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The Surprising Story of IL-2

From Experimental Models to Clinical Application

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Equilibrium in the immune system is maintained by a balance between activation, which generates effector and memory cells, and suppression, which is mediated mainly by regulatory T cells. Understanding this balance and how to exploit it therapeutically is one of the dominant themes of modern immunology. The cytokine IL-2 was discovered as a growth factor for T cells and thus a key component of immune activation. It was initially used to boost immune responses in patients with cancer. Studies in experimental models and humans showed that the major function of IL-2 is to maintain functional regulatory T cells, and thus its essential function is in immune suppression. How the same cytokine can serve two opposing roles is a subject of current investigation. Because of these advances, IL-2 is now being tested as a cytokine for suppressing pathologic immune responses in autoimmune diseases and graft rejection. Fully understanding the biology of IL-2 may enable us to custom-design this cytokine for different applications in humans. (*Am J Pathol* 2020, 190: 1776–1781; <https://doi.org/10.1016/j.ajpath.2020.05.007>)

Discovery and Early History of IL-2

IL-2 was discovered in the 1970s as a soluble factor that stimulated the proliferation of T cells *in vitro* and was able to maintain T cells in culture for prolonged times. It was hence called T-cell growth factor (“factor” was the term used for secreted molecules in blood or culture supernatants that were defined according to biological activities but not molecular properties).^{1,2} It was the first cytokine whose encoding gene was cloned and sequenced, and it was designated IL-2.³ An interesting fact is that when cytokine genes were molecularly cloned, the cytokines were given the IL designation and numbered in sequence. So why is the first IL #2? It seems some investigators believed that another cytokine stimulated the production of IL-2 and because it was above IL-2 in a functional hierarchy, the designation #1 was held for this supposed factor. However, a lymphocyte-activating factor that induced IL-2 was not identified, and thus the first IL remains #2. The name IL-1 was later given to a cytokine with different functions, and thus the second cytokine to be cloned ended up with the #1.

IL-2 is produced mainly by T cells, particularly CD4⁺ helper cells. The cellular receptor for IL-2 is a three-chain molecule. The receptor’s signaling function is mediated by the β and γ chains (CD122 and CD132, respectively), which are expressed on T cells (and natural killer cells) constitutively, can be up-regulated by activation, and dimerize to bind IL-2 with low affinity (dissociation constant approximately 1 nmol/L). The α chain (CD25) has no signaling capacity but confers on the receptor the ability to bind IL-2 with high-affinity (dissociation constant approximately 10 pmol/L).⁴ Signals from this receptor activate the transcription factors STAT5 and NF- κ B, and these transcription factors induce the molecules that promote cell

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survival and proliferation, the two principal actions of IL-2. CD25 is transiently increased upon activation of T cells by antigen and other stimuli, enabling antigen-activated T cells to be the preferential responders to IL-2. Thus, upon antigen stimulation, T cells both produce and respond to IL-2, leading to the preferential expansion of antigen-specific clones. CD25 is also expressed on regulatory T cells (Tregs).

Many studies relying on *in vitro* experiments and some in which forms of IL-2 were administered or expressed *in vivo* collectively led to the wide acceptance that IL-2 functioned to stimulate the proliferation of antigen-stimulated T cells. As these clones of T cells expand, they also differentiate into effector and memory cells, providing immediate and long-lived defense against pathogens. The idea that IL-2 was a potent stimulator of immune responses led to clinical trials of IL-2 in patients with metastatic cancer.⁵ Because the half-life of administered IL-2 is very short, large doses had to be given to achieve biologically effective levels, which stimulated the production of many other cytokines, leading to severe toxicities resulting mainly from vascular leakage. As a result, although occasional responses were observed, IL-2 was not adopted as a first-line or adjunct cancer therapy.

Rediscovering the Function of IL-2

The function of IL-2 started to be re-evaluated when IL-2 gene knockout mice were analyzed. It was predicted that in the absence of the cytokine, mice would be immunodeficient, with a reduction in the number of effector and memory T cells. However, mice lacking IL-2 developed massive lymphadenopathy and splenomegaly and manifestations of autoimmune disease, such as colitis and autoimmune hemolytic anemia.⁶ The same phenotype was observed in knockout mice lacking the IL-2 receptor α or β chain.^{7,8} In fact, even brief treatment of mice with antibodies that neutralize IL-2 or block the IL-2 receptor resulted in acute autoimmune manifestations.^{9,10} These analyses were complemented by human studies showing that T cells in patients with lupus and other autoimmune diseases produce reduced amounts of IL-2, not the expected increase of this immune stimulator.¹¹ Thus, despite initial skepticism, it became clear that a major and essential function of IL-2 is to maintain self-tolerance and prevent autoimmunity, and depletion or decreased production of this cytokine is associated with systemic autoimmunity.

How a major stimulator of immune responses serves to also inhibit or prevent some reactions, particularly those against self-antigens, was puzzling. Initial studies suggested that IL-2 potentiated activation-induced cell death (apoptosis) of lymphocytes,¹² and this action was postulated to be a mechanism for maintaining unresponsiveness (tolerance) to self-antigens. However, there were few *in vivo* data to confirm this idea, and IL-2 has also been shown to protect

T cells from death; thus, the role of IL-2 in T-cell apoptosis remains unclear. A different mechanistic hypothesis came from the observation that normal T cells could suppress the autoimmune potential of T cells from IL-2^{-/-} mice, implying that IL-2 worked in trans: IL-2 from one cell could suppress the reaction of another cell.¹³ The breakthrough came when, shortly after the findings of the gene knockout mice were reported, it was shown that T cells (which express high levels of CD25) were essential for maintaining self-tolerance, and their depletion resulted in autoimmunity.¹⁴ These T cells are now known as regulatory T cells (Tregs) and are defined by the co-expression of CD25 and the transcription factor forkhead box P3 (FOXP3). In humans, Tregs are more heterogeneous, and some effector cells also express FOXP3 and CD25, at least transiently. Nevertheless, the stable expression of both these molecules remains the clearest marker of Tregs. Collectively, these studies indicated that IL-2 not only stimulated immune responses and generated effector cells but also was required for Treg-mediated suppression of immune responses. Many subsequent studies showed that introducing Tregs into mice lacking IL-2 receptors prevented the development of autoimmunity,¹⁵ firmly establishing the role of IL-2 in maintaining Tregs. The following sections summarize studies from our laboratory as well as from others to decipher the mechanism by which IL-2 acts on Tregs to maintain self-tolerance and how these actions can be exploited to develop therapeutic strategies.

Dual Functions of IL-2

IL-2 is now known to promote the generation of the complete set of Tregs and to maintain these cells in peripheral tissues.¹⁶ Our own studies have focused on the role of this cytokine in peripheral Treg maintenance. The diversity of the immune system poses a major challenge to studying antigen-specific immune responses; because the system has to recognize and respond to an almost unlimited number and variety of antigens, very few cells respond to any one antigen, and tracking these cells is technically difficult. We and others have overcome this problem experimentally by generating transgenic mice that express a single T-cell receptor (TCR) specific for a known antigen and either introducing this antigen or transferring the specific T cells into recipients that express the antigen to follow the responses of the T cells. A great advantage of TCR transgenics is that mutations that would cause autoimmunity can be bred into these mice, and the animals do not develop disease unless they are exposed to the antigen that the specific TCR recognizes. For instance, a TCR transgenic mouse strain can be crossed with an IL-2-deficient mouse so that all of the T cells are incapable of producing IL-2. These mice will not by themselves develop autoimmunity because there is no antigen to activate the T cells, but reactions characteristic of autoimmunity will develop if the T cells are exposed to the specific antigen. We have used this

strategy to analyze the consequences of exposing mice with T cells specific for the model antigen ovalbumin (Ova) to Ova, either systemically or selectively in the skin, in the context of normal or defective IL-2 genes.

Transfer of Ova-specific wild-type (IL-2 sufficient) CD4⁺ T cells into mice expressing Ova systemically results in an acute inflammatory disease that peaks in severity within 2 to 3 weeks.¹⁷ Similarly, transfer of the wild-type T cells into mice expressing Ova in the skin induces acute dermatitis.¹⁸ In both cases, the development of the disease is associated with the generation of large numbers of FOXP3[−] effector T cells that produce inflammatory cytokines such as interferon- γ and IL-17. Remarkably, in both situations, the disease resolves spontaneously, and resolution is associated with a gradual accumulation of FOXP3⁺ Tregs. This sequence of pathogenic T cells followed by protective Tregs has been observed in other models of inflammatory disease. It is unclear if the Tregs develop from effector cells or from naive T cells that have not fully differentiated into effector cells; distinguishing these possibilities will require single-cell analyses using fate-mapping reporter mice.

This experimental system gave us the opportunity to study the consequences of absence of IL-2. When IL-2-deficient TCR-transgenic T cells were transferred into antigen-expressing recipients, the disease developed more slowly. The most striking difference from wild-type cell transfers, however, was that the disease was progressive, with no resolution, and frequently fatal. The delayed disease was due to reduced generation of effector cells, and the failure to resolve the disease was due to an inability to generate Tregs.

These experimental studies illustrate a key feature of IL-2: the cytokine has dual functions, one being to induce effector T cells (part of the immune response) and the other to generate Tregs (which mediate immunologic control) (Figure 1). The unexpected result is that stimulation of T cells to generate effector cells, which has been the accepted role of IL-2, is a redundant function, because effector cells are generated even in the absence of IL-2, albeit more slowly and in lower numbers (accounting for the delayed inflammatory disease in the mouse models). The obligatory (nonredundant) function of IL-2 is to induce and maintain Tregs. This conclusion could have been predicted from the phenotypes of the knockout mice lacking IL-2 or its receptor. Thus, IL-2 can be considered more of an immunologic control factor than a growth factor.

Treg Maintenance by IL-2

The realization that IL-2 is essential for the maintenance of Tregs has raised many questions about the role of this cytokine in T-cell biology. First, similar to the effect of IL-2 on other T cells, it is predictable that it promotes Treg survival. Tregs are not highly proliferative, and therefore inducing cycling of these cells is likely not a critical action of IL-2. Normally, the survival of cells is dependent on signals from growth factors and

extracellular proteins, all of which block apoptosis and prevent the death of the cells. To analyze the prosurvival function of IL-2 and to determine if it played other roles, we developed a model in which apoptotic pathways could be manipulated. Mice lacking IL-2 have greatly reduced numbers of FOXP3⁺ Tregs and develop autoimmune hemolytic anemia. We postulated that in the absence of IL-2, there would be a deficiency of survival signals, leading to apoptosis of IL-2-dependent T cells. The absence of survival signals is typically detected by the cytosolic sensor BCL2 like 11 (Bim, also known as Bcl2l11), which then activates proapoptotic members of the Bcl-2 apoptosis regulator family. By eliminating Bim, we could prevent this pathway of cell death. We showed that if IL-2^{−/−} mice were crossed with Bim^{−/−} (*Bcl2l11*^{−/−}) mice, Tregs were restored in the double-knockouts, confirming that IL-2 promotes cell survival by preventing Bim-dependent apoptosis, and that in the absence of Bim, IL-2 is dispensable for Treg survival.¹⁹ Thus, one key function of IL-2 is to prevent apoptotic death of Tregs. However, even though Tregs were present when apoptosis was eliminated, the autoimmune disease was not prevented. This observation led to the hypothesis that IL-2 not only promoted survival of Tregs but was also required for the functional competence of these cells. Treatment of the double-knockout mice with IL-2 restored the function of the Tregs and prevented the autoimmune disease. Studies by other groups have shown that IL-2 promotes the expression of FOXP3 and the activation of STAT5, the transcription factors that drive much of the suppressive function of Tregs.²⁰

A second important question arose from the realization that Tregs do not synthesize IL-2. This is inconsistent with the accepted model for IL-2 action, according to which CD4⁺ T cells both produce and respond to IL-2 via an autocrine pathway. If Tregs cannot make their own IL-2, what is the source of the cytokine for Treg maintenance? We initially developed an experimental model for defining the targets of IL-2 action by transferring FOXP3[−] TCR-transgenic T cells into a normal mouse, exposing the T cells to their cognate antigen, and evaluating which cells expressed phospho-STAT5, the transcription factor downstream of the IL-2 receptor. The surprising result was that when the conventional CD4⁺ T cells produced IL-2, the initial responders were not these T cells themselves but FOXP3⁺ Tregs in the lymphoid organ.²¹ Thus, IL-2 made by T cells in an immune response functions to activate adjacent Tregs. These results led to the idea that every immune response is accompanied by concomitant control mechanisms, which prevent both autoimmunity and collateral damage during the response. Detailed imaging analyses subsequently showed that conventional IL-2-producing FOXP3[−] T cells and IL-2-responsive FOXP3⁺ Tregs formed a cluster around dendritic cells presenting antigen. This co-localization enables the conventional T cells to produce IL-2 in response to antigen displayed by dendritic cells. These T cells secrete IL-2, which then acts on the nearby Tregs and activates the Tregs to suppress activation of the conventional T cells, in a classical feedback loop.²²

Figure 1 Dual activities of IL-2. IL-2 is produced by $CD4^+$ T cells following their activation by antigen-presenting cells (APCs), and it stimulates the proliferation and differentiation of these cells. IL-2 also acts on forkhead box P3-positive (FOXP3⁺) regulatory T cells (Tregs) to maintain them in a functional state, capable of suppressing the development of effector and memory cells. The **dashed arrow** indicates that the IL-2 that acts on Tregs is likely derived from conventional $CD4^+$ cells responding to antigens (because Tregs do not produce their own IL-2).

More detailed analysis of the source of IL-2 for Treg maintenance has come from mice in which IL-2 is selectively depleted from various cell populations. Although by far the major physiologic source of IL-2 is antigen-activated $CD4^+$ T cells, small amounts of the cytokine may be produced by other cell populations. By removing IL-2 from individual cells, it has been shown that the major source of the cytokine for maintaining Tregs in most secondary lymphoid organs is, predictably, conventional $CD4^+$ T cells.²³ It is possible, however, that Tregs in different tissue compartments vary in their dependence on IL-2.²⁴

Regulating the Dual Action of IL-2

Because it is now established that IL-2 has two opposing functions (to stimulate effector cell responses and to maintain Tregs), an important question is, how are these activities regulated so IL-2 produces optimal outcomes under different conditions? Although there is no definitive answer to this question, important insights have emerged. Tregs respond to IL-2 at concentrations 10 to 100 times lower than the amount needed to activate conventional FOXP3⁺ T cells.²⁵ This high sensitivity of Tregs to IL-2 is partly because Tregs constitutively express high levels of the high-affinity trimeric IL-2 receptor, whereas conventional T cells express CD25 (which is required for the high-affinity receptor complex) transiently and only after activation. In addition to IL-2 receptor expression, Tregs may have developed signaling pathways that make them highly responsive to the cytokine. T-cell activation is induced by signals generated from at least three sets of stimuli: antigen, co-stimulators, and cytokines. Many of these signals drive the generation of effector and memory T cells, but Tregs

have to tune down the pathways that lead to effector responses.²⁶ It is possible, therefore, that Tregs have evolved to reduce their responsiveness to antigen and co-stimulation and are thus much more dependent on IL-2 for their activation (Figure 2). Another possibility is that Tregs express high levels of tyrosine phosphatases that promote signaling from the IL-2 receptor.²⁵ Furthermore, because Tregs contain a larger intracellular pool of IL-2 receptor chains, they can rapidly replenish the receptor on the cell surface after it is endocytosed following cytokine binding.²⁷ Based on these findings, we postulate that conventional T cells respond best to the short-lived, high-level bursts of IL-2 that are produced upon exposure to foreign (eg, microbial) antigens, whereas Tregs are maintained by continuous low-level production of IL-2 in response to self-antigens (or perhaps commensals and other environmental stimuli). This hypothesis is difficult to prove because it is not currently possible to quantify the amount of any cytokine produced in lymphoid organs under different conditions.

Therapeutic Applications of IL-2

Because the first defined function of IL-2 was to stimulate immune responses, it was initially used in patients to boost responses to cancer⁵ and in HIV-seropositive patients to enhance T-cell immunity.²⁸ In neither case was the treatment sufficiently effective and safe to be widely adopted.

With increasing emphasis on the role of IL-2 in controlling immune activation, the emphasis has shifted to using the cytokine to suppress harmful responses. The problem remains, however, that IL-2 has dual functions and can be a stimulator or an inhibitor. The first attempts to selectively exploit its inhibitory function relied on simply reducing the dose of IL-2,

Figure 2 Postulated signaling pathways in conventional and regulatory T cells (Tregs). Naive conventional forkhead box P3-negative (FOXP3⁻) T lymphocytes (Tconv) integrate signals from multiple receptors to initiate the activation programs that result in cell proliferation and differentiation into effector and memory cells. Tregs may tune down several of these pathways to prevent the generation of effector cells, resulting in a greater dependence on signals from the IL-2 receptor (IL-2R). APC, antigen-presenting cell; Ca⁺⁺, calcium ions; MAPK, mitogen-activated protein kinases; mTOR, mechanistic target of rapamycin; PI3K, phosphatidylinositol 3-kinase; TCR, T-cell receptor.

because Tregs are much more responsive to the cytokine than are effector cells, and thus at low doses the Tregs should be preferentially activated. The initial proof-of-concept trials showed that low-dose IL-2 was safe and effective in treating vasculitis²⁹ and chronic graft-versus-host disease.³⁰ Subsequent clinical trials have tested the efficacy of low-dose IL-2 in systemic lupus erythematosus, type 1 diabetes, other autoimmune diseases, and allograft rejection (reviewed elsewhere³¹). There is, however, concern that simply altering the dose may not be a consistent or reliable way to selectively manipulate the cellular target of IL-2 in patients. If IL-2 administration activates T-cell responses in patients with ongoing autoimmune disease, it could exacerbate the disease. Conversely, if it induces broad immunosuppression, it may make patients susceptible to opportunistic infections. Thus far, these adverse events have not been observed in the ongoing trials. Alternative approaches that are currently being explored include engineering mutated forms of IL-2 that bind preferentially to Tregs, using anti-IL-2 antibodies that selectively target the cytokine to one or the other cell population, and conjugating IL-2 with polyethylene glycol in ways that make it active on conventional T cells or Tregs.

Although we have emphasized the therapeutic potential of the cytokine for treating inflammatory diseases, it is known that blocking the high-affinity IL-2 receptor with an anti-CD25 antibody is an effective treatment for acute graft rejection.³² On face value, it seems paradoxical that both administering the cytokine and blocking its action may be useful for controlling different inflammatory reactions. One possibility to reconcile these apparently conflicting observations is that blocking the IL-2 receptor is effective in situations of temporary and strong T-cell activation when CD25 is rapidly but transiently induced on responding T cells, and IL-2 drives the effector response. This would be the situation in acute graft rejection. It would, however, be risky to maintain patients on IL-2 receptor blockade for prolonged periods because this treatment would be expected to deplete Tregs and trigger chronic inflammation. Thus, IL-2 blockade could be a therapy for acute inflammatory

reactions and Treg-selective IL-2 for chronic inflammatory diseases.

The next phase of cytokine therapy will likely rely on chemical modifications and combinations. One idea is to use mutants or pegylated forms of IL-2 that preferentially activate effector cells in combination with immune checkpoint blockade to treat cancer patients. Conversely, forms of IL-2 that activate Tregs may be combined with anti-inflammatory agents, such as tumor necrosis factor antagonists, or with tolerogenic peptide administration, to induce maximal immunologic control in autoimmune diseases and for controlling graft rejection.

Conclusions

The evolution of our understanding of IL-2 is a remarkable example of how basic research, mostly in experimental models, informs therapeutic strategies in humans. Starting with the phenotypes of gene knockout mice, and using information from related studies, immunologists have challenged the dogmas about what IL-2 does and have established new paradigms. The dual actions of this cytokine have increased its potential for use in multiple ways. The detailed understanding of the cytokine, its receptor, and signaling pathways holds promise for using structure-based drug design to construct versions of IL-2 that have distinct actions and are useful for treating different types of diseases. The exciting possibility is that similar approaches may be useful for custom-designing the actions and therapeutic effects of other, pleiotropic cytokines. If this potential is realized, the first molecularly defined cytokine will pave the way for fully exploiting this class of molecules as therapeutic agents.

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