ-specific autoimmune disorders. In contrast, the signature cytokines of T_H2 cells are IL-4, IL-5, and IL-13, and this subset is involved in the induction of humoral immune responses against helminths, isotype switching to IgE, and allergic diseases. A third subset of T_H cells, termed T_H17 cells, has been recently identified and will be discussed further below.

Naive CD4⁺ T cells activated in the presence of exogenous IL-12 and IFN- γ are believed to differentiate into T_H1 cells, whereas exogenous IL-4 favors the generation of T_H2 cells. Activated CD4⁺ T cells generally secrete vast amounts of IL-2, although T_H1 cells are believed to be the major source of this cytokine. Most studies investigated the role of IL-2 signaling during the primary response in typical T_H1 cytokine environments by using viral challenges, allograft transplants, or superantigens but focused on CD8⁺ T cells. However, CD4⁺ T_H cells were reported to be functional in the absence of IL-2/IL-2R, despite showing some defects, including delayed response kinetics, reduced proliferation, and disruption of effector function, such as IFN- γ production (Fig 1).

Contrarily, a few studies reported increased survival of CD4⁺ T cells in the absence of IL-2 signals during the contraction phase.²⁰ This phenomenon might be explained by IL-2-mediated activation-induced cell death, whereby IL-2 is able to sensitize CD4⁺ T cells for cell death through the proapoptotic Fas/Fas ligand pathway.²⁰ This contrasts with other findings, in particular with administration of exogenous IL-2 during the contraction phase of viral infections, in which antigen-specific CD4⁺ T cells from mice receiving IL-2 showed increased survival.¹⁶ This was true for the contraction phase but not for the expansion phase, during which IL-2 administration caused a decrease of antigen-specific CD4⁺ T-cell counts.¹⁶

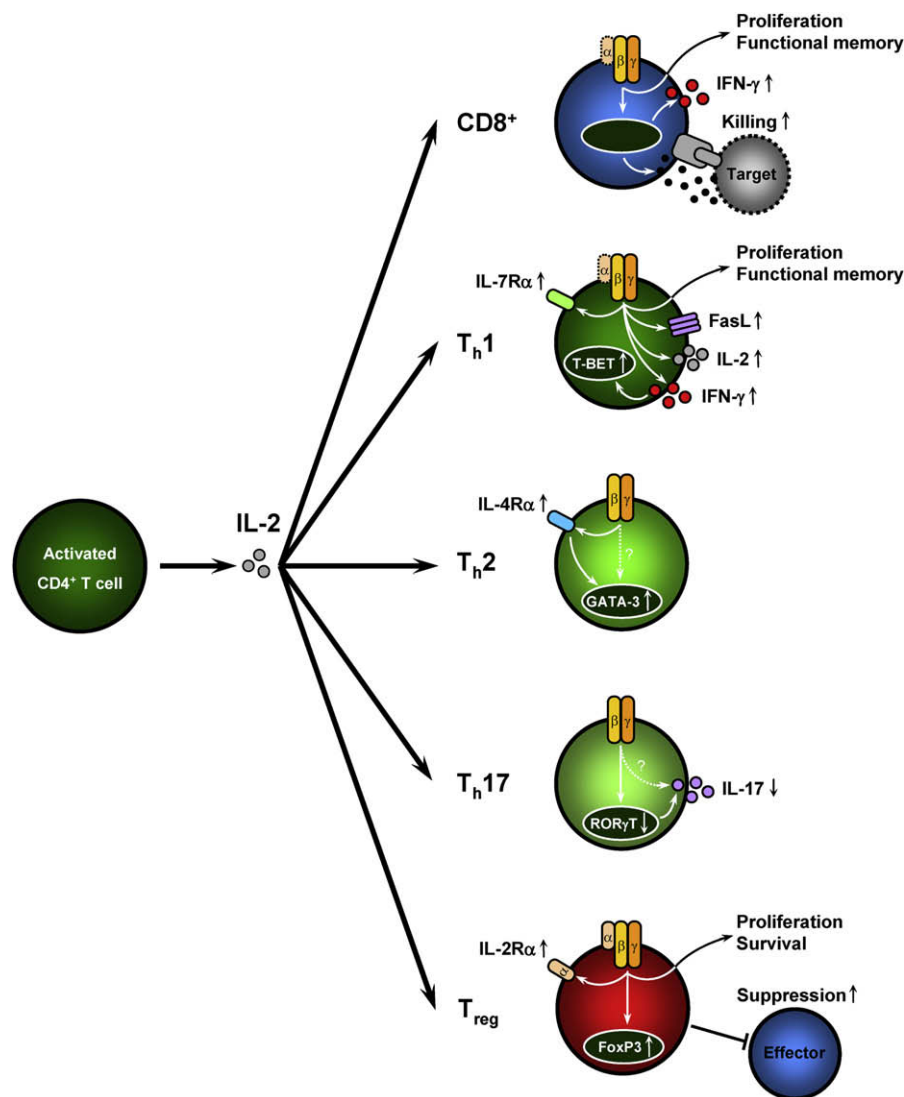


FIG 1. Effect of IL-2 on T-cell subsets. IL-2 binding to its receptor triggers the upregulation or downregulation of transcription factors, as depicted in dark green ovals; cytokine receptors, as depicted on the left side of the T cell; or effector functions, as depicted on the right side of the T cell.

Homeostasis of memory CD4⁺ T cells is regulated mainly by IL-7 and also IL-15, which is required for the long-term survival of this subset.¹⁷ Nonetheless, poor survival of memory CD4⁺ T cells of CD25^{-/-} and IL-2^{-/-} origin has also been described, suggesting an important role for IL-2 signaling.^{21,22} This has recently been linked to a lack of IL-2-mediated IL-7Rα expression during the primary response.²² Thus IL-2 signals were necessary during the primary response both to generate optimal CD4⁺ T-cell responses and to generate long-lived memory CD4⁺ T cells.

In contrast to T_H1 responses, less attention was devoted to T_H2 cells in the context of IL-2 signaling. It has been reported that IL-2 signaling contributes to the differentiation of naive CD4⁺ T cells into T_H2 cells, among other mechanisms through *IL4* locus activation.²³⁻²⁵ A recent study supports these findings, reporting a requirement for IL-2 signaling during the priming phase for the induction and maintenance of IL-4Rα expression and T_H2 lineage commitment of CD4⁺ T cells (Fig 1).²⁶ However, further

investigation will be needed to ascertain the exact role of IL-2/IL-2R in T_H2 immune responses.

T_H17 CELLS

Recent studies have identified a novel IL-17-producing effector CD4⁺ population, which is commonly referred to as T_H17. This distinct T_H subset is believed to be involved in defense against certain extracellular bacteria and some fungi, promotes neutrophilic tissue inflammation, and has been linked to the pathology of chronic inflammatory and autoimmune disorders, such as Crohn disease and psoriasis.²⁷ Little is known about the mechanisms guiding T_H17 homeostasis, but the opposing physiologic role of T_H17 and Treg cells has led investigators to examine the role of IL-2. Interestingly, IL-2 was able to inhibit generation of T_H17 cells both in mice and human subjects while favoring the differentiation of naive CD4⁺ T cells into Treg cells. This was shown to be essentially achieved by blocking IL-17 production,

presumably by interfering with the transcription factor ROR- γ t (Fig 1).^{28,29} However, as mentioned above for other memory T_H subsets, IL-2 seems to be beneficial for the expansion of memory T_H17 cells.³⁰

TREG CELLS AND IMMUNE TOLERANCE

As mentioned previously, mice lacking IL-2 or one of its receptor subunits have a lethal T cell-mediated inflammatory autoimmune disease along with hyperreactivity to commensal bacteria.¹ Similar clinical manifestations also accompany CD25 mutation in human subjects, in whom lymphadenopathy and hepatosplenomegaly, along with dense lymphocytic infiltration of tissue and increased susceptibility to viral, fungal, and bacterial infections, are observed.³¹ Moreover, use of a neutralizing anti-IL-2 mAb *in vivo* leads to autoimmune gastritis in mice.³² Strong evidence now links these autoimmune phenotypes to a dysfunction or deficiency of FoxP3⁺CD4⁺CD25⁺ Treg cells and highlights the role of IL-2 signaling in mediating immune tolerance.^{1,33} Because this topic has recently been reviewed extensively,^{1,2,33,34} we focus below on novel findings in the area.

CD4⁺CD25⁺ Treg cells express the transcription factor FoxP3, which in synergy with other transcription factors tightly regulates the development and function of this subset, inducing upregulation of CD25 and other Treg cell-associated molecules, such as cytotoxic T lymphocyte-associated antigen 4 and the glucocorticoid-induced TNF receptor, and suppressing the production of IL-2, IFN- γ , and IL-4 by effector T cells.¹ So-called natural FoxP3⁺ Treg cells are typically generated in the thymus, although it has been proposed that Treg cells can also arise from naive T cells in the periphery, in which case they are referred to as induced Treg cells.³⁴ The *in vivo* presence of the latter subset remains to be demonstrated. Several studies have shown that IL-2 signaling through the high-affinity IL-2R is essential for the homeostasis of Treg cells, promotion of survival, and immunosuppressive function through FoxP3, and CD25 expression (Fig 1).^{1,33} Interestingly, Treg cells are highly dependent on exogenous sources of IL-2 but do not produce any IL-2 themselves. Treg cells proliferate considerably *in vivo*, and exogenous IL-2 and IL-2/anti-IL-2 mAb complexes can induce vigorous proliferation of Treg cells and further upregulation of CD25 expression.¹³

Treg cells are capable of efficiently suppressing the proliferation and differentiation of effector T cells *in vivo*, as well as effector functions of mature T cells, B cells, NK cells, NK T cells, macrophages, and DCs. Several suppression mechanisms have been proposed, including production of immunosuppressive cytokines, such as IL-10 and TGF- β ; direct cell-to-cell inhibition; or even killing of T cells and DCs. However, this aspect of Treg cells remains poorly understood.

Mice lacking IL-2/IL-2R exhibit a dramatic reduction in FoxP3⁺ thymocytes, thus strongly suggesting that IL-2 signaling is required for Treg cell development. However, the presence of small numbers of FoxP3⁺ thymocytes in mice lacking IL-2/IL-2R indicates that CD4⁺CD8⁻ precursors are able to differentiate into FoxP3⁺CD4⁺ thymocytes in the absence of IL-2 signaling. There it has been suggested that other γ c cytokines, notably IL-7 and IL-15, might partially overcome the lack of IL-2 signals. Similarly, *in vitro* generation of Treg cells with TGF- β also required IL-2 costimulation to induce FoxP3 expression.¹

CYTOKINE DEPRIVATION: A NOVEL MECHANISM OF ACTION FOR TREG CELLS?

Mice lacking CD25 exhibit increased levels of IL-2 in the serum, presumably because of their inability to efficiently bind and use the cytokine through the high-affinity receptor. In turn, these increased serum levels of IL-2 induced vigorous proliferation of adoptively transferred naive CD8⁺ T cells and their differentiation into memory CD8⁺ T cells.¹⁸ Recent evidence suggests that these observations might be linked to a lack of IL-2 "scavenging" or deprivation by Treg cells.

First, adoptive transfer of CD4⁺CD25⁺ Treg cells to CD25^{-/-} mice was reported to reduce IL-2 levels in the serum to background levels and restore a normal ratio of naive to memory T cells in the host.³⁵ Second, Treg cells were shown to induce Bim-mediated apoptosis of activated effector CD4⁺ T cells *in vitro* through consumption of IL-2 and other γ c cytokines.³⁶ The same investigators also demonstrated Bim-mediated apoptosis of colitogenic effector CD4⁺ T cells in the presence of Treg cells in a model of inflammatory bowel disease, suggesting that cytokine deprivation by Treg cells is occurring *in vivo*. Third, CD25 is also expressed constitutively on nonimmune cells, and expression levels of CD25 on nonimmune cells increase *in vivo* after high-dose IL-2 treatment (our unpublished results).^{4,5} Altogether, CD25 on Treg and nonimmune cells might be involved in T-cell homeostasis by consuming soluble IL-2 and thus limiting overactivation of the immune system in vital organs, such as the lungs.

CONCLUSION

IL-2 exerts apparently contradictory functions, promoting proliferation, differentiation, and function of activated CD4⁺ and CD8⁺ T cells while inducing activation-induced cell death of CD4⁺ T cells and mediating the survival of Treg cells. Increasing evidence now suggests a key role for IL-2 in maintaining the balance between protection from pathogens and suppression of self-reactive T cells by providing a powerful negative feedback loop to immune responses. Tight regulation of IL-2 signal delivery is at least partially achieved through expression of CD25, conferring Treg cells and activated T cells a significantly increased affinity to the cytokine and a crucial competitive advantage. Interestingly, CD25 can also be expressed by a large variety of cells, including B cells and macrophages, as well as nonimmune cell lines *in vitro* and nonimmune cell lines *in vivo* (unpublished results).^{4,5} Thus it is conceivable that different cell types other than Treg cells participate in IL-2-mediated homeostasis of effector T cells. Further investigation of these aspects of IL-2 regulation are likely to lead to a better understanding of the complex mechanisms underlying the fine equilibrium between immunity and tolerance.

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