Supplement Review

The contrasting roles of IL-2 and IL-15 in the life and death of lymphocytes: implications for the immunotherapy of rheumatological diseases

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Chapter summary

Interleukin-15 (IL-15) is a 14–15-kDa member of the 4α helix bundle family of cytokines that stimulate T and NK (natural killer) cells. IL-15 and IL-2 utilize heterotrimeric receptors that include the cytokine-specific private receptors IL-2Rα and IL-15Rα, as well as two receptor elements that they share, IL-2Rβ and γc. Although IL-2 and IL-15 share two receptor subunits and many functions, at times they provide contrasting contributions to T-cell-mediated immune responses. IL-2, through its pivotal role in activation-induced cell death (AICD), is involved in peripheral tolerance through the elimination of self-reactive T cells. In contrast, IL-15 in general manifests anti-apoptotic actions and inhibits IL-2-mediated AICD. IL-15 stimulates the persistence of memory phenotype $CD8^+$ T cells, whereas IL-2 inhibits their expression. Abnormalities of IL-15 expression have been described in patients with rheumatoid arthritis or inflammatory bowel disease and in diseases associated with the retrovirus HTLV-I (human T-cell lymphotropic virus I). Humanized monoclonal antibodies that recognize IL-2Rα, the private receptor for IL-2, are being employed to inhibit allograft rejection and to treat T-cell leukemia/lymphoma. New approaches directed toward inhibiting the actions of the inflammatory cytokine, IL-15, are proposed for an array of autoimmune disorders including rheumatoid arthritis as well as diseases associated with the retrovirus HTLV-I.

Keywords: interleukin-2, interleukin-15, rheumatoid arthritis

Introduction

Intracellular communications involved in immune responses are often mediated by cytokines that show a high degree of redundancy and pleiotropy, controlling a wide range of functions in various cell types. Disordered expression of cytokines has been shown to play a role in autoimmune diseases such as rheumatoid arthritis (RA). In particular, abnormalities of TNF-α and such downstream mediators of proinflamatory activity as IL-1, IL-6, granulocyte/macrophage-colony-stimulating factor (GM-CSF), and inflammatory chemokines have been demonstrated in RA [1]. Recently, disorders involving interleukin (IL)-15 have been demonstrated in this autoimmune disease as well [2–10]. IL-2 and IL-15 utilize heterotrimeric receptors that include cytokine-specific private receptors IL-2Rα and IL-15Rα respectively, as well as two receptor elements, IL-2Rβ and γc, that they share [11–14]. We and others have shown that although IL-2 and IL-15 share two receptors and therefore share many functions, they also provide distinct and at times contrasting contributions to the life and

A glossary of specialist terms used in this chapter appears at the end of the text section.

death of lymphocytes [15–19]. IL-2, through its pivotal role in activation-induced cell death (AICD), is involved in peripheral tolerance through the elimination of self-reactive T cells [20]. In contrast, IL-15 in general manifests anti-apoptotic actions and inhibits AICD and stimulates the persistence of memory phenotype $CD8^+$ T cells [17,18]. Abnormalities of IL-15 expression have been reported in inflammatory, autoimmune, and neoplastic diseases [2–10,21–24]. In particular, abnormally high levels of IL-15 transcription and translation are observed in human T-cell lymphotropic virus I (HTLV-I)-associated diseases such as the neurological disorder tropical spastic paraparesis/HTLV-I associated myelopathy (TSP/HAM) [23,24]. Furthermore, abnormalities of IL-15 expression have been noted in patients with autoimmune diseases such as RA and inflammatory bowel disease [2–10, 21–24]. Therapeutic agents are being developed to target the receptor and signaling elements shared by IL-2 and IL-15 to provide effective treatment for such autoimmune disorders as well as the leukemia/lymphomas that are associated with the retrovirus HTLV-I [9,10,19].

Historical background

Two separate groups simultaneously reported the recognition of the novel cytokine now known as IL-15, which was recognized as novel on the basis of the ability of culture supernatants from two cell lines, CV-1/EBNA and the HTLV-I-associated HuT-102, to stimulate proliferation of the cytokine-dependent murine T cell CTLL-2 in the absence of IL-2 [12,13]. During studies to define pathogenic mechanisms that underlie the IL-2-independent proliferation of HTLV-I-associated adult T-cell leukemia cells, our group found that the ATL (adult T-cell leukemia) cell line HuT-102 secretes a 14–15-kDa lymphokine, which we provisionally designated IL-T, that stimulates T-cell proliferation and induces activation of large, granular lymphocytes [12,25]. In addition, we showed that IL-T-mediated stimulation requires the expression of the IL-2Rβ subunit [12]. Grabstein and co-workers simultaneously reported a cytokine they designated IL-15, which was isolated from the supernatant of the simian kidney epithelial-cell line CV-1/EBNA [13]. IL-15 shared many characteristics with IL-T, including an apparent molecular mass of 14–15 kDa, as well as a signaling pathway in T and natural killer (NK) cells that utilized the IL-2Rβ and γc subunits of the IL-2 receptor. By use of an appropriate anti-cytokine antibody, IL-T and IL-15 were shown to be identical [19].

IL-2/IL-15 cytokine family

Cytokines exhibit a high degree of redundancy and pleiotropy, which is explained in part by the sharing of common receptor subunits among members of the cytokine receptor family. Each cytokine has its own private receptor, but may also share public receptor subunits with other cytokines. This is the case in the IL-2 receptor system. The IL-2R is made up of at least three distinct membrane components: the 55-kDa alpha chain (IL-2Rα); the 70–75-kDa β chain (IL-2Rβ); and the 64-kDa common γ chain (γc) chain, which is shared with other members of this system, including IL-4, IL-7, IL-9, IL-15, and IL-21. IL-2 and IL-15 also share the IL-2Rβ subunit [11–14].

The regulation of IL-15 expression

IL-2 and IL-15 exhibit major differences in the levels of control of their synthesis and secretion and in their sites of synthesis [19,26,27]. IL-2 is produced by activated T cells and its expression is regulated predominantly at the levels of mRNA transcription and message stabilization. In contrast, there is widespread constitutive expression of IL-15 mRNA in a variety of tissues, including placenta, skeletal muscle, kidney, lung, heart, fibroblasts, and activated monocytes [13,19].

The regulation of IL-15 expression is multifaceted. Modest control occurs at the level of transcription, whereas a dominant control occurs post-transcriptionally, at the levels of translation and intercellular trafficking [19,26,28]. Although IL-15 mRNA is widely expressed constitutively, it has been difficult to demonstrate IL-15 within the cells or the supernatants of cells that express such IL-15 mRNA. Multiple controlling elements impede the translation of IL-15 mRNA, including a long 5′ UTR containing IL-13 upstream AUGs, an unusually long (48-amino-acid) IL-15 signal peptide, and an inhibitory element in the C terminus of the IL-15 mature coding sequence or protein [19,26,27]. These multiple negative regulatory features controlling IL-15 expression may be required, in light of the potency of IL-15 as an inflammatory cytokine that stimulates the expression of TNF-α, IL-1β, and inflammatory chemokines, which if indiscriminately expressed could lead to inflammatory autoimmune diseases. In terms of a more positive role for IL-15, by maintaining a pool of translationally inactive mRNA, cells may respond rapidly to an intracellular infection by transforming the IL-15 mRNA into a form that can be translated effectively, yielding secreted IL-15 that may activate T and NK cells that could then aid in the host response to the invading pathogen.

The shared and contrasting roles of IL-2 and IL-15 in the life and death of lymphocytes

Functions mediated by IL-2 and IL-15 may be evaluated with regard to the fundamental goals of the immune system, which may be considered to include the generation of a rapid innate and adapative response to invading pathogens; the maintenance of a specific memory response to these pathogens; and the elimination of host-reactive T cells, to yield tolerance to self.

As might be anticipated from their sharing of the IL-2Rβ and γc subunits in T and NK cells, IL-15 and IL-2 share a number of biological activities, including stimulation of the proliferation of activated $CD4^+CD8^+$ as well as γδ subsets

of T cells [19,29–31]. IL-2 and IL-15 also facilitate the induction of cytolytic effector cells, including CTL and LAK cells [19,29–31]. In addition, both IL-2 and IL-15 act as chemoattractants for T cells. The two cytokines stimulate the proliferation of NK cells and can synergize with IL-12 to facilitate their synthesis of IFN-γ and TNF-α [31]. Both cytokines induce the proliferation and immunoglobulin synthesis by human B cells stimulated with anti-IgM or CD40 ligand [32].

A major advance emerging from work in our laboratory and those of others is that although IL-2 and IL-15 share two receptor subunits and some functions, they also provide distinct and at times contrasting contributions to the life and death of lymphocytes [15–19]. Although IL-2 is an important growth and survival factor, it also plays a critical role in Fas-mediated activation-induced cell death (AICD) of CD4 T cells [20]. Receptor-mediated stimulation of CD4 T cells by antigen at high concentration (or by CD3 plus CD28) induces the expression of IL-2 and the IL-2 receptor, which in turn interact to yield T-cell activation and T-cell cycling. Antigen stimulation of the cycling T cells at this stage through the T-cell antigen receptor increases the transcription and surface expression of the death-effector molecule Fas ligand (FasL). The interaction of FasL with Fas then leads to death of the self-reactive T cells [20]. My colleagues and I showed that IL-15, in contrast, acts to extend the survival of lymphocytes, both by acting as a growth factor and by inhibiting IL-2-mediated AICD of CD4 T cells [17]. In *ex vivo* studies, $CD4^+$ T cells from IL-15 transgenic mice that we developed did not manifest IL-2-mediated AICD.

In addition to their distinct actions on AICD, IL-2 and IL-15 play opposing roles in the homeostasis of $CD8^+$ memory phenotype T cells [17]. Zhang and Ku and their coworkers [15,16] reported that the division and survival of $CD8^+$ T cells of memory phenotype is stimulated by IL-15. We in turn showed that our transgenic mice had abnormally elevated numbers of $CD8^+$ memory phenotype T cells. Furthermore, we defined a role for IL-15 and its receptor in the HTLV-I-associated neurological disease tropical spastic paraparesis (TSP/HAM) [33]. The number of circulating MHC class I restricted antigen (amino acids 11–19 of the HTLV-I-encoded tax protein) specific memory $CD8^+$ cells that have been suggested to be involved in the pathogenesis of TSP was shown by tetramer technology to be markedly increased in the circulation of patients with HTLV-I. My colleagues and I studied the persistence of such CD8-antigen-specific T cells *ex vivo* in the presence of antibodies to the IL-2 or IL-15 cytokines or to their receptors and showed that the *ex vivo* addition to IL-15 or to IL-2Rβ of antibodies that inhibit IL-15 action to such mononuclear cells *ex vivo* led to the rapid reduction (within six days) in the number of such antigen-specific memory and effector cytotoxic $CD8^+$ cells, whereas antibodies to IL-2 or to its private IL-2Rα receptor did not have this effect [33]. In this system, IL-15 both increased the proliferation of the CD8 cells and reduced their death by apoptosis.

These conclusions concerning the distinct functional roles manifested by IL-2 and IL-15, derived from *ex vivo* studies, are supported by the analysis of knockout mice with disrupted cytokine and cytokine-receptor genes as well as from the study of transgenic mice. $IL\text{-}2^{-/-}$ and IL-2Rα null mice developed massive enlargement of peripheral lymphoid organs and polyclonal T- and B-cell expansion, as well as autoimmune diseases, including hemolytic anemia and inflammatory bowel disease, that are related to the impaired AICD [34,35]. In contrast to this phenotype, mice genetically deficient in IL-15 ($IL\text{-}15^{-/-}$) or its receptor (IL-15Rα) did not manifest lymphoid enlargement, high immunoglobulin levels, or autoimmune disease. Rather, they displayed a marked reduction in the number of thymic and peripheral NK cells, NK T cells, and intestinal intraepithelial lymphocytes (IELs). Furthermore, they manifested a marked reduction in memory phenotype $CD8^+$ T cells [36,37].

Taken together, these studies support the view that in their special adaptive immune functions, IL-2 and IL-15 favor opposing actions that tend to emphasize one or the other of the two competing major goals of the immune response. IL-2, through its contribution to AICD for CD4 cells and its interference with the persistence of $CD8^+$ memory phenotype T cells, favors the elimination of selected lymphocytes that are directed toward self-antigens and thus IL-2 plays a critical role in the maintenance of peripheral self-tolerance. In contrast, IL-15 through its inhibition of IL-2-mediated AICD and its positive role in the maintenance of $CD8^+$ memory phenotype cells, favors the maintenance and survival of CD4 and CD8 T cells. The persistence of memory phenotype $CD8^+$ T cells mediated by IL-15 is of value in maintaining a specific immune response to foreign pathogens. However, IL-15 expression carries with it the risk to the organism of the survival of self-reactive T cells that could lead to the development of autoimmune diseases.

Aberrant IL-15 expression in retroviral diseases

Increased IL-15 expression has been observed in retroviral diseases and neoplasia [23,24]. HTLV-I-infected T cells of patients with the neurological disorder TSP/HAM express the HTLV-I-encoded transactivator $p40^{tax}$. The expression of tax leads to the induction of IL-15 and IL-15Rα, and to the expression of IL-2 and IL-2Rα. The induction of IL-15 and IL-15R expression involves NF-κB and IRF-1 or interferon regulatory factor (IRF)-4 [23,24,38]. The *ex vivo* proliferation of HTLV-I-infected T cells in TSP/HAM can be partially inhibited by an antibody to IL-15 or to IL-2 and can be virtually abrogated by the simultaneous administration of antibodies to both cytokines or to both cytokine receptors,

suggesting that these two cytokines mediate autocrine/paracrine stimulatory systems as a consequence of HTLV-I infection. IL-15 also appears to play a role in the expression of antigen-specific MHC I restricted memory phenotype $CD8^+$ cells that participate in the pathogenesis of TSP/HAM. In patients with TSP/HAM, tetramer technology showed that 3% to over 20% of their CD8 cells were MHC class I restricted, antigen-specific cells (directed to amino acids11–19 of the tax protein transactivator) [33]. The number of such cells that persisted for six days in *ex vivo* cultures of patient peripheral blood mononuclear cells was decreased in the presence of antibodies to IL-15 or to its receptor. This observation is in accord with the view, presented above, that IL-15 plays a major role in the generation and persistence of antigen-specific $CD8^+$ memory and effector cells. An increased production of IL-15 by HTLV-I-associated T cells is also observed in ATL, an aggressive leukemia of mature CD4 cells that is associated with HTLV-I [23]. Taken as a whole, the evidence supports the view that the retrovirus-induced IL-15 and its private receptor play meaningful roles in the pathogenesis and persistence of both autoimmune and leukemic disorders associated with HTLV-I infection.

Abnormalities of IL-15 expression in inflammatory autoimmune diseases including RA

Feldmann and co-workers proposed that TNF-α is at the apex of a cytokine cascade that includes IL-1β, IL-6, GM-CSF, and a series of inflammatory chemokines, including Mip1α, Mip1β, and IL-8, that are intimately involved in the development and progression of RA [1]. McInnes and co-workers have reported abnormalities of IL-15 in this disease and have suggested that IL-15 may precede TNF-α in the cytokine cascade [2,3,8]. In particular, IL-15-activated T cells can induce TNF synthesis by macrophages in RA via a mechanism dependent on cell contact [3]. Those workers reported the presence of high concentrations of IL-15 in RA synovial fluid and showed that IL-15 is expressed by cells of the synovial membrane lining. Nevertheless, the presence of rheumatoid factor in the fluids may yield specious high estimates for IL-15 assessed by an ELISA. Harada and co-workers showed that freshly isolated cells from synovial tissues strongly expressed mRNA for IL-15 and in comparison with cells from osteoarthritis tissues could spontaneously release large amounts of IL-15 in culture [4]. The IL-15 could stimulate the proliferation of synovial-tissue T cells from RA patients. Klimiuk and co-workers also showed high levels of IL-15 as well as TNF-α in the serum of patients with RA [7]. Synovial fluids in RA contain chemotactic and T-cell-stimulatory activities attributable in part to IL-15. Oppenheimer-Marks and co-workers showed that IL-15 is produced by endothelial cells in rheumatoid tissues and that this cytokine markedly increases transendothelial migration of both CD4 and CD8 cells [6]. Furthermore, they showed that IL-15 leads to the accumulation of T cells in RA synovial tissues engrafted into mice with severe combined immune deficiency (SCID) *in vivo*. In a parallel murine model, the intra-articular injection of IL-15 induced a local tissue inflammatory infiltrate consisting predominately of T lymphocytes. These data suggest that IL-15 can recruit and activate T cells into the synovial membrane, possibly contributing to the pathogenesis of RA. Ziolkowska and co-workers also suggested that IL-15 plays an important role in the pathogenesis of RA, in part by inducing IL-17 in the joints of RA patients: this cytokine is known to stimulate synoviocytes to release several mediators of inflammation, including IL-6, IL-8, GM-CSF, and prostaglandin E_2 [39]. Finally, as noted below, the injection of inhibitors of IL-15 action suppressed the development of collagen-induced arthritis [9,10]. In summary, these reports suggest a role for IL-15 in the development of inflammatory RA and imply that antagonists to IL-15 action may have therapeutic potential in this disease.

Therapy directed toward IL-15 and IL-15 receptor subunits

The majority of therapeutic trials directed toward the IL-2/IL-2R or IL-15/IL-15R systems have focused on the alpha subunit of the IL-2 receptor. Such efforts directed toward IL-2Rα have met with considerable success in the treatment of leukemia and select autoimmune disorders and in the prevention of allograft rejection [40]. However, efforts targeting IL-2Rα have limitations. In particular, antibodies to IL-2Rα do not inhibit the actions of IL-15, a cytokine that does not bind to this subunit. They also do not act on resting NK or NK T cells that express IL-2Rβ and γc but not IL-2Rα. Additional limitations are suggested by our discussion above of the role of IL-2R in the elimination of memory T cells and in AICD, where antibody-mediated inhibition of AICD may prevent the generation of peripheral tolerance to host antigens targeted in autoimmunity and to the transplatation antigens expressed on the allografts. In addition, the role of IL-2 in the termination of memory cells directed toward self-antigens is not desirable. Finally, blockade of IL-2/IL-2R interaction could prevent the development and persistence of $CD4^+CD25^+$ (IL-2Rα^+) negative regulatory cells that normally would inhibit the development and maintenance of autoimmune diseases [41]. Due to these limitations in therapy directed toward IL-2Rα, therapy directed toward IL-15 receptor is being developed for use in organ tranplantation protocols and for application to the treatment of autoimmune disorders, as well as for diseases caused by the retrovirus HTLV-I. The administration of an IL-15 inhibitor, the soluble high-infinity IL-15R receptor chain linked to the immunoglobulin Fc element, prevented the development of murine collagen-induced arthritis and inhibited allograft rejection [9]. Furthermore, an IL-15 receptor antagonist produced by mutation of a glutamine residue within the C-terminus of IL-15 to aspartic acid competitively inhibited IL-15-triggered

cellular proliferation [10]. The administration of this IL-15 mutant markedly attenutated antigen-specific delayed hypersensitivity responses in mice and enhanced the acceptance of pancreatic islet cell allografts [10].

Our own therapeutic approaches directed toward IL-15 have focused on the IL-2Rβ receptor subunit shared by IL-2 and IL-15 [42]. A humanized version of Mikβ1, an antibody directed toward IL-2Rβ that is used by both IL-2 and IL-15 and that inhibits IL-15 action on T and NK cells, prolonged cardiac allograft survival in cynomolgus monkeys [42]. In our initial clinical trial, we are evaluating the antibody Mikβ1 in the therapy of patients with T-cell-type large granular lymphocytic leukemia associated with hematocytopenia. The monoclonal large granular lymphocytes involved in this disease respond to IL-15 and express IL-2Rβ and γc but not IL-2Rα [43]. In addition, this monoclonal antibody will soon be evaluated in the treatment of autoimmune diseases where abnormalities of IL-15 have been demonstrated, including RA, multiple sclerosis, and TSP/HAM.

Future prospects

Abnormalities of IL-15 expression caused by HTLV-I tax-mediated transactivation of IL-15 have been demonstrated in the abnormal T cells in HTLV-I-associated ATL and in TSP/HAM. Abnormalities of IL-15 expression may also be involved in the pathogenesis of inflammatory autoimmune disorders such as RA and inflammatory bowel disease. Although these observations are interesting, they are not sufficient to warrant the conclusion that a disorder of IL-15 expression is a meaningful element in the pathogenesis of these disorders. However, the clinical application of new therapeutic agents that target IL-15 or the receptor used by IL-15 may aid in determining if there is a role played by IL-15 in such autoimmune disorders as TSP/HAM and RA. In particular, IL-15R-directed therapeutic studies of TSP/HAM would involve tetramer technology to define the effect of therapy on the number of circulating antigen-specific (tax aa 11–19) $CD8^+$ cells. Similarly, IL-15/IL-15R-directed therapy of RA should be monitored for its impact on serum concentrations of TNF-α and on the activity of the disease.

Additional efforts are directed toward developing an inhibitor of Janus kinase 3 (JAK3) as an agent for controlled immunosuppression in transplantation protocols and in the treatment of RA. Expression of JAK3 is limited largely to lymphocytes and hematopoietic cells. Furthermore, JAK3 is activated by the cytokines that use γc, including IL-15, IL-2, IL-4, IL-7, IL-9, and IL-21, but is not essential for signaling by other cytokines. JAK3 is defective in an autosomal form of severe combined immunodeficiency disease (SCID) in humans, in which immunodeficiency but no disorders of other systems are found [44,45]. Furthermore, mice made JAK3-deficient by homologous recombination manifest an absence of NK cells and abnormalities of T and B cells but do not have disorders in nonimmunological systems [46]. Finally, JAK3 is constitutively activated in some cell lines in IL-2-independent HTLV-I-associated adult T-cell leukemia [47,48]. Taken together, these observations suggest that drugs that inhibit JAK3 action may be of value as antileukemia agents and in the therapy of autoimmune diseases, associated with abnormal production of IL-15.

In conclusion, our emerging understanding of the IL-15/IL-15R system, including the definition of the actions that this cytokine manifests – both those that are shared with IL-2 and those that are distinct – is opening new possibilities for the development of more rational immune interventions directed toward IL-15 and IL-15 receptors that may be of value in the treatment of cancer, the prevention of allograft rejection, the therapy of diseases associated with the retrovirus HTLV-I, and the treatment of autoimmune diseases such as RA.

Glossary of terms

AICD = activation-induced cell death: a multi-step process involved in peripheral tolerance, initiated by stimulation of T-cell receptors (TCRs)/CD3 and inducing the expression and interaction of the induced IL-2 and IL-2 receptors (IL-2Rs). When the cell cycling induced by this interaction is followed by restimulation of TCR/CD3, these events lead to the induction of the cell-death-effector Fas ligand, which interacts with the Fas receptor, culminating in the death of the self-reactive T cell; ATL = adult T-cell leukemia: an aggressive malignancy of mature lymphocytes expressing CD3, CD4, and CD25 (IL-2Rα), caused by the retroviruses HTLV-I; FasL = Fas ligand; HTLV-I = human T-cell lymphotropic virus I: a retrovirus, found predominantly in Japan, the Caribbean Islands, and sub-Saharan Africa, which induces the expression of IL-2, IL-15, and their private receptors and which is the etiological agent of a number of human diseases including inflammatory arthritis, myositis, adult T-cell leukemia, and the neurological disorder tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM); IL-15Rα = cytokine-specific private receptor for IL-15; IL-2Rα = cytokine-specific private receptor for IL-2; tax = transactivator (protein); TSP/HAM = tropical spastic paraparesis/HTLV-I-associated myelopathy: a demyelinating neurological disease caused by the retrovirus HTLV-I and associated with progressive weakness and bowel and bladder dysfunction.

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