

## Commentary

# Targeting the interleukin-15/interleukin-15 receptor system in inflammatory autoimmune diseases

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### Abstract

Interleukin (IL)-15 is a dangerous inflammatory cytokine that induces tumor-necrosis factor- $\alpha$ , IL-1 $\beta$  and inflammatory chemokines. It inhibits self-tolerance mediated by IL-2 mediated activation-induced cell death and facilitates maintenance of CD8<sup>+</sup> memory T-cell survival including that of self-directed memory cells. Disordered IL-15 expression has been reported in patients with an array of inflammatory autoimmune diseases. A series of therapeutic agents that inhibit IL-15 action have been introduced, including the soluble IL-15 receptor (IL-15R)  $\alpha$  chain, mutant IL-15, and antibodies directed against the IL-15 cytokine and against the IL-2R/IL-15R  $\beta$  subunit used by IL-2 and IL-15.

**Keywords:** autoimmune disease, interleukin-15, memory T cells, rheumatoid arthritis

### Introduction

Cytokines are crucially involved in the regulation of the normal human immune response. Furthermore, dysregulation of cytokine expression also has a complex role in the pathogenesis of autoimmune diseases [1]. In particular, disordered expression of interleukin (IL)-2, IL-12, IL-17, IL-18, interferon, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) as well as downstream mediators of inflammation such as IL-1, IL-6, and inflammatory chemokines have been invoked as pathogenic elements underlying the development and maintenance of inflammation and autoimmunity [2]. These insights concerning cytokine-mediated inflammation have been translated into the development of novel therapeutic agents. In particular, TNF- $\alpha$  has been identified as an important target in the therapy of such autoimmune diseases as rheumatoid arthritis (RA), inflammatory bowel disease, and psoriasis [2]. Such cytokine-directed blockade with anti-TNF- $\alpha$  monoclonal antibodies or soluble TNF- $\alpha$  receptors has revolutionized the therapy of these autoimmune diseases. Nevertheless these TNF- $\alpha$ -directed approaches do not provide effective therapy for all patients with autoimmune disease: new therapeutic targets are needed. Recently, disorders involving interleukin-15 (IL-15) have been shown

in such autoimmune diseases as RA, multiple sclerosis, ulcerative colitis, celiac syndrome, psoriasis, sarcoidosis, and hepatitis-C, as well as in diseases associated with the retrovirus human T cell lymphotropic virus-I (HTLV-I) [3–6]. An array of therapeutic strategies are therefore being developed to target IL-15, its receptor subunit or its signaling elements to provide effective therapy for such autoimmune disorders [7–10].

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

Two groups simultaneously reported the identification of a 14–15 kDa stimulatory factor acting on T cells and natural killer (NK) cells that was termed IL-15 [11,12]. The heterotrimeric IL-15 receptor includes a private IL-15-specific receptor subunit (IL-15R $\alpha$ ) together with the IL-2R/IL-15R $\beta$  subunit that is shared with IL-2 and the common gamma chain ( $\gamma_c$ ) receptor subunit that is also used by IL-2, IL-4, IL-7, IL-9, and IL-21. As might be expected from their sharing of the  $\gamma_c$  and IL-2R/IL-15R $\beta$  subunits, IL-2 and IL-15 share several biological activities. However, they also provide distinct and at times contrasting contributions to the life and death of lymphocytes, especially in adaptive immune responses [13].

AICD = activation-induced cell death; HAM/TSP = HTLV-I-associated myelopathy/tropical spastic paraparesis; HTLV-I = human T cell lymphotropic virus I; IL = interleukin; IL-2R = interleukin-2 receptor; IL-15R = interleukin-15 receptor; NK = natural killer; RA = rheumatoid arthritis; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ .

These shared and contrasting roles can be considered in relation to a series of goals of the immune system that include the following: first, the generation of a rapid innate and adaptive response to invading pathogens; second, the elimination of autoreactive T cells to yield tolerance to self, and third, the maintenance of a specific memory response to pathogens. IL-2 and IL-15 share functions including the initial stimulation of the proliferation of activated T and B cells as well as the maintenance and activation of NK cells. However, IL-2 is pivotally involved in the maintenance of CD4<sup>+</sup>, CD25<sup>+</sup> T-regulatory cells and in activation-induced cell death (AICD) – a process that leads to the elimination of self-reactive T cells. By contrast, IL-15 inhibits IL-2 induced AICD. Furthermore, IL-15 stimulates the maintenance of CD8<sup>+</sup> memory-phenotype T cells, whereas IL-2 inhibits their persistence *in vivo* [13–15].

An analysis of mice with disrupted genes for IL-2, IL-15, and their cytokine receptors supports these competitive roles for IL-2 and IL-15. In particular, IL-2<sup>-/-</sup> and IL-2R $\alpha$ <sup>-/-</sup> mice undergo massive enlargement of peripheral lymphoid organs and develop autoimmune diseases [16]. In contrast, mice genetically deficient in IL-15 or IL-15R $\alpha$  do not manifest lymphoid enlargement, high concentrations of immunoglobulins, or autoimmune diseases; rather, they display a marked reduction in the numbers of NK cells and CD8<sup>+</sup> memory T cells [17]. These studies support the view that through its inhibition of IL-2-mediated AICD and its role in the maintenance of memory CD8<sup>+</sup> T cells, IL-15 favors the persistence of lymphocytes that are of value in long-lasting specific immune responses to foreign pathogens. Although these IL-15-mediated immune responses are of importance in the response to foreign pathogens, the uncontrolled expression of IL-15 carries with it the risk to the organism of the survival of autoreactive T cells that could lead to the development of autoimmune diseases.

The opposing effects of IL-2 and IL-15 have implications for immunotherapy. IL-2 is used in the treatment of patients with metastatic renal cell carcinoma or malignant melanoma and as a component of vaccines. However, owing to the role of IL-2 in AICD, the maintenance of CD4<sup>+</sup>, CD25<sup>+</sup>, negative regulatory cells, and its termination of memory T cell responses, it is not optimal. In view of these observations with its contrasting role in the survival of lymphocytes through its inhibitory role in AICD and its facilitation of the persistence of memory CD8<sup>+</sup> cells, IL-15 might be superior to IL-2 in the treatment of cancer and as a component of vaccines directed against cancer or infectious agents.

### **Abnormalities of IL-15 expression in inflammatory autoimmune diseases**

IL-15 is a dangerous inflammatory cytokine that inhibits self-tolerance mediated by AICD and facilitates the

survival of CD8<sup>+</sup> memory T cells, including those that are self-directed. Furthermore, IL-15 induces TNF- $\alpha$  and IL-1 $\beta$  [3]. Despite an array of regulatory controls, disordered IL-15 expression has been observed in patients with a series of inflammatory autoimmune diseases. McInnes and colleagues reported abnormalities of IL-15 in RA and have suggested that IL-15 might precede TNF- $\alpha$  in the cytokine cascade [3]. In particular, IL-15-activated T cells can induce TNF- $\alpha$  synthesis by macrophages in RA through a mechanism that is dependent on cell contact. Harada and colleagues showed that freshly isolated cells from synovial tissues strongly expressed mRNA for IL-15 [18]. Oppenheimer-Marks and colleagues reported that IL-15 is produced by endothelial cells in RA and that this cytokine markedly increases the transendothelial migration of both CD4 and CD8 T cells [19]. Furthermore, they showed that IL-15 leads to the accumulation of T cells in RA synovial tissues engrafted into mice with severe combined immunodeficiency. In a murine model the intra-articular injection of IL-15 induced a local tissue inflammatory infiltrate that was predominantly of T lymphocytes.

Disordered overexpression of IL-15 that perpetuates epithelial damage and promotes the emergence of T cell clonal proliferations has also been observed in refractory celiac sprue [5]. In addition, there was a resolution of psoriasis after blockade of IL-15 activity in a xenograft mouse model of human psoriasis [4]. IL-15 has also been suggested to have a pathogenic role in an array of other chronic inflammatory diseases including sarcoidosis, chronic hepatitis C and ulcerative colitis. Furthermore, there was an abnormality of the IL-15–IL-15R $\alpha$  system defined in diseases caused by the retrovirus HTLV-I. Through the action of the HTLV-I-encoded Tax protein there was transactivation of the genes encoding IL-15 and IL-15R $\alpha$  [6]. The interaction of the expressed IL-15 and IL-15R $\alpha$  was associated with an autocrine, self-stimulatory, proliferative loop in patients with the HTLV-I-associated neurological disease HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [6]. Furthermore, patients with this disease had a marked increase in the number of circulating HLA-A2 restricted antigen-specific (amino acids 11–19 of the HTLV-I-encoded Tax protein), memory and effector CD8<sup>+</sup> T cells that have been suggested to be involved in the pathogenesis of HAM/TSP. Using *ex vivo* cultures of the peripheral blood mononuclear cells from patients with HAM/TSP, we showed that blockade of IL-15 action resulted in a decrease in the number of such virus-specific CD8<sup>+</sup> cells, supporting the view that in humans, as in mice, IL-15 is crucial for the maintenance of effector and memory CD8<sup>+</sup> lymphocytes [6].

### **Opportunities for therapeutic strategies directed against IL-15 or its receptor**

A series of biological agents that block the action of inflammatory molecules, particularly TNF- $\alpha$ , are being

used in the immunotherapy of autoimmune diseases [7–10]. However, there are limitations to the use of TNF- $\alpha$  as a target for immunotherapy. Such treatment is not of value in all patients with RA and does not seem to be appropriate in the therapy of patients with multiple sclerosis or HAM/TSP. Another limitation in the use of TNF- $\alpha$  as a target for immunotherapy is that this cytokine is not involved in the regulation of immunological memory. Thus, on withdrawal of TNF- $\alpha$ -directed therapy there is a high likelihood of the recurrence of the autoimmune disorder. We propose targeting IL-15 to deal with some of these limitations, because it is involved in the inflammatory cascade acting as a major stimulus for TNF- $\alpha$  synthesis and because, as just noted, it is involved in the pathogenesis of autoimmune diseases. In particular, IL-15 has been suggested to have a role in the pathogenesis of HAM/TSP and multiple sclerosis, disorders that are not responsive to TNF- $\alpha$ -directed immunotherapy [16,20]. Furthermore, IL-15 is the dominant cytokine required for the maintenance of CD8<sup>+</sup> memory T cells [13–15,21]. The disruption of IL-15 action might interrupt both the inflammatory components and whatever self-directed immunological memory exists in autoimmune diseases.

A series of agents that inhibit IL-15 action have been introduced, including the soluble IL-15R $\alpha$  chain linked to the immunoglobulin Fc element, mutant IL-15 molecules, antibodies directed against IL-15 itself or alternatively against the IL-2R/IL-15R $\beta$  cytokine receptor subunit [7–10]. An IL-15 antagonist produced by mutating a glutamine residue to aspartic acid within the carboxy terminus of IL-15 inhibited IL-15-triggered cell proliferation and enhanced the survival of pancreatic islet cell allografts in mice [8]. The administration of the IL-15 inhibitor, the soluble IL-15R $\alpha$  chain, prevented the development of collagen-induced arthritis in mice [7].

Antibodies against IL-15 have been used effectively in murine models of autoimmune diseases including psoriasis [4]. Furthermore, such an antibody has shown efficacy in a Phase I/Phase II trial involving patients with RA [9]. Our own IL-15-directed therapeutic approach involves an antibody humanized MiK-Beta-1 (Hu-MiK-Beta1) directed against the IL-2R/IL-15R $\beta$  cytokine receptor that is shared by IL-2 and IL-15 [10]. This humanized antibody interacts with the IL-2R/IL-15R $\beta$  receptor subunit and blocks IL-15-mediated stimulation of NK and T cells *ex vivo*. Furthermore, the anti-IL-2R/IL-15R $\beta$  antibody inhibits the action of IL-2 on the intermediate affinity  $\beta\gamma_c$  receptor expressing resting T and NK cells but does not inhibit the action of IL-2 on cells expressing high-affinity heterotrimeric IL-2 receptor, such as regulatory T cells. This antibody, when used as a single agent, prolonged cardiac allograft survival in cynomolgus monkeys [10]. Only minimal toxicity was observed in a Phase I trial that involved patients with T cell large granular

lymphocytic leukemia who were treated with a murine version of MiK-Beta-1. In an effort to test the hypothesis that IL-15 has a role in the pathogenesis of select autoimmune diseases, we are initiating clinical trials with Hu-MiK-Beta-1 in patients with RA, inflammatory bowel disease, multiple sclerosis, and such HTLV-I-associated disorders including HAM/TSP and adult T cell leukemia.

## Conclusions

Our emerging understanding of the IL-15/IL-15R system is providing the scientific basis for the development of rational approaches for the IL-15-targeted treatment of autoimmune diseases, disorders associated with the retrovirus HTLV-I and also selected leukemias and lymphomas. In particular, given the putative role of IL-15 in the maintenance of memory CD8<sup>+</sup> T cells as well as in the expression of inflammatory cytokines involved in the pathogenesis of autoimmune disease, we suggest that the introduction of strategies that inhibit IL-15 action might prove to be of great value in the treatment of such T cell-mediated inflammatory autoimmune disorders.

## Competing interest

Thomas A Waldmann holds a US Government patent to monoclonal antibodies directed against IL-2/IL-15R. No competing financial interests.

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