CYTOKINES

Revisiting IL-2: Biology and therapeutic prospects

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Interleukin-2 (IL-2), the first cytokine that was molecularly cloned, was shown to be a T cell growth factor essential for the proliferation of T cells and the generation of effector and memory cells. On the basis of this activity, the earliest therapeutic application of IL-2 was to boost immune responses in cancer patients. Therefore, it was a surprise that genetic deletion of the cytokine or its receptor led not only to the expected immune deficiency but also to systemic autoimmunity and lymphoproliferation. Subsequent studies established that IL-2 is essential for the maintenance of Foxp3$^+$ regulatory T cells (T_{reg} cells), and in its absence, there is a profound deficiency of T_{reg} cells and resulting autoimmunity. We now know that IL-2 promotes the generation, survival, and functional activity of T_{reg} cells and thus has dual and opposing functions: maintaining T_{reg} cells to control immune responses and stimulating conventional T cells to promote immune responses. It is well documented that certain IL-2 conformations result in selective targeting of T_{reg} cells by increasing reliance on CD25 binding while compromising CD122 binding. Recent therapeutic strategies have emerged to use IL-2, monoclonal antibodies to IL-2, or IL-2 variants to boost T_{reg} cell numbers and function to treat autoimmune diseases while dealing with the continuing challenges to minimize the generation of effector and memory cells, natural killer cells, and other innate lymphoid populations.

HISTORICAL BACKGROUND

Interleukin-2 (IL-2) was discovered as an autocrine growth factor for cultured T cells and was the first cytokine cloned in 1983 (*1*). Its role in stimulating T cell proliferation and the generation of effector and memory T cells was soon established in mice and humans. This led to clinical trials to evaluate the ability of high doses of IL-2 to stimulate antitumor immune responses in patients with melanoma, renal cancer, and other tumors (*2*). In fact, IL-2 was the first biological produced by using recombinant DNA technology that was administered to humans with cancer or AIDS to enhance T cell numbers and function—and thus laid the foundation for what has been one of the great revolutions in biomedical science and clinical medicine. The success of IL-2 as an immunotherapy for cancer was limited by toxicities caused by the high doses that had to be administered, including vascular leak syndrome and other manifestations of a cytokine storm, and even today, it remains a treatment with limited utility. However, a monoclonal antibody (mAb), basiliximab, specific for the α chain of the IL-2 receptor (IL-2R) CD25, is used to inhibit IL-2 signaling to suppress the rejection of transplanted organs (*3*), lending support to the notion that IL-2 serves as an important T cell growth factor in vivo.

In the 1980s and 1990s, several observations had begun to question the dogma that the principal, or sole, function of IL-2 is to stimulate effector responses. T cells from humans with autoimmune disease and mouse models of autoimmunity produced less IL-2 upon stimulation in vitro than did T cells from normal individuals (*4*, *5*). Surprisingly, mice with germline knockout of IL-2 or the α or β chain of IL-2R all developed various manifestations of systemic autoimmunity, including lymphoproliferation, and not the expected immune deficiency (*6*–*8*). Subsequent studies showed that blocking IL-2 (*9*) or CD25 (*10*) resulted in rapid-onset autoimmunity, which is consistent with the knockout mouse results. Rare families with CD25 deficiency, discussed later, also develop autoimmune diseases. All these findings suggested that an essential function of IL-2 is to control immune responses and maintain self-tolerance, and its absence results in defective control of effector cells, which leads to autoimmunity.

IL-2 AND REGULATORY T CELLS

The realization that IL-2 functioned in self-tolerance led to numerous attempts to define the mechanism. Initial studies focused on the ability of this growth factor to promote activation-induced cell death (*11*) and tested the hypothesis that deficiency of IL-2 resulted in defective deletion of self-reactive lymphocytes. However, there was no convincing evidence to support this mechanism in vivo. The study that convincingly established that IL-2 functioned in a cell-extrinsic manner was a mouse bone marrow chimera experiment that showed that normal cells could correct the abnormality of IL-2–deficient cells in a radiation-induced bone marrow chimera (*12*). At about the same time, regulatory T cells (T_{reg} cells) had been identified as a population of suppressive T cells that constitutively expressed high levels of CD25 (*13*). Collectively, these results raised the possibility that the function of IL-2 was to maintain T_{reg} cells, now defined as the $CD4^+Foxp3^+CD25^+CD127^{low}$ population, and in the absence of IL-2 or signaling by its receptor, there is a numerical and/or functional deficiency of T_{reg} cells, and this is the cause of autoimmunity. Definitive proof of the importance of IL-2 and its signaling pathway for maintaining self-tolerance has come from mice in which either the α or β chain of the receptor or the transcription factor downstream of the IL-2R, signal transducer and activator of transcription 5 (Stat5), has been knocked out selectively in Foxp3$^+$ cells (*14*).

The function of IL-2 in T_{reg} cells has been extensively analyzed and is now understood in considerable detail. IL-2 is required for the survival and suppressive functions of Foxp3$^+$ T cells and possibly also for their generation in the thymus. One of the earliest studies showed that mice in which IL-2Rβ had been knocked out had a defect in the generation of T_{reg} cells in the thymus, and the defect could be corrected through enforced thymic expression of IL-2Rβ (*15*). Subsequent studies of IL-2 and CD25 deficiency have shown that thymic generation of Foxp3$^+$ T_{reg} cells may be only partially dependent on IL-2. However, it has been demonstrated by many experimental

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approaches that IL-2 is critical for the maintenance of functional T_{reg} cells (*16*–*18*). In the absence of IL-2, $Foxp3^+$ T_{reg} cells disappear from peripheral lymphoid organs, presumably because the deficiency of this growth factor leads to apoptotic death of the cells (*19*). As important as its role in T_{reg} cell survival, IL-2 is also essential for the functional capacity of T_{reg} cells. It is required for the expression of Foxp3 (*16*) and other mediators of T_{reg} cell–suppressive activity such as CTLA-4 (*19*). IL-2–induced Stat5 can bind to a noncoding sequence in the Foxp3 promoter and promote stable expression of Foxp3 (*20*). Predictably, the limited availability of IL-2 in local inflammatory tissues can lead to T_{reg} cell instability, loss of Foxp3 expression, and consequent production of pathogenic cytokines by effector cells that can exacerbate autoimmunity (*18*). However, it should be mentioned that T_{reg} cells are heterogeneous, and IL-2 may be required more for the maintenance of T_{reg} cells in lymphoid organs than in nonlymphoid peripheral tissues under steady-state (noninflammatory) conditions (*21*).

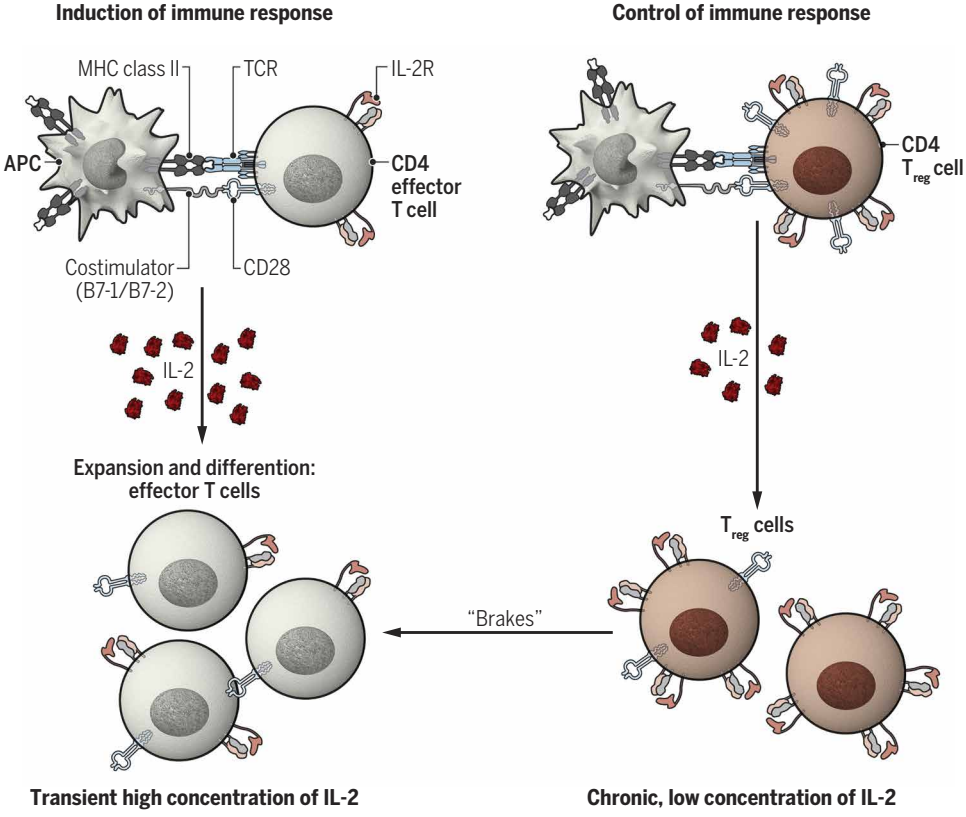

Fig. 1. Dual role of IL-2 in T cell activation. IL-2 participates in the induction of immune responses by stimulating proliferation and differentiation of "conventional" T cells and in the control of immune responses by maintaining T_{reg} cells. These two activities likely differ in the kinetics and amount of IL-2 produced. MHC, major histocompatibility complex; TCR, T cell receptor; APC, antigen-presenting cell.

Because mature T_{reg} cells do not make IL-2, and IL-2 was thought to function in an autocrine manner, an interesting puzzle has been the source of the IL-2 that maintains T_{reg} cells in the periphery. Several studies suggested that conventional ($Foxp3^-$) T cells responding to self or other antigens produce IL-2, which then acts on T_{reg} cells (*22*). Intravital imaging studies have shown that T_{reg} cells and conventional T cells colocalize with antigen-presenting dendritic cells, and in these three-cell clusters, the conventional cells are the ones that respond to antigen by secreting IL-2, whereas the T_{reg} cells are the recipients of IL-2 signals (*23*).

Although the pendulum has swung from IL-2 being an inducer of effector and memory responses to its primary role being to maintain T_{reg} cells, the reality is that it likely serves both functions (Fig. 1). In a transgenic mouse model of severe but self-limited systemic inflammation, elimination of IL-2 from T cells results in less severe initial disease because of delayed generation of effector T cells (T_{eff} cells) and a complete failure of recovery because of the absence of T_{reg} cells (*17*). An interesting question is which function dominates under what circumstance. One possibility is that the dominant function is determined by the amount and kinetics of IL-2 production: effector cell development in response to brief high-level IL-2 and T_{reg} cell maintenance in response to persistent low-level cytokine (*18*). The activation of different populations of T cells by IL-2 is also influenced by the kinetics of IL-2R expression. Conventional $CD4^+$ T cells express IL-2R only after activation, in part because the receptor is internalized after binding to the cytokine, and these cells have a small pool of intracellular IL-2Rβ, so receptor molecules have to be synthesized de novo. By contrast, T_{reg} cells may have larger intracellular pools of receptor chains and are able to maintain receptor expression for long periods (*24*). Furthermore, T_{reg} cells may show greater and more sustained IL-2 signaling than that of other T cell populations (*25*). Last, it should be mentioned that IL-2 has important actions on cells other than T cells, including natural killer (NK) cells and innate lymphoid cells (Fig. 2) (*26*). In some cases, IL-2 can expand a subset of $CD56^+$ NK cells, which are proposed to be a suppressive population in the tumor microenvironment (*27*). In other settings, IL-2 promotes the expansion and differentiation of a small subset of innate lymphoid cells, termed ILC2, resulting in increased IL-5 production, which leads to eosinophilia and alternatively activated macrophages that control type 2 immunity (*28*, *29*). In addition, IL-2 controls these and other $CD25^+$ innate cells in tissues critical for homeostatic tissue functions. These results highlight the potential role of this growth factor in general tissue repair and other non–immune-mediated diseases.

IL-2 GENETICS

Genetic studies in humans support a critical role for the IL-2 signaling pathway in modulating risk of autoimmunity. Rare coding mutations that disrupt this pathway can cause severe forms of Mendelian immune dysregulation. Human *IL2RA* deficiency results in chronic immunodeficiency and variable autoimmunity that develops in the first year of life, which is reminiscent of immune dysregulation, polyendocrinopathy, and enteropathy X-linked syndrome, which is caused by *FOXP3* mutations and is consistent with a critical role for this receptor in T_{reg} cells (*30*–*33*). Mutations in *STAT5B*, which was originally

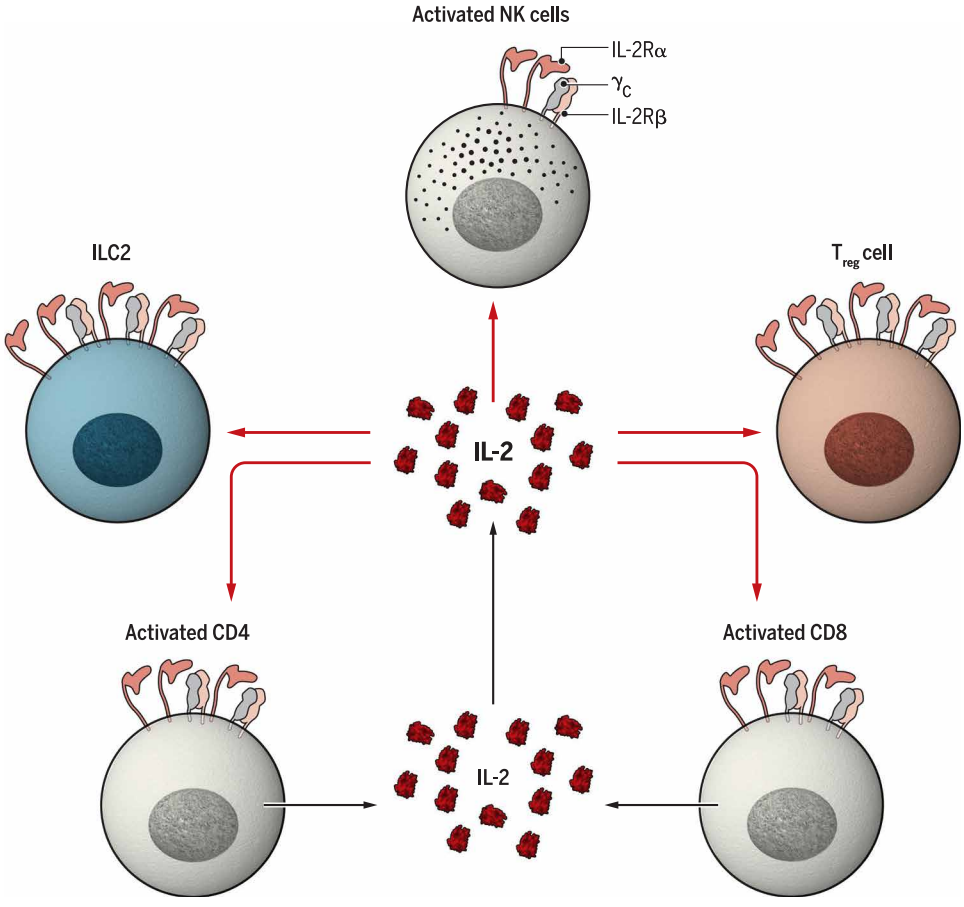

Fig. 2. Cellular targets of IL-2 action. In addition to conventional T cells and T_{reg} cells, IL-2 acts on NK cells and ILCs.

identified in patients with dwarfism and growth hormone insensitivity, are also associated with primary immunodeficiency and variable autoimmunity, often leading to recurrent infections, eczema, chronic diarrhea, and lymphoid interstitial pneumonia because of the role of STAT5 transcription factors in mediating IL-2 signals (*34*–*37*). In addition to these rare Mendelian mutations, genome-wide association studies for multiple common autoimmune diseases implicate more subtle dysregulation of the IL-2 pathway in tuning risk of disease. Risk variants associated with multiple different autoimmune diseases have been uncovered in the genetic loci encoding IL-2 (*38*–*47*), its receptors [both IL2-RA (*48*–*53*) and IL-2RB (*54*)], and associated downstream signaling factors [including STAT5A/STAT5B (*41*) and PTPN2 (*41*, *53*, *55*–*60*)]. Together, dysregulation of multiple mediators of IL-2 signaling can contribute to the risk of human autoimmune disease.

In the *IL2RA* locus, noncoding autoimmunity-associated single-nucleotide polymorphisms (SNPs) affect levels of *IL2RA* transcript (*61*, *62*), soluble IL-2RA receptor (*63*), expression of IL-2RA on specific immune cell types, and the abundance of IL-2RA–expressing memory T cells in the blood (*64*). Recent fine mapping has pointed to individual candidate causal SNPs with improved resolution (*65*, *66*). As a notable example, the risk association for Crohn's disease at the *IL2RA* locus has now been fine-mapped to a single noncoding variant in the first intron. Paradoxically, the same SNP is associated with protection against type 1 diabetes (*67*), which is consistent with context-restricted effects on IL-2 signaling that have discordant effects on the two different diseases. Noncoding genetic variants associated with complex autoimmune disease can cause altered gene regulation in specific cell types, shaping transcriptional programs in response to specific signaling cues. Clustered regularly interspaced short palindromic repeats (CRISPR) engineering demonstrated that the fine-mapped *IL2RA* autoimmunity risk variant conserved between mouse and human impairs the timing of IL-2RA induction in naïve T cells upon stimulation (*68*). Future work has the potential to reveal how altered stimulation-responsive induction of IL-2RA can modulate disease risk in Crohn's disease and type 1 diabetes. Selective gene engineering can be used to modify these disease-associated variants to assess mechanistic effects on IL-2RA regulation and direct future drug development toward the affected cellular pathways. Furthermore, CRISPR provides an opportunity to "correct" severe mutations that impair IL-2 signaling (*69*) or rewrite noncoding genome sequences that control context-specific regulation of IL-2 signaling components to engineer next-generation cellular therapies.

STRUCTURE OF IL-2 AND ITS RECEPTOR

IL-2 is a typical four–α helix cytokine, tightly regulated at the mRNA level by signals from the T cell receptor and CD28 (*70*). IL-2 binds to and signals through a receptor complex consisting of three distinct subunits designated IL-2Rα (CD25), IL-2Rβ (CD122), and common γ chain (γ_c; CD132) (*71*). The crystallization of IL-2 bound to the external domains of the three receptor chains in a quaternary complex (*72*) revealed that the sites on IL-2 that interact with the three chains of the IL-2R do not overlap, and the α chain itself does not contact either the β or γ_c to be consistent chains (Fig. 3). The high affinity of the IL-2/IL-2Rα/β trimeric complex clearly indicates that the complex is more stable than IL-2 bound to either the α chain alone or to the β chain alone. During engagement of IL-2R, the IL-2/α/β trimer recruits the γ chain into a quaternary complex, leading to intracellular signaling. Because only a few residues of IL-2 interact with both β and γ_c chains, binding of IL-2 may induce conformational changes in the β chain that would further promote recruitment of the γ_c chain. Moreover, it was also found that the α chain does not participate in signaling, whereas both the β and γ_c chains are necessary for signaling (*73*–*75*). In the absence of IL-2Rα expression, IL-2Rβ and γ_c can form an intermediate affinity receptor that is fully competent to signal. The high-affinity receptor is the most physiologically relevant form of the IL-2R because CD25-deficient mice (which express only the intermediate-affinity IL-2R) are phenotypically indistinguishable from IL-2–deficient mice, as noted above. Thus, the structure of IL-2 and its receptor is flexible and can naturally exist in different conformations that appear to favor either the high-affinity trimeric IL-2R or the intermediate-affinity dimeric IL-2R, respectively, resulting in the activation of different immune cells.

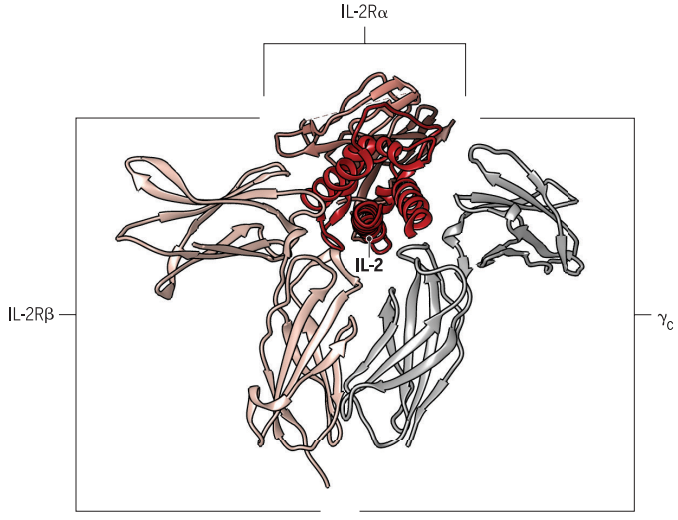

Fig. 3. Structure of IL-2/IL-2R complex. A ribbon diagram depiction of the crystal structure of IL-2 with its trimeric receptor shows how the cytokine interacts with each of the three chains of the receptor. This illustration was adapted from the protein structure (*89*).

DEVELOPMENT OF IL-2 THERAPEUTICS

The elucidation of the role of IL-2 in the life of T_{reg} cells suggested that it may be possible to use the cytokine to control harmful immune responses. Other functions of IL-2, such as its ability to inhibit the generation of proinflammatory T helper 17 cells (*76*) and follicular helper T cells, which are central to the production of autoantibodies (*77*), may synergize with its effects on T_{reg} cells in the treatment of autoimmune and inflammatory diseases. The challenge in using IL-2 to suppress pathologic immune responses is that the cytokine can activate the effector arm of the immune system, thus carrying the risk of exacerbating disease. Multiple approaches are being developed to preferentially or selectively target IL-2 to T_{reg} cells.

Low-dose IL-2

The trimeric IL-2Rαβγ_c is typically expressed at high levels by T_{reg} cells, whereas the dimeric IL-2Rβγ_c is expressed mostly on activated $CD8^+$ T cells and NK cells. It is now well established that low-dose IL-2 therapy preferentially activates T_{reg} cells because of the constitutive high expression of IL-2Rα, and in addition, a recent report has suggested that other cell-intrinsic factors may contribute to this increased sensitivity (*25*). The first clinical trials testing this approach were small proof-of-concept trials that showed that low-dose IL-2 was effective in treating hepatitis virus–associated vasculitis (*78*) and chronic graft-versus-host disease (GVHD) (*79*). Subsequent trials have been carried out in systemic lupus erythematosus and type 1 diabetes (*80*). The results so far are promising, and it is especially advantageous that the biological agent has already been approved for clinical use. However, a continuing concern with this approach is that the therapeutic window for doses may be small.

Antibody-cytokine conjugates

Another approach used to alter IL-2 structure has been the generation of antibodies to IL-2 that, when complexed with IL-2, can preferentially stimulate expansion of T_{reg} or effector T (T_{eff} cells. This approach is based on the discovery that IL-2 attachment to different anti–IL-2 antibodies targets the cytokine to different cell populations by blocking sites on the cytokine that bind to the β chain of the receptor and by inducing allosteric changes that alter IL-2Rα chain binding (*81*). By covering up the site that binds to the β chain and altering IL-2Rα binding, signaling requires both high CD25 expression and a reduced threshold to drive proliferation, which results in selective T_{reg} cell activation and expansion. Garcia's group showed that the anti–IL-2 antibody JES6-1 (*82*) sterically blocked the IL-2/IL-2Rβ and IL-2/IL-2Rγ interactions, inducing a preferential activation of IL-2Rα^{hi} cells because of allosteric changes induced in the molecule after antibody binding. Conversely, a different anti–IL-2 antibody, S4B6, altered IL-2 conformation, resulting in blockade of the IL-2/IL-2Rα interaction, while also stabilizing the IL-2/IL-2Rβ interaction, resulting in selective targeting of T_{eff} cells (*82*). These findings have now been replicated in a human system by the development of an mAb to human IL-2 that, when bound to human IL-2, leads to a conformational change that selectively enhances T_{reg} cell expansion and function (*83*). These mouse and human antibody/IL-2 complexes have been shown to be effective in models of autoimmune disease, including type 1 diabetes and experimental autoimmune encephalomyelitis, as well as in a model of GVHD (*83*). Developing such drugs for clinical use may be improved by directly linking the antibody to IL-2, resulting in a single agent that can increase IL-2 half-life and, at the same time, limit off-target toxicities.

Chemical modifications of IL-2

Several efforts have been made to engineer or modify IL-2 so as to improve its therapeutic potential. Shanafelt *et al.* generated an IL-2 mutein with ~3000-fold in vitro selectivity for T cells over NK cells relative to the wild type cytokine (*84*) and demonstrated the activity of this mutein in vivo in animal models. In 2012, the Garcia laboratory generated a CD25-independent version of IL-2 with increased binding affinity for IL-2Rβ, which showed superior expansion of cytotoxic T cells, leading to improved antitumor response (*85*). Several companies—including Celgene, Roche, Amgen, and others—are developing new IL-2 mutein Fc fusion proteins that preferentially increase T_{eff} or T_{reg} cells. Newly generated IL-2 variants consist of mutated forms of IL-2 with high affinity for IL-2Rβ and a weakened interaction with the γ_c, therefore attenuating the extent of IL-2Rβ–γ_c heterodimerization. These IL-2 analogs act as partial agonists and differentially affect lymphocyte populations at distinct activation thresholds (*86*). All have shown efficacy in small-animal models, but whether these molecules are immunogenic in humans remains to be determined.

Other approaches to increase the efficacy of IL-2 consist of coupling the cytokine to large carrier molecules such as albumin or polyethylene glycol (PEG) or genetically fusing IL-2 to an immunoglobulin Fc. Nektar Therapeutics has developed a clinical-stage biologic (NKTR-214) that consists of IL-2 bound to PEG. This compound has a reduced affinity for the trimeric IL-2R, therefore favoring CD8 T cells over T_{reg} cells, providing antitumor efficacy in multiple syngeneic models (*87*). Distinct PEGylated IL-2 approaches are now being developed by Nektar Therapeutics and others to promote the T_{reg} cell axis.

Cell therapy with IL-2

Recent data from the Garcia laboratory have also provided convincing evidence that the growth potential of IL-2 for individual T cell or NK subsets can be exploited directly by generating an orthogonal cytokine system in which receptor and ligand pairs are restricted to exclusively signal together (*88*). T cells can be genetically engineered to express a mutated version of IL-2Rβ, which will be selectively expanded by a

specific mutated IL-2. This raises the prospect of selectively expanding a specific T cell population and therefore could be used to treat both autoimmune disease and cancer.

CONCLUSIONS

The story of IL-2 provides remarkable lessons about how concepts change, and are even reversed, on the basis of rigorous scientific advances. For many years, IL-2 was thought to be an essential growth factor for T cells and was implicated in the initiation of immune responses. More recent results from knockout mice, human Mendelian disorders, and complex autoimmune diseases, as well as diverse experimental approaches, suggest that a major, nonredundant function of IL-2 is to maintain stable T_{reg} cells in lymphoid organs and tissues. These new developments, and our revised view of the biology of IL-2, have been the foundation for novel therapeutic strategies that use this cytokine to suppress rather than stimulate immune responses. Of course, much remains to be learned to realize the full potential of this remarkable cytokine. For instance, these protolerogenic therapeutic approaches have to take into account the ability of IL-2 to act on various cell populations, many of which may promote inflammatory reactions and thus be harmful in autoimmune diseases. Achieving the optimal balance between activating T_{eff} and T_{reg} cells also remains a continuing challenge in the therapeutic applications of this cytokine. The many ongoing clinical developments should provide answers to these problems in the near future.

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