The Biology of IL-15: Implications for Cancer Therapy and the Treatment of Autoimmune Disorders

Thomas A. Waldmann[1]

IL-15 has a pivotal role in life and death of natural killer (NK) and CD8 memory T cells. IL-15 signals through a heterotrimeric receptor involving the common gamma chain (γc) shared with IL-2, IL-4, IL-7, IL-9, and IL-21, IL-2/IL-15 receptor β (IL-15Rβ) shared with IL-2 and a private IL-15Rα subunit. IFN- or CD40 ligand–stimulated dendritic cells coordinately express IL-15 and IL-15Rα. Cell surface IL-15Rα presents IL-15 *in trans* to cells that express IL-2/IL-15Rβ and γc. IL-15 is being used to treat patients with metastatic malignancy. However, IL-15 is an inflammatory cytokine involved in immunological memory including that to self, thereby playing a role in autoimmune diseases. These insights provide the scientific basis for clinical strategies directed toward diminishing IL-15 action. Dysregulated IL-15 expression was demonstrated in patients with rheumatoid arthritis, inflammatory bowel disease, psoriasis, celiac disease, and alopecia areata. The monoclonal antibody Hu-Mik-β-1 targets the cytokine receptor subunit IL-2/IL-15Rβ (CD122), blocks IL-15 transpresentation, and is being used in clinical trials in patients with autoimmune diseases. In parallel, clinical trials have been initiated involving the Jak2/3 (Janus kinase-2/3) inhibitor tofacitinib and Jak1/2 inhibitor ruxolitinib to block IL-15 signaling.

Journal of Investigative Dermatology Symposium Proceedings (2013) **16,** S28–S30; doi:10.1038/jidsymp.2013.8

IL-15 has a pivotal role in the control of the life and death of natural killer (NK) and memory phenotype CD8 T cells (Waldmann, 2006). IL-15 signals through a heterotrimeric receptor that involves the common cytokine receptor γ chain (CD132), which is shared by IL-2, IL-4, IL-7, IL-9, and IL-21, the IL-2/IL-15 receptor β (IL-15Rβ) (CD122) shared with IL-2 and a third unique receptor subunit IL-15Rα. IL-15 uses a signaling pathway that involves Jak1 (Janus kinase-1), Jak3, and signal transducer and activator of transcription-5. IL-15 and IL-2 share a number of functions; both cytokines stimulate the proliferation of many T cell subpopulations, facilitate the proliferation and synthesis of immunoglobulins by activated B cells, and are pivotal in the generation and maintenance of natural killer (NK) cells. However in many adaptive immune responses, IL-2 and IL-15 have distinct and often competing functions. IL-2 through its participation in the maintenance of peripheral CD4+ CD25+ Foxp3 regulatory T cells and its unique role in activation-induced cell death is involved in the elimination of self-reactive T cells that have a role in the pathogenesis of autoimmune diseases. In contrast, IL-15 has no marked effect on regulatory T cells, is anti-apoptotic in several systems including IL-2–induced activation-induced cell death, and by supporting the survival of CD8 memory T cells, IL-15 is critical in the maintenance of long-lasting, high-affinity T cell responses to invading pathogens. One factor underlying the functional differences between IL-2 and IL-15 involves the distinct modes of action of the two cytokines. In contrast to IL-2 that is a secreted cytokine, IL-15 is a cell-surface molecule that signals in the context of an immunological synapse (Dubois *et al.*, 2002). Following stimulation of monocytes or dendritic cells with type 1 or type 2 IFNs or the ligation of CD40 with CD40 ligand or an agonistic anti-CD40 monoclonal antibody, there is the coordinate induction of IL-15 and IL-15Rα expression. IL-15Rα on the cell surfaces of monocytes or dendritic cells presents IL-15 *in trans* to cells such as CD8+ memory T cells and NK cells that express IL-2/IL-15Rβ and γc but not IL-15Rα (Dubois *et al.*, 2002).

The basic insights concerning the IL-15 cytokine/receptor system are being translated into novel IL-15-mediated approaches to the therapy of cancer and as a component of vaccines. IL-15 has been produced under current good manufacturing practices (Waldmann *et al.*, 2011). When IL-15 was administered by continuous intravenous infusion at 20 μg/kg per day for 10 days, it led to a 7-fold increase in the number of circulating NK cells and a massive 80- to 100-fold increase in the number of circulating effector memory T cells (Sneller *et al.*, 2011). We have just completed a Phase I study that involved recombinant IL-15 in patients with refractory metastatic malignant melanoma and metastatic renal cell cancer. Furthermore, molecular vaccines have been generated incorporating IL-15 for HIV, AIDS, bioterrorism agents, and cancer.

DISORDERS OF IL-15/IL-15R SYSTEM IN AUTOIMMUNE DISEASES

The scientific studies we have just discussed focus on augmenting IL-15 action in an effort to increase patient

[1]*Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA*

Correspondence: Thomas A. Waldmann, Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Drive, MSC 1374, Building 10, Room 4N115, Bethesda, Maryland 20892-1374, USA. E-mail: tawald@helix.nih.gov

Abbreviations: IL-15Rβ, IL-15 receptor β; Jak, Janus kinase-1; NK, natural killer; NKG2D, natural killer group 2D

immune responses to their tumor and its use as a component of molecular vaccines. Efforts are also underway with the opposite goal of defining situations where disorders of IL-15 and its receptor have a pathogenic role in leukemia and autoimmune diseases, thereby providing the scientific basis for clinical approaches that are directed toward diminishing IL-15 actions. IL-15 is a proinflammatory cytokine. Further, IL-15 facilitates the fitness and survival of CD8+ memory phenotype T cells including self-reactive memory T cells, suggesting that disordered IL-15 expression may lead to autoimmune disease. We have developed an assay for serum IL-15/IL-15Rα and have demonstrated elevations in its level in groups of patients with T cell large granular lymphocytic leukemia, γΔ/Δ T cell lymphoma, refractory celiac disease, and with type 1 diabetes (Chen *et al.*, 2012). Furthermore, dysregulated IL-15 expression has also been demonstrated in patients with rheumatoid arthritis, inflammatory bowel disease, psoriasis, celiac disease, and alopecia areata. Therefore, we have undertaken a multifaceted research program to develop novel therapeutic strategies for diseases that are associated with disordered γc cytokines with a special emphasis on disorders of the IL-15/IL-15Rα system. One element of this program includes the development of Hu-Mik-β-1, a monoclonal antibody directed toward IL-2/IL-15Rβ that blocks IL-15 transpresentation (Waldmann, *et al*, 2013).

As part of our program, we have obtained Food Drug Administration permission to use Hu-Mik-β-1 in patients with refractory celiac disease. Celiac disease is an autoimmune inflammatory disorder observed predominantly in humans who carry the HLA-DQ2 or DQ8 alleles. In affected individuals, intraperitoneal CD8 T lymphocytes show massive infiltration into the affective intestinal mucosa that causes extensive destruction of enterocytes and underlying tissues primarily by T cell receptor–independent mechanisms that utilize NKG2D and other coactivating NK receptors. Emerging evidence has implicated a pivotal role for IL-15 in this disorder. IL-15 is indispensable for the generation, maintenance, and homeostasis of IEL. IL-15 also induces proliferation of CD8 T lymphocytes and their action in part by the coordinate induction of the NKG2D signaling pathway. In completing the cycle of this tissue damage, IL-15 also induces the surface expression of the cognate ligand of NKG2D, the MHC class I–related antigen-A. Collectively, these findings implicate a central role for IL-15 in the pathogenesis of celiac disease and provide a rationale for selective targeting of IL-15 in patients with the type II form of refractory celiac disease who have a 40% incidence of enteropathy-associated T cell lymphoma within 5 years.

In collaboration with S Yokoyama and T Hiroi, we evaluated blockade of IL-15 action in IL-15 transgenic mice that express IL-15 in intestinal cells using an enterocyte-specific $T3^b$ promoter to drive the transgene (Yokoyama *et al.*, 2013). These mice developed florid inflammation of the duodenal region, extensive villous atrophy, and massive accumulation of NK–like CD8+ T cells, a phenomenon that recapitulates the pathognomic lesions of celiac disease. The administration of TM-β-1 (the anti-mouse equivalent of Hu-Mik-β-1) directed toward IL-2/IL-15Rβ was associated with the complete reversal of the macroscopic and microscopic pathologic changes in the intestine of $T3^b$-h IL-15 Tg mice. In a second trial with this model, we demonstrated that the administration of the Jak2/3 inhibitor tofacitinib completely reversed the pathological changes of the transgenic mice. Our results taken together with the results of studies of patients with refractory celiac disease provided the rationale for our ongoing collaboration with Drs Bana Jabri of the University of Chicago and Joseph A Murray of the Mayo Clinic (Rochester, MN) to initiate a clinical trial to evaluate Hu-Mik-β-1 in the IL-2/IL-15Rβ directed blockade of IL-15 action.

In an alternative strategy to treat autoimmune and leukemic diseases associated with disorders of IL-15 action, we are focusing on the Jak1/Jak3/signal transducer and activator of transcription-5 signaling pathway utilized by this cytokine. Our initial studies focused on a human T cell lymphotropic virus-1–associated adult T cell leukemia. Previously, we demonstrated that human T cell lymphotropic virus-1 Tax transactivates two autocrine (IL-2/IL-2R and IL-15/IL-15R) and one paracrine (IL-9) stimulatory pathway (Chen *et al.*, 2008). As a consequence of these stimulatory loops, the peripheral blood mononuclear cells from patients with smoldering and chronic associated T cell lymphoma spontaneously proliferate *ex vivo*. This proliferation could be inhibited by the addition of the Jak2/3 inhibitor tofacitinib or the Jak1/2 inhibitor ruxolitinib (Ju *et al.*, 2011). Taken as a whole, these preclinical studies suggest the importance of the Jak1/Jak3/signal transducer and activator of transcription-5 signaling pathway in the survival of smoldering and chronic associated T cell lymphoma malignant lymphocytes. To translate these observations, we have initiated a Phase II trial with ruxolitinib, a Jak1/Jak2 inhibitor in patients with smoldering or chronic associated T cell lymphoma. In our future plans, we wish to use a Jak1–specific inhibitor *in lieu* of ruxolitinib so that therapeutic doses can be used that maintain full inhibition of signal transducer and activator of transcription-5 phosphorylation throughout the therapy period without associated dose-limiting thrombocytopenia.

In conclusion, our emerging understanding of the IL-15/IL-15R systems opens the possibility for the development of more rational immune interventions that could involve the evaluation of cytokines, receptor-directed monoclonal antibodies, and small-molecule inhibitors of cytokine signaling for the treatment of a broad range of leukemias/lymphomas as well as autoimmune diseases including celiac disease, type 1 diabetes, and alopecia areata.

CONFLICT OF INTEREST

TAW holds patent no. 5,833,983 IL-2 receptor and application, that relates to the Hu-Mik-β-1 discussed in the article.

ACKNOWLEDGMENTS

This work was supported by the Intramural Research Program of the NIH, National Cancer Institute, and Center for Cancer Research. Funding for the Summit and publication of this article was provided by the National Alopecia Areata Foundation.

REFERENCES

Chen J, Petrus M, Bamford R *et al.* (2012) Increased serum soluble IL-15Rα levels in T-cell large granular lymphocyte leukemia. *Blood* 119: 137–43

Chen J, Petrus M, Bryant BR *et al.* (2008) Induction of the IL-9 gene by HTLV-I Tax stimulates the spontaneous proliferation of primary adult T-cell leukemia cells by a paracrine mechanism. *Blood* 111: 5163–72

Dubois S, Mariner J, Waldmann TA *et al.* (2002) IL-15R alpha recycles and presents IL-15 in trans to neighboring cells. *Immunity* 17:537–47

Ju W, Zhang M, Jiang JK *et al.* (2011) CP-690,550, a therapeutic agent, inhibits cytokine-mediated Jak3 activation and proliferation of T cells from patients with ATL and HAM/TSP. *Blood* 117:1938–46

Sneller MC, Kopp WC, Kory J *et al.* (2011) IL-15 administered by continuous intravenous infusion to rhesus macaques induces massive expansion of the CD8+ T effector memory population in peripheral blood. *Blood* 118:6845–8

Waldmann TA. (2006) The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design. *Nat Rev Immunol* 6:595–601

Waldmann TA, Conlon KC, Stewart DM *et al.* (2013) Phase 1 trial of IL-15 trans presentation blockade using humanized Mik-Beta-1 mAb in patients with T-cell large granular lymphocytic leukemia. *Blood* 121:476–84

Waldmann TA, Lugli E, Roederer M *et al.* (2011) Safety (toxicity), pharmacokinetics, immunogenicity and impact on elements of the normal immune system of recombinant human IL-15 in rhesus macaques. *Blood* 117:4787–95

Yokoyama S, Perera P-Y, Waldmann TA *et al.* (2013) Tofacitinib, a Janus kinase inhibitor demonstrates efficacy in an IL-15 transgenic mouse model that recapitulates pathologic manifestations of celiac disease. *J Clin Immunol* 33:586–94