CHAPTER FOUR

The implications of IL-15 trans-presentation on the immune response

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Abstract

Interleukin-15 is a pleiotropic cytokine type I four alpha-helical bundle cytokine that along with IL-2, IL-4, IL-7, IL-9, and IL-21 shares the common cytokine receptor γ chain, γ_c. IL-15 is vital for the development, survival, and expansion of natural killer cells and for the development of $CD8^+$ memory T cells. Whereas other family γ_c cytokines signal by directly binding to their target cells, IL-15 is distinctive in that it binds to IL-15Rα, a sushi domain containing binding protein that is expressed on a number of cell types, including monocytes and dendritic cells as well as T cells, and then is trans-presented to responding cells that express IL-2Rβ and γ_c. This distinctive mechanism for IL-15 relates to its role in signaling in the context of cell-cell interactions and signaling synapses. The actions of IL-15 and ways of manipulating its actions to potential therapeutic benefit are discussed.

1. Introduction

Interleukin-15 (IL-15) is a pleiotropic cytokine, a master regulator that passes a heterogeneous repertoire of activation signals to various cells (Tagaya, Bamford, DeFilippis, & Waldmann, 1996). IL-15 is a 14–15 kDa 4-alpha-helical-bundle type I cytokine. It is produced in association with IL-15Rα by a diverse range of populations of cells including monocytes, macrophages, dendritic cells (DCs), fibroblasts, keratinocytes, epithelial cells of various tissues, the placenta, and uterine decidua (Kitaya et al., 2000). IL-15 has a major functional impact on diverse cells including $CD44^{high}$ $CD8^+$ T cells, natural killer (NK), NKT, gamma-delta T cells, innate $CD8^+CD122^+CD28^-$ regulatory cells, and intraepithelial lymphocytes (IELs) (Huntington et al., 2009; Richer et al., 2015; Terabe et al., 2008). It signals via a heterodimeric receptor that includes the IL-2 receptor β chain

(IL-2Rβ), which is shared by IL-2 and IL-15, and the common cytokine receptor γ chain, γ_c, which is shared by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. IL-15 induces the activation of JAK1 and JAK3, which associate with IL-2Rβ and γ_c, respectively, then activating STAT proteins, primarily STAT5A and STAT5B (Leonard, Lin, & O'Shea, 2019; Lin & Leonard, 2019). These STAT proteins form heterodimers and homodimers that are translocated to and act in the nucleus (Leonard et al., 2019; Lin & Leonard, 2019). In contrast to other γ_c family cytokines, IL-15 is largely not a secreted molecule but instead functions as part of an immunological synapse involved with cell-cell contact. IL-15 is expressed in association with the high-affinity IL-15Rα subunit on the surface of a range of cells including monocytes, macrophages, and dendritic cells (DCs) and is trans-presented by IL-15Rα to target cells that express IL-2Rβ and γ_c. There have been more than 7,000 publications and over 170 clinical trials involving IL-15. Furthermore, there have been numerous reviews focusing primarily on IL-15 as an anticancer immunotherapeutic agent (Guo, Luan, Patil, & Sherwood, 2017; Mishra, Sullivan, & Caligiuri, 2014; Rochman, Spolski, & Leonard, 2009; Steel, Waldmann, & Morris, 2012; Waldmann, 2006; Waldmann, Miljkovic, & Conlon, 2020). These immunotherapeutic studies are beyond the scope of the present review. Rather, this current review focuses on the unique immunological features of IL-15 as a cytokine that acts via trans-presentation.

2. IL-15Rα recycles and presents IL-15 *in trans* to neighboring cells

Dubois and coworkers introduced the concept of IL-15 trans-presentation, revolutionizing our understanding of IL-15 biology (Dubois, Mariner, Waldmann, & Tagaya, 2002). It was observed that cells grown in IL-2 lost their proliferative response within 24 hours of IL-2 deprivation; however, for cells cultured with IL-15, strong proliferation was present even 24 hours after IL-15 withdrawal. Consistent with high-affinity interactions between IL-15 and IL-15Rα, these two molecules form stable complexes on the surface of activated monocytes (Dubois et al., 2002). Monocytes or DCs stimulated with CD40 ligand (CD40L), type I or type II interferons, or Toll-like receptor (TLR) activators such as lipopolysaccharide (LPS) induce expression of IL-15 (Carson et al., 1995; Colpitts et al., 2012; Musso et al., 1999), which then should promote the formation of IL-15Rα/IL-15 complexes. Trans-endosomal recycling of IL-15Rα/IL-15 can promote the

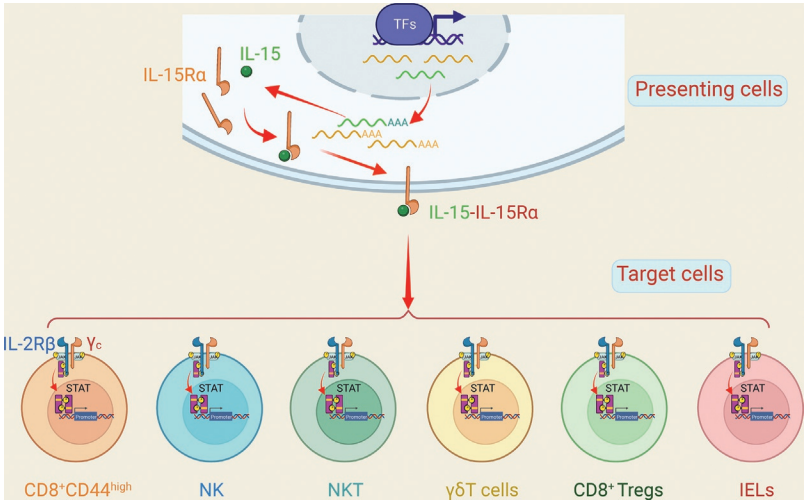

Fig. 1 Transpresentation of IL-15 to its target cells. IL-15 and IL-15Rα are co-produced by IL-15-IL-15Rα presenting cells, form high-affinity IL-15-IL-15Rα complexes, and are expressed on the cell surface. This process can occur on a range of cells, including macrophages, dendritic cells, monocytes, B cells, stromal cells, epithelial cells, and fibroblasts from various tissues. These cells can then trans-present IL-15 to adjacent target cells that express IL-2Rβ and γ_c, including $CD8^+CD44^{high}$ T cells, NK cells, NKT cells, γδ T cells, $CD8^+$ Tregs, and IELs. Created using BioRender.

persistence of such complexes on the cell surface. As might be expected, cell surface IL-15Rα can present IL-15 *in trans* to neighboring target cells that express IL-2Rβ and γ_c but not IL-15Rα (Dubois et al., 2002) (Fig. 1). Biophysical evidence has confirmed such trans-presentation of IL-15 (Kenesei et al., 2021). Trans-presentation of IL-15 is required for the *in vivo* survival of NK cells, NK T-cells, select gamma-delta T-cells, $CD44^{high}$ $CD8^+$ T cells, IELs, and $CD122^{high}$ $CD28^-$ regulatory T cells (Huntington et al., 2011). These observations of trans-presentation provide an explanation for the interesting observations that normal $CD8^+$ T cells transferred into *Il15ra*$^{-/-}$ cells lost their proliferative response, whereas *Il15ra*$^{-/-}$ $CD8^+$ T cells could proliferate in a normal host environment (Lodolce, Burkett, Koka, Boone, & Ma, 2002). Moreover, adoptive transfer of NK cells into mice lacking IL-15Rα resulted in the rapid loss of these cells due to diminished survival, whereas IL-15Rα-deficient NK cells survived in normal but not in IL-15Rα-deficient mice (Koka et al., 2003). Together, these data suggest that NK and $CD44^{high}$ $CD8^+$ T cells require trans-presentation of membrane IL-15 by IL-15Rα that is expressed on monocytes, DCs, or stromal cells. The absence of IL-15Rα from these

"environmental" cells in IL-15Rα-deficient mice renders these cells unable to trans-present IL-15, whereas environmental cells from normal mice can efficiently present IL-15 to NK or $CD8^+$ T cells even if these cells do not express IL-15Rα.

Trans-presentation of the IL-15Rα/IL-15 complex acts through three processes to act on NK cells. First, IL-15Rα/IL-15-expressing antigen-presenting cells interact with IL-2Rβ/γ_c-expressing NK cells by direct cell-cell contact, with the formation of an immunological synapse that mediates IL-15 signaling. The IL-15Rα/IL-15 complex accumulates at the synapse between the DCs and NK cells. In addition to the IL-15/IL-15Rα/IL-2Rβ/γ_c interaction (Dubois et al., 2002), other co-stimulatory interactions occur, including for example between CD40L and CD40, and between CD80/CD86 and CD28. Second, the IL-15Rα/IL-15 complex is shed following trans-presentation, which is essential for the survival of IL-15-responding NK and T cells. In this process, membrane-bound IL-15Rα/IL-15 complexes are cleaved following trans-presentation and internalized by the responding cells, but the complexes can then recycle, inducing more proliferation of these cells (Tamzalit et al., 2014). Third, in the process of trans-endocytosis, membrane-associated IL-15Rα/IL-15 complexes transfer from presenting cells to NK cells (Anton et al., 2020). Trans-endocytosis promotes the phosphorylation of ribosomal protein S6. IL-15Rα/IL-15 complexes expressed on the surface of antigen-presenting cells (APCs) can induce STAT5 phosphorylation and augment NK-cell survival at concentrations much lower than those required for S6 phosphorylation (Anton et al., 2020). STAT5 phosphorylation was reduced after inhibition of metalloprotease-induced IL-15Rα/IL-15 shedding from trans-presenting cells, whereas S6 phosphorylation was unaffected. Moreover, inhibiting trans-endocytosis by either silencing the small GTPase TC21 or expressing a dominant-negative form of TC21 reduced S6 phosphorylation without affecting STAT5 phosphorylation. These results illustrate how the cellular compartment in which receptor ligand interaction occurs can influence the functional outcome (Anton et al., 2020; Anton, Vielkind, Peterson, Tagaya, & Long, 2015).

It is interesting to consider why IL-15 is the only γ_c cytokine that functions predominantly by trans-presentation. Trans-presentation might be presumed to occur when cell-cell contact is required, so that IL-15 signals are often if not entirely occurring together in concert with other signals on T cells that originate from CD40 with CD40L, TCR with antigen-MHC, CD28 with CD80 or CD86, and ICOS with 4-1BB and OX40

(Edner, Carlesso, Rush, & Walker, 2020). Trans-presentation is in fact an efficient mechanism for using the limited IL-15 levels that are produced and provides an approach with great specificity of action.

The IL-15Rα/IL-15 complex can diffuse along the membrane of an APC but not from one APC to another. Ridge et al. proposed that $CD4^+$ cells can engage and condition DCs, which then are enabled to stimulate the cytotoxic $CD8^+$ cells (Ridge, Di Rosa, & Matzinger, 1998). Thus, the signal from $CD4^+$ T helper cells interacting with HLA class II/antigen is potentially transmitted to $CD8^+$ T cells interacting with HLA class I/antigen on the same DC. Trans-presentation of IL-15 potentially may help to direct oligopeptides derived from the same peptide to the $CD8^+$ T cell, even though the molecules that interact with the $CD4^+$ T cells are different from those that interact with the $CD8^+$ T cells. Given antigen processing by APCs, this is perhaps the only known basis for antigen specificity of $CD4^+$ helper T cell signals to $CD8^+$ killer T cells (Ridge et al., 1998), in contrast to the more easily understood specificity of the interaction of $CD4^+$ helper T cells and B-cells in germinal centers. Trans-presented signals spread over microns rather than centimeters as is the case for soluble mediators or angstroms as occurs for protein/protein interactions. Also, trans-presentation of IL-15 can reflect ongoing cellular distress (Jabri & Abadie, 2015).

IL-15 can also be presented *in cis* for optimal NK activation, although this is the minor mechanism used and further studies are required to validate IL-15 cis presentation under physiological and pathophysiological conditions (Zanoni et al., 2013). Interestingly, in contrast to IL-15, whereas IL-2 can be trans-presented, its major action occurs *in cis*. Thus, the major mechanism of signaling—*cis* for IL-2 versus *trans* for IL-15—represents a major difference between these cytokines.

3. IL-15Rα/IL-15 and IL-15Rα/IL-15L are ancient receptor/cytokine systems

IL-2, IL-15, and IL-15Rα, as well as IL-15 like (IL-15L) are ancient genes, with all 4 genes present in extant fishes. Teleosts, cartilaginous fishes, reptiles, and most mammals express IL-15-like molecules; however, humans and mice have a pseudo-gene instead of a functional IL-15L. The capacity for binding IL-15 by IL-15Rα is an ancient characteristic, and IL-15L also requires binding to IL-15Rα, consistent with IL-15 and IL-15L having arisen by gene duplication. The binding of IL-15L to IL-15Rα leads to

phosphorylation of STAT5 and the production of IL-4 and IL-13, indicative of a Th2 response. Interestingly, the ability of IL-2 to act primarily as a soluble cytokine and of IL-15 as a heterodimer with IL-15Rα was already established in fish. Thus, IL-2, IL-15, IL-15Rα and the IL-15 trans-presentation system evolved at least 460 million years ago, with a shared IL-15L between cattle and trout (Gunimaladevi, Savan, Sato, Yamaguchi, & Sakai, 2007; Wang, Holland, Carrington, Zou, & Secombes, 2007; Yamaguchi et al., 2020).

4. Genetic organization of the *IL15* gene and regulation of IL-15 production

IL-15 has a 162 amino acid long open reading frame with a 48 amino acid long signal peptide and a 114 aa mature protein. Human IL-15 is encoded by a 34-kilobase locus at chromosome-4q31. The IL-15 gene comprises 9 exons and 8 introns, with 5 exons (exons 4–8) encoding the mature protein. An alternative exon encoding an alternative signal peptide has been described in humans and mice between exons 4 and 5. Thus, two isoforms for the signal peptide of human IL-15 exist, with putative signal peptides of either 48 or 21 amino acids. The longer signal peptide of IL-15 is targeted to the Golgi apparatus, early endosomes, and endoplasmic reticulum secretory pathway, whereas the shorter signal peptide exhibits a distinctive tissue distribution pattern and appears to be restricted to the cytoplasm and nucleus (Fehniger & Caligiuri, 2001).

5. Organization of the IL-15Rα locus complex includes an alternative exon that prevents cleavage of IL-15Rα from the cell membrane and facilitates trans-presentation of IL-15

Based on alternative splicing, the *IL15R* gene can produce 8 isoforms of IL-15Rα. One splicing variant includes the deletion of Exon 2, which includes the "sushi domain," thereby resulting in a defective IL-15Rα that cannot bind IL-15. Müller and coworkers identified 8 new isoforms that were predicted to modify the intracellular C-terminus of IL-15Rα (Muller, Waldmann, Kruhlak, & Dubois, 2012). An N-terminal exon, Exon 2A, which was present in all but one of the C-terminal isoforms, encodes a 48 amino acid domain that allows the shuttling of the IL-15Rα/IL-15 complex to the cell surface but prevents its cleavage from the cell membrane and

thereby prevents its secretion, facilitating trans-presentation as part of the immunological synapse. These data suggest that paracrine and trans-presentation functions of IL-15 are mediated by different spliced versions of IL-15Rα in human monocytes and dendritic cells (Muller et al., 2012).

6. Control of IL-15 transcription

In mouse and human DCs, stimulation with IFNα led to increased expression of IL-15Rα/IL-15, as did treatment with NF-κB Rel-A inducers such as CD40L, LPS, CpG, and poly-IC (Bennett et al., 1998). Interestingly, treatment with IFNα led to the expression of IL-15 and IL-15Rα on the surface of DCs (Colpitts et al., 2012). An essential interferon regulatory factor (IRF1) binding site was identified between -348 and -336 relative to the cap site of the mouse IL-15 promoter. *Irf1*-deficient mice lacked inducible IL-15 expression and NK cells (Ogasawara et al., 1998). IRF4 participates in the HTLV-1-mediated activation of the IL-15Rα promoter (Mariner, Mamane, Hiscott, Waldmann, & Azimi, 2002). Furthermore, HTLV-1 activates the expression of IL-15Rα and IL-15 gene transcription through NF-κB sites (Azimi et al., 1998; Azimi, Shiramizu, Tagaya, Mariner, & Waldmann, 2000).

7. Control of IL-15 translation

In addition to control at the level of transcription, IL-15 is controlled at the level of translation and intracellular trafficking. There are 3 primary checkpoints that regulate the translation of IL-15 mRNA into IL-15 precursor protein (Tagaya et al., 1996). First, the IL-15 5′ UTR is relatively long (316 nucleotides in humans) and contains multiple AUGs upstream of the translation start site. Second, the IL-15 48 aa long signal peptide has a lower translational efficiency than that of the IL-2 signal peptide. Third, there is a negative regulatory sequence near the C-terminus of the precursor protein. By eliminating these 3 checkpoints—removing upstream AUGs, replacing the endogenous human IL-15 signal peptide with that of IL-2, and fusing the C-terminus of the IL-15 mature protein with the FLAG-epitope tag, the synthesis of IL-15 protein increased 250-fold (Waldmann & Tagaya, 1999).

8. IL-15Rα and IL-15 must be expressed by the same cell for efficient trans-presentation

Two groups using mixed bone marrow chimeric mice showed that the development of NK cells as well as memory phenotype ($CD44^{hi}$) $CD8^+$ T cells requires that both IL-15Rα and IL-15 are expressed by the same cells to facilitate trans-presentation. *Il15ra*$^{-/-}$ mice were lethally irradiated and reconstituted with bone marrow cells from *Il15*$^{-/-}$*Il15ra*$^{-/-}$, *Il15*$^{-/-}$*Il15ra*$^{+/-}$, *Il15*$^{+/-}$*Il15ra*$^{-/-}$, or *Il15*$^{+/-}$*Il15ra*$^{+/-}$ mice. Mixed chimera knockouts expressing either IL-15 alone or IL-15Rα alone lacked NK cells. Both IL-15Rα and IL-5 were required, with processing in the endoplasmic reticulum/Golgi and shuttled to the cell surface. Like NK cells, antigen-specific memory phenotype $CD8^+$ T cells require both IL-15Rα and IL-5. In summary, trans-presentation is the dominant mechanism of IL-15 action, with the same cell synthesizing IL-15 and IL-15Rα for efficient signaling after trans-presentation to either NK or $CD44^{high}$ $CD8^+$ T cells (Burkett et al., 2004; Sandau, Schluns, Lefrancois, & Jameson, 2004).

9. IL-15 signaling pathways

IL-15 utilizes three signaling pathways following trans-presentation to cells expressing IL-2Rβ and γ_c (Mishra et al., 2014; Rochman et al., 2009; Wang & Zhao, 2021). The first involves JAK1 and JAK3 activation with subsequent phosphorylation of STAT3 and STAT5 via docking sites on IL-2Rβ. Phosphorylated STAT proteins form homodimers or heterodimers that then translocate to the nucleus where they activate transcription of a range of genes, including those encoding BCL-2, BCL-xL, and MCL-1 to facilitate cell survival, as well as c-MYC, c-FOS, c-JUN, NF-κB, IFNγ and TNFα. In the second pathway, activation of phosphatidylinositol 3-kinase (PI3K) occurs, with both JAK1 and IL-2Rβ contributing to its recruitment (Migone et al., 1998). Moreover, SHC, which binds to phosphorylated tyrosine 338 on IL-2Rβ (Friedmann, Migone, Russell, & Leonard, 1996), can also lead to the activation of the Grb2/Gab2/PI3K/AKT/mTOR/S6 pathway to augment cell proliferation and survival (Gu et al., 2000). The third signaling pathway involves SHC-mediated activation of Gab2, which binds to the guanosine nucleotide exchange factor SOS to form a Gab2/SOS complex. This then activates the Ras-Raf

endogenous mitogen-activated protein kinase (MAPK) pathway and promotes cellular proliferation. Together, the PI3K and MAPK pathways induce activation of NF-κB and c-MYC to promote cell survival and proliferation.

10. NKG2D signaling is coupled to the IL-15 signaling pathway

NK cells and tissue resident $CD8^+$ T cells do not express CD28. They express NKG2D, which recognizes atypical class I MHC stress-induced ligands (MICA in humans and Raf in mice). Medzhitov's group reported that such NF-κB signaling is coupled to the IL-15 signaling pathway (Horng, Bezbradica, & Medzhitov, 2007). Mice harboring a fusion between DAP10 and ubiquitin downregulated expression of NKG2D, and the NK cells in these animals had defective NKG2D-dependent cytotoxicity, with dysregulated IL-15-dependent actions. Interestingly, DAP10 interacted with IL-15R, and after activation by IL-15, JAK3 phosphorylated DAP10, priming it for NKG2D dependent signaling. In addition to its role in the proliferation and survival of NK cells, IL-15 promotes the priming of NK cells for NKG2D-mediated cytotoxic responses (Horng et al., 2007).

11. IL-15 trans-presentation is critical for NK-cell development and function

As noted above, mice deficient in IL-15 or any of its three receptor subunits lack NK cells (Rochman et al., 2009; Zanoni et al., 2013). However, there is normal survival of IL-15Rα-deficient NK cells if IL-15 can be transpresented to these cells, whereas even normal NK have greatly diminished survival in mice lacking IL-15Rα, supporting the view that NK cells require trans-presentation of IL-15 for their survival/maintenance. NK-cell maturation occurs primarily in the bone marrow but also in the spleen and liver. In mice, the earliest stages of NK cell development are confined to the bone marrow and involve the transition of common lymphoid precursors into NK-cell precursor (NKp) cells. The commitment to NK development presumably does not require IL-15 since the cells do not yet express IL-2Rβ (CD122), which is required for IL-15 action.

The induction of CD122 at the NKp stage is dependent on RUNX3, whereas EOMES maintains the expression of CD122 to promote further NK-cell maturation (Wang & Zhao, 2021). In mice, the transition from NKp to immature NK cells involves expression of NKG2D, NK1.1, and the CD94/NKG2D heterodimer. Subsequently there is a further expression of both activating and inhibitory Ly49 receptors (Takei et al., 2001). The transition from immature to mature NK cells is characterized by the development of responsiveness to proinflammatory cytokines and is indicated by the expression of DX5 (CD49b). NK maturation is a process during which committed cells acquire effector function, with CD11b and CD27 being key markers for dividing cells into immature, versus mature 1 (M1) and mature 2 (M2) cells (Goh & Huntington, 2017). The transition of the M1 maturation stage to M2 is characterized by the upregulation of CD11b, CD47, CD43, and CD27. Maturation of $CD27^{hi}CD11b^{lo}$ NK cells proceeds through $CD27^{hi}CD11b^{hi}$ cells to the most mature $CD27^{lo}CD11b^{hi}$ stage. NK cell maturation in humans progresses from the $CD56^{hi}CD16^{-}KIR^{-}$ to $CD56^{lo}CD16^{+}KIR^{-}$ through to $CD56^{lo}CD16^{+}KIR^{+}$. The transition from NKp involves IL-15Rα/IL-15 trans-presentation by bone marrow stromal cells and then hematopoietic cells as well as bone marrow stromal cells. In peripheral blood macrophages, DCs and monocytes trans-present IL-15, causing M2 NK cells to reach final maturation stage. IL-15 is also critical for NK-cell activation since IFN-γ and granzyme B expression in NK cells is induced by trans-presented IL-15 and deficient in the absence of IL-15. Anti-IL-15 antibody dependent ADCC depends on NK cells and macrophages and their interaction (Wang & Zhao, 2021; Zhang et al., 2018). NK cell proliferation induced by IL-15 trans-presentation but not by soluble IL-15 was negatively affected by regulatory NK inhibitory receptors (Anton et al., 2015). HLA-E mediated inhibition did not affect STAT5 phosphorylation. However, the Akt mTOR S6 ribosomal pathway was inhibited. Sustained stimulation with IL-15Rα/IL-15 (in the absence of macrophages) leads to impaired NK effector function, with inhibition of proliferation that affects NK cells, whereas $CD8^{+}$ T cells maintain a robust proliferation. The inhibition of NK function is mediated in part by the action of $CD8^{+}$ T cells (Felices et al., 2018; Fiore et al., 2020; Frutoso et al., 2018; Frutoso & Mortier, 2019). Moreover, whereas STAT5 dimers were effective for early NK development including proliferation and cytotoxicity, STAT5 tetramers are required for further NK maturation and survival (Lin & Leonard, 2019).

12. IL-15 trans-presentation and the differentiation of iNKT cells

iNKT cells are a subset of T cells that express invariant TCR recognizing lipid antigens presented by MHC class I-like molecule CD1d (Hogquist & Georgiev, 2020). In the absence of IL-15, the number of iNKT cells is profoundly depressed, especially in the liver, due to both synthetic and survival factors related to the absence of the anti-apoptotic factors BCL-2, BCL-xL and MCL-1. There are three stages in iNKT cell development, stage 1 ($CD44^{lo}NK1.1^{+}$), stage 2 ($CD44^{hi}NK1.1^{+}$), and stage 3 ($CD44^{hi}NK1.1^{+}$) cells. In the thymus, medullary thymic epithelial cells present IL-15 *in trans* to stage 3 iNKT cells. Some stage 2 iNKT cells leave the thymus and enter the liver. In the liver, DCs, Kupffer, and non-hematopoietic stellate cells present IL-15 *in trans* to stage 2 iNKT cells, whereas DCs trans-present IL-15 to stage 3 cells, which produce IFNγ under conditions of homeostatic proliferation (Kennedy et al., 2000; Terabe et al., 2008).

13. IL-15 trans-presentation regulates homeostasis of $CD4^{+}$ T lymphocytes

IL-15 trans-presentation regulates the homeostasis of naïve $CD4^{+}$ lymphocytes (Huntington et al., 2011; Rochman et al., 2009; Waickman et al., 2017). A crucial role has been demonstrated for IL-15 induced signaling in DCs for the induction of T_{H1} cell mediated immunity via IL-12 production. CD122 (IL-2Rβ)-deficient mice have defective IL-12 signaling and function. Interestingly, IL-2-deficient mice do not have a comparable deficiency, but IL-15-deficient mice have a comparable deficiency in IL-12 production, indicating a crucial role for IL-15 but not IL-2 signaling in DCs for the induction of T_{H1} cells and IL-12 production. The exposure of T_{H1} cells to trans-presented IL-15 but not to soluble IL-15 alone favors a T_{H1} gene program (Cooley, Read, & Oestreich, 2015). Trans-presentation of IL-15 mediates the expression of T_{H1} associated genes, including *Tbx21, Tfng, Prdm1, Il2ra, and Il2rb*, as well as increased IL-12-mediated phosphorylation of STAT4 (Cooley et al., 2015). Furthermore, IL-15 promotes T_{H1}-mediated immune responses in the intestinal environment by modulating the effect of retinoic acid to

promote inflammation and modulate DC function (Arranz & Garrote, 2011). IL-15 can also regulate the homeostasis of native $CD4^+$ T cells. In the NOD model of type 1 diabetes, $CD4^+$ cells expanded without IL-15 do not acquire Treg like function and instead show impaired antigen-mediated activation and IFNγ production (Chen et al., 2014).

14. IL-15 trans-presentation plays a role in the development, homeostasis, and activation of dendritic epidermal T cells (DETCs)

DETCs are a skin-specific member of the TCR γδ T-cell population that migrates to the skin in mice during fetal life. DETCs were absent in mice deficient in IL-15Rα/IL-15. DETCs express IL-15Rα and respond to IL-15, suggesting that IL-15 is critical for DETC growth and survival after activation and that it may also influence the localization of these cells to the skin (Mackay et al., 2013).

15. The role of IL-15 in the homeostasis of γδ cells

Targeted deletion/inactivation of IL-2Rβ (CD122) results in a marked reduction in the number of circulating γδ cells. With the depletion of αβ T cells, NK cells, or γδ cells themselves, there is an increase in the homeostatic proliferation of γδ cells, indicating that these cells respond to the available IL-7 and IL-15, with IL-15 enhancing the proliferation and survival of γδ cells (Baccala et al., 2005; French, Roark, Born, & O'Brien, 2005). Such cells have an ability to kill a variety of tumor cells with broad specificity. Thus, γδ cells have the capacity to respond to IL-15 (Fehniger & Caligiuri, 2001; Rochman et al., 2009).

16. IL-15 trans-presentation controls the expression and survival of $CD44^{high}$ $CD8^+$ T cells

Kennedy and coworkers demonstrated a marked reduction in the proliferation and survival of a subset of $CD8^+$ T cells in IL-15 genetically deficient mice (Kennedy et al., 2000). A comparable deficiency was observed in IL-15Rα-deficient mice (Burkett et al., 2004). *Il15ra*$^{-/-}$ mice had a marked deficiency in $CD44^{high}$ $CD8^+$ T cells, whereas those deficient in the signaling molecule ITK were deficient in $CD44^{low}$ $CD8^+$ T cells. Mice lacking both IL-15Rα and ITK had a marked reduction of both $CD8^+$ T cell

subpopulations (Dubois, Waldmann, & Muller, 2006). Interestingly, $CD44^{high}$ $CD8^+$ T cells represents a mixed population of IL-15-dependent and IL-15-independent cells. The majority of $CD122^{low}$ $CD44^{high}$ $CD8^+$ T cells were IL-15-independent, whereas most $CD122^{high}$ $CD44^{high}$ $CD8^+$ T cells were IL-15-dependent. Thus, both the proliferation and survival of only a subset of $CD44^{high}$ $CD8^+$ T cells were IL-15-dependent (Judge, Zhang, Fujii, Surh, & Sprent, 2002).

The IL-15Rα/IL-15 complex maintained on the cell surface of hematopoietic cells sustained IL-15 activity and controlled the long survival of $CD8^+$ memory T cells (Berard, Brandt, Bulfone-Paus, & Tough, 2003; Boyman, Letourneau, Krieg, & Sprent, 2009; Sato, Patel, Waldmann, & Tagaya, 2007; Sosinowski et al., 2013; Zhang, Sun, Hwang, Tough, & Sprent, 1998). Furthermore, IL-15 can function as a mediator of $CD4^+$ T cell help or of $CD8^+$ T-cell longevity and the avoidance of TRAIL-mediated apoptosis (Oh et al., 2008). *Il15*$^{-/-}$ mice have a defective response to multiple pathogens, with defective antigen-specific memory $CD8^+$ T cells (Kennedy et al., 2000). This is evident during the contraction phase, resulting from a more profound T-cell death and that it was associated with decreased expression of the survival protein BCL-2 (Castro, Yu, Dee, & Malek, 2011). T cell memory is regulated in part by IL-15 but also by IL-7 (Boyman et al., 2009). IL-15 contributes to a conversion of metabolic pathway involving oxidative phosphorylation rather than glycolysis used by naïve and classical memory $CD8^+$ T cells. IL-15 upregulates BCL-2 in $CD44^{high}$ and $CD44^{low}$ $CD8^+$ T cells, whereas elevated expression of BCLxL was only observed in $CD44^{high}$ cells (Berard et al., 2003).

17. Dendritic cells and macrophages mediate the effect of IL-15 on $CD8^+$ $CD44^{high}$ memory phenotype T cells

IL-15 and IL-15Rα were induced on DCs by a combination of IFN-γ and activators of NF-κB such as LPS. In DCs, an IL-15 autocrine loop protects against apoptosis, and mice deficient in IL-15 or its receptor have few DCs. Interestingly, a connection was defined between deficiency in $CD44^{high}$ $CD8^+$ T cells in IL-15-deficient mice and the lack of DCs. Injecting DCs into IL-15Rα-deficient mice was associated with the appearance of $CD8^+CD44^{high}$ T cells (Dubois, Waldmann, & Muller, 2005). Placing IL-15Rα expression under the control of a CD11c promoter in an *Il15Ra*$^{-/-}$ background restricts IL-15Rα expression to DCs. Such DCs trans-presenting IL-15 was also assessed by conditional deletion of

IL-15Rα. In both systems, IL-15Rα expression by DCs was shown to be important for the presence of memory phenotype $CD44^{high}CD8^{+}$ T cells. Macrophages and DCs displaying IL-15Rα supported the homeostasis of distinct $CD8^{+}$ T-cell subsets. IL-15Rα expression on macrophages but not DCs supported the early transition of antigen specific effector T cells to memory cells. After memory $CD8^{+}$ T-cell differentiation, IL-15Rα expression on DCs selectively supported central memory $CD8^{+}$ T cells, whereas IL-15Rα on macrophages supported both central and effector memory T cells. Taken together, macrophages and DCs support the homeostasis of $CD44^{high}$ T cells with distinct $CD8^{+}$ T cell subset expression (Boyman et al., 2009; Castro et al., 2011; Mortier et al., 2009).

18. The effect of IL-15 trans-presentation from DCs to NK cells

Naïve NK cells require *in vivo* priming to make effective responses to viral and bacterial pathogens. Such priming requires the presence of $CD11c^{high}$ $CD8^{+}$ DCs. After peripheral Toll- like receptor (TLR) stimulation, NK cells are recruited to local lymph nodes, and their functional cooperation with DCs results in accumulation in the periphery of effector NK cells. IL-15 promotes the survival of mature NK cells, consequently promoting both the survival and function of NK cells, with DCs serving a key role in presenting IL-15 and priming NK cells (Lucas, Schachterle, Oberle, Aichele, & Diefenbach, 2007). Accordingly, DCs have important actions for both NK as well as $CD44^{high}$ $CD8^{+}$ T cells.

19. IL-15-dependent IELs are a heterogeneous group of cells in the small and large intestine where they contribute to the first level of defense against infections

IELs are distributed over the basolateral surfaces of the epithelium of the small and large intestines. They are mostly $CD8^{+}$ T cells, and mainly express CD8αα. IELs are solely dependent on the trans-presentation of IL-15 by non-hematopoietic cells of the gut epithelium (Ma, Acero, Zal, & Schluns, 2009). Overall, they comprise induced $TCR\alpha\beta^{+}CD8\alpha\alpha^{+}CD8\alpha\beta^{+}$ or $TCR\alpha\beta^{+}CD4^{+}CD8\alpha\alpha^{+}$ cells derived from peripheral T cells, or $TCR\alpha\beta^{+}CD8\alpha\alpha^{+}$ or $TCR\gamma\delta^{+}CD8\alpha\alpha^{+}$ IELs derived from thymic precursors. $CD8\alpha\alpha^{+}$ IELs are selected in the thymus from a population of immature

$CD4^+CD8\alpha\alpha^+CD8\alpha\beta^+$ thymocytes that develop into double negative $CD4^-CD8^-$ TCRαβ and TCRγδ populations that then develop into TCRαβ and TCRγδ IELs (Kwong & Lazarevic, 2014). Interestingly, the differentiation of $Thy1^{hi}$ DN thymocytes into $Thy1^-$ CD8αα IELs required the trans-presentation of IL-15. IELs up-regulate the gut-homing receptor CCR9 and integrin α4β7 and migrate to the intestinal epithelium to complete their differentiation into IELs that express CD8αα, CD103, NK1.1, and CD122. The T-box transcriptional factor T-bet is induced by IL-15. Mice deficient in T-bet lack both TCRαβ and TCRγδ $CD8\alpha\alpha^+$ IELs. T-bet participates in the upregulation of CD122 (IL-2Rβ) and hence for IL-15 dependent expansion of thymus derived IEL precursors in the periphery. IL-15 also augments expression of RUNX3, which is induced in a T-bet dependent fashion, although RUNX3 expression is partially independent of T-bet (Klose et al., 2014). CD8αα IELs can also be generated in the periphery after undergoing a process characterized by loss of classical $CD4^+$ T-cell helper function and of the T-helper transcription factor ThPOK, with T-bet induction of RUNX3 involved in CD8αα production (Reis, Rogoz, Costa-Pinto, Taniuchi, & Mucida, 2013). In addition to its effects on IEL differentiation, trans-presentation of IL-15 by IELs leads to an increase in BCL-2 expression such that again IL-15 is involved in survival of CD8αα precursors. The differentiation of CD8αα cells involves IFNγ and IL-27, which can induce T-bet. The differentiation of $TCR\alpha\beta^+CD4^+CD8\alpha\alpha^+$ IELs requires IFNγ, whereas IL-27 was needed for $TCR\gamma\delta^+CD8\alpha\alpha^+$ and $TCR\alpha\beta^+$ $CD8\alpha\beta^+CD8\alpha\alpha^+$ IELs. Thus, multiple signals are required for the production of IELs, with an important role for IL-15, where IL-15Rα expression on IELs is required for the optimal development of $CD8\alpha\alpha^+$ IELs (Klose et al., 2014; Kwong & Lazarevic, 2014; Reis, Hoytema van Konijnenburg, Grivennikov, & Mucida, 2014).

Another IL-15-responsive cell that is not strictly IL-15-dependent is the intraepithelial type 1 innate lymphoid cell. Intraepithelial ILC1s in mice were observed to express CD160 and require *Nfil3* and *Tbx21* for their development but not IL-15. The ILC1 subset contains a unique $NKp44^+$ $CD103^+$cell that produces IFN-γ in response to IL-12 and IL-15. They contribute to the pathology in the anti-CD40 induced colitis of mice (Fuchs et al., 2013). Another subset of intraepithelial IELs known as IE-ILC1s is distinct from CD8αα innate type lymphocytes. IE-ILC1s express the transcription factors eomesodermin and T-bet, produce IFNγ and exhibit cytotoxic activity toward NK target cells in mice. These cells are IL-15-dependent and exhibit some T-cell traits. In mice, they contain

Id2-independent innate CD8αα cells. Interestingly, their differentiation requires NOTCH1, IL-15, and Granzyme B (Ettersperger et al., 2016). In Notch-activated hematopoietic precursors, IL-15 induced granzyme B, which cleaved and inactivated NOTCH1. This results in the silencing of T cell differentiation and redirection into innate cells that retain T-cell markers including intracellular CD3ε and CD3γ and *TCRG* and *TCRD* gene rearrangements. Such cells have a selective advantage, especially when they express JAK1 or STAT3 in transition toward clonal evolution into lymphoma in patients with celiac disease (Ettersperger et al., 2016).

20. IL-15Rα trans-presents IL-15, thereby regulating tissue resident T cells and tissue specific destruction

The health of tissues is frequently challenged by intracellular infection or non-infectious stress, with associated production of IFNγ. Tissue resident cytotoxic $CD8^+$ T cells play a key role in tissue protection (Abadie & Jabri, 2014; Mackay et al., 2013; Xie et al., 2020). IL-15 is frequently involved, promoting T-cell activation by impairing SMAD dependent TGFβ signaling and by rendering $CD8^+$ T cells unresponsive to Treg-mediated suppression. In contrast to circulating $CD8^+$ T cells, which express CD28, tissue resident effector memory $CD8^+$ T cells do not express CD28. Furthermore, tissue cells do not express CD80. Accordingly, a different type of co-stimulation is required for effector cytotoxic T cells to act. Following stress or intracellular infection, IFNγ production and IL-15Rα expression occur, along with expression of unconventional MHC molecules MICA and MICB in humans and Rae in mice, and IL-15 binds to IL-15Rα. These molecules interact with IL-2Rβ/γc and NKG2D to provide the required co-stimulation for the activation of NF-κB/DAP10. This cellular action is of value to the host to protect against infection but also is detrimental in that it is involved in autoimmunity, including type 1 diabetes, celiac disease, alopecia areata, inflammatory bowel disease, vitiligo, and sarcoidosis (Abadie & Jabri, 2014; Jabri & Abadie, 2015; Mackay et al., 2013; Xie et al., 2020)

21. IL-15 and autoimmune diseases

IL-15 plays a pathogenic role in virtually all organ-specific autoimmune diseases. IL-15 is up-regulated in various autoimmune diseases including rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus,

alopecia areata, psoriasis, inflammatory bowel disease, vitiligo, sarcoidosis, celiac disease, and type 1 diabetes (Fehniger & Caligiuri, 2001). However, the upregulated IL-15 levels are not sufficient to consider it having a role in an autoimmune disorder, since in diseases such as autoimmune thrombocytopenia and Crohn's disease IL-15 plays a host regulatory role protecting from the autoimmune disorder (Li et al., 2017; Silva, Menezes, Deslandres, & Seidman, 2005). Moreover, it was proposed that IL-15 functions as a danger signal to regulate tissue resident T cells and to lead to destruction of infected and stressed tissues (Abadie & Jabri, 2014; Jabri & Abadie, 2015). However, chronically dysregulated IL-15 expression promotes organ specific autoimmune diseases, and this is associated with increased expression of activating NK receptors, including NKG2D and CD94-NKG2C. Humans cells increase expression of non-classical MHC class I or the class I-related molecules HLA-E and MICA, which are ligands for CD94-NKG2C. NKG2D is a homodimer that associates with DAP10. IL-15 upregulates DAP10 expression on peripheral blood $CD4^+$ NKG2D cells from patients with celiac disease (Abadie et al., 2020).

To investigate the role of IL-15/IL-15Rα in the pathogenesis of type 1 diabetes both IL-15Rα and IL-15 were expressed in double transgenic mice in pancreatic islet β cells (Chen et al., 2013). As anticipated, the mice developed hyperglycemia, pancreatic islet β cell destruction, and anti-insulin autoantibodies mimicking human type 1 diabetes. Importantly, the hyperglycemia was reversed by inhibiting IL-15 signaling or administration of tofacitinib, a JAK inhibitor (Chen et al., 2013). In humans with type 1 diabetes, their pancreatic β islet cells express IL-15 and IL-15Rα, whereas controls do not (Chen et al., 2013). Interestingly, in celiac disease, IL-15 expression in mouse models requires IL-15 both in the epithelium and submucosa (Abadie et al., 2020).

Evidence for the role of IL-15 in tissue destruction is provided by observations in patients with two human diseases. First, in latent autoimmune diabetes of adults (LADA), the presence of adaptive immunity against antigen-expressing pancreatic β islet cells is predictive of but not sufficient for the development of type 1 diabetes (Chen et al., 2013). Second, in celiac disease, there is an adaptive immune response specific for gluten, but this does not result in the activation of CTLs or villous atrophy in the absence of epithelial stress with the required expression of IL-15 and heat shock proteins (Abadie et al., 2020). Thus, IL-15 along with stress-induced MHC class I molecules (e.g., MICA) expressed by disease cells provide co-stimulatory signals to cytotoxic effector memory T cells that license them to become killer cells, causing the destruction of tissue cells.

22. $CD8^+$ $CD122^+$ $CD127^-$ PD-1^+ $CD28^{+/-}$ regulatory T cells are essential for the maintenance of T-cell homeostasis

In addition to its positive role, IL-15 can support the expression of $CD8^+CD122^+$ regulatory cells, where it reduces disease activity, for example in experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (Lee et al., 2008; Najafian et al., 2003). Mice treated with an antibody to IL-2Rβ (CD122) and IL-15-deficient mice had augmented EAE and collagen induced arthritis (CIA), suggesting that IL-15 was supporting a regulatory cell (Gomez-Nicola, Spagnolo, Guaza, & Nieto-Sampedro, 2010; Lee et al., 2008). There are multiple markers that are associated with various groups of $CD8^+$ regulatory cells, including such elements as PD-1, CD25, Ly49, and the absence of CD28 (Dai et al., 2010; Fenoglio et al., 2008). Two such $CD8^+$ regulatory cells are dependent on IL-15 for their expression and action; both are $CD8^+CD122^{high}CD127^-$ and PD-1^+ but one expresses granzyme, perforin, and $CD28^+$ whereas the other is $CD28^-$. Blockade with TMβ1 antibody to mouse IL-2Rβ or anti-IL-15 profoundly decreased the percentage of $CD122^{high}$ cells in the total $CD8^+$ T cell population of the spleen (Lee et al., 2008). A common theme among the regulatory cells is the requirement of cell-cell contact between antigen-presenting cells including macrophages, monocytes, and DCs, and the $CD122^+CD8^+$ regulatory cell, as might be anticipated for IL-15 trans-presentation. Furthermore, the regulatory cells produced IL-10 and suppressed IFNγ production. In EAE, the blockade of IL-15 or its genetic deletion was associated with more severe and longer duration of the inflammation due to the diminished $CD8^+CD122^+$ cells but not NK cells (Lee et al., 2008; Mangalam et al., 2012). Moreover, the transfer of activated $CD28^+$ $CD122^+$ cells into TMβ-1 Fab treated mice led to reduced IL-17A secretion (Yu, Bamford, & Waldmann, 2014). Furthermore, the addition of neutralizing antibodies to IL-10 led to rescue of IL-17A levels (Yu et al., 2014). Interestingly, in humans, in idiopathic thrombocytopenic purpura, $CD8^+$ T cells are predominantly protective and limit disease, and treatment with dexamethasone expanded $CD8^+$ Tregs but decreased cytotoxic $CD8^+$ T cells (Ma et al., 2015). Furthermore, there was a similar negative regulatory/anti-inflammatory role for IL-15 in the control of Crohn's disease (Silva et al., 2005).

Accordingly, when treating autoimmune diseases with increased IL-15 levels, one must consider the possibility that IL-15 is supporting

the expression of $CD8^+CD122^+$ suppressor cells and that inhibiting IL-15 may aggravate the autoimmune disease. In other words, IL-15 blockade is rational in situations where it plays a central role in the pathogenesis of disease but should be avoided in situations where its role is facilitating the actions of regulatory $CD8^+$ $CD122^+$ T-cells that are ameliorating disease activity.

23. IL-15 in cancer

Infection with the retrovirus HTLV-1 infection results in adult T cell leukemia (ATL) in approximately 2 to 5% of infected individuals, ATL is a leukemia of $CD4^+$ tissue resident Treg cells. HTLV-1-associated Tax protein transactivates two autocrine (IL-2/IL-2R and IL-15/IL-15R) and one paracrine (IL-9) pathway (Mariner et al., 2002; Migone et al., 1995)]. IL-15 transgenic mice developed fetal lymphocytic leukemia with a $CD8^+$ phenotype and NK surface markers. It was shown that IL-15 can act as a growth and viability promoting factor in cutaneous T-cell lymphoma (CTCL) (Dobbeling et al., 1998). Interestingly, ZEB1 is a transcriptional repressor of IL-15 in T cells, and hypermethylation of the ZEB1 binding region within the IL-15 promoter in CTCL prevented ZEB1 binding and was associated with increased IL-15 transcription (Mishra et al., 2014).

T-cell like innate IELs develop in the intestine and as noted above, can undergo malignant transformation into lymphoma in celiac disease. Their differentiation requires sequential activation of NOTCH1 and IL-15 signals, and gain-of-function JAK1 or STAT3 mutations can favor malignant clonal expansion (Ettersperger et al., 2016). IL-15Rα/IL-15 serum levels were also noted to be elevated in patients with T-cell large granular lymphocytic leukemia (LGL) and IL-15 and platelet derived growth factor are sufficient to reproduce the deregulation of T cells of LGL leukemia (Mishra et al., 2014). Finally, IL-15 mRNA was detected in the peripheral blood mononuclear cells of patients with the Sézary syndrome, consistent with a possible contribution to that disease (Leroy et al., 2001).

24. Conclusions and therapeutic perspectives

Our still evolving understanding of the IL-15/IL-15R system is providing the scientific basis for the development of rational approaches for the therapy of autoimmune diseases and malignancy. Specific disorders of IL-15 play a pathogenic role in multiple organ-specific autoimmune disorders, and

a range of approaches have been developed to block the actions of IL-15. When evaluating the efficacy of such IL-15 inhibitory agents, a valuable biomarker is a marked reduction in the number of circulating NK cells, whereas the lack of such a reduction reflects a failure of inhibition of IL-15 action. Monoclonal antibodies, Hu-Mikβ-1 for humans and TM-β1 for mice are directed toward the IL-2Rβ subunit. In a trial of patients with HTLV-1 associated neurological disease, HAM/TSP, Hu-Mikβ1 administration led to a marked reduction in the number of NK cells, STAT5 phosphorylation, T-cell degranulation, and spontaneous proliferation of peripheral blood T cells *ex vivo* (Enose-Akahata et al., 2019). Another approach for blocking the interaction of IL-15 with its receptor involves the agent, BNZ-1, a 24 amino acid long peptide corresponding to the shared elements of the D-helix of IL-2 and IL-15 that binds to γ_c rather than to IL-2Rβ. BNZ-1 prevents the binding of IL-2 and IL-15 and prevents receptor heterodimerization as is required for signaling (Nakamura et al., 1994; Nelson, Lord, & Greenberg, 1994). In control individuals, PEGylated BNZ-1 had a survival $t_{1/2}$ of approximately 5 days and led to a 76% decline in circulating NK cells and a 69–93% decline in Tregs due to the action on IL-2 and IL-15. BNZ-1 is being evaluated in clinical trials in patients with T-cell LGL and CTCL (Frohna et al., 2020). BNZ-2 is another inhibitor, with the ability to block IL-15 and IL-21 binding, which is being evaluated for the treatment of patients with refractory celiac disease (Ciszewski et al., 2020). Another inhibitor under evaluation is the IL-2 mutant, H9-RETR. This molecule binds tightly to IL-2Rβ (based on the H9 "super-IL-2" background) thereby blocking IL-2 and IL-15 binding to their receptors and preventing cytokine-mediated receptor dimerization, proliferation, and cytotoxicity (Mitra et al., 2015). Ruxolitinib (a JAK1/2 inhibitor), tofacitinib (a JAK inhibitor that primarily inhibits JAK3 but also JAK1 and JAK2 to a lesser degree), as well as more specific JAK1 and JAK3 inhibitors, have shown efficacy. In patients with alopecia areata, where $CD8^+$ T cells develop in the hair follicle and IL-15 is overexpressed, there was nearly complete restoration of hair growth after treatment with ruxolitinib (Phan & Sebaratnam, 2019).

In order to more effectively treat patients with cancer and develop more effective vaccines, novel approaches are being developed to yield agents that maximize increases of NK and $CD8^+$ T cells (Guo et al., 2017; Papaevangelou, Smolarek, Smith, Dasgupta, & Galustian, 2020; Steel et al., 2012; Waldmann, 2006; Waldmann et al., 2020). When IL-15 was administered by continuous intravenous infusion for 10 days to

patients with cancer, there was a marked (38-fold) increase in the total number of NK cells, and a profound (358-fold) increase in the number of $CD56^{bright}$ NK cells versus a 5.8-fold increase in $CD8^+$ T cells (Conlon et al., 2019). However, IL-15 by continuous intravenous infusion would not be practical/acceptable for patients or physicians. When the IL-15 superagonist, N-803 (an IL-15 mutant plus the sushi domain of IL-15Rα) was administered subcutaneously, it led to a broad erythematous rash, and the apparent $t_{1/2}$ of 30 days of N-803 resulted from the fact that 97% of N-803 was consumed by γδ T cells in the rash, so that only 3% of the administered N-803 was delivered, resulting in much lower increases in NK cells and $CD56^{bright}$ NK cells compared to the high levels achieved with continuous infusion indicated above (Van der Meer et al., 2021). Accordingly, agents including very long-acting IL-15 and PEGylated IL-15 perhaps will be superior. However, despite increases in NK and $CD8^+$ T cells, no IL-15 preparations administered as monotherapy of solid tumors have been effective, due to the actions of immunological checkpoints (Yu et al., 2014), failure to target the tumor, lack of co-stimulatory signals, and possibly the lack of NK cell activation. For IL-15 to be more effective, IL-15 may have to be used in combination therapy with other agents and with co-stimulators, perhaps including agonistic anti-CD40 mAbs to enhance beneficial effect of $CD4^+$ T helper cells with co-stimulation, to increase expression of CD80/CD86 as well as CD28. In the TRAMP-C2 prostate tumor model, there was an additive/synergistic antitumor efficacy of IL-15 and anti-CD40 agonistic antibody. Furthermore, there was an increase in the number of circulating tumor specific tetramer positive $CD8^+$ T cells. When anti-PD-1 was added to the intratumoral anti-CD40 and IL-15 in mice with established TRAMP-C2 tumors there was a sustained, complete response in both injected and uninjected tumors[90]. (Zhang et al., 2012).

As noted earlier, IL-15 administration to patients with cancer was associated with a dramatic increase in the number of circulating NK cells but this was not associated with antitumor efficacy (Conlon et al., 2019). Thus, to be effective, combination approaches are needed, potentially including the combination of IL-15 with antitumor specific monoclonal antibodies to increase their antibody-dependent cellular cytotoxicity (ADCC) and antitumor efficacy (Zhang et al., 2018). For example, in clinical trials involving IL-15 in combination with the anti-T-cell antibody, alemtuzumab/CAMPATH/anti-CD52 in the treatment of patients with mature T-cell malignancies, predominantly ATL, partial and complete responses were observed (Miljkovic et al., 2022), and circulating leukemic cells were

virtually eliminated in patients receiving IL-15 and the combination of alemtuzumab and mogamulizumab (anti-CCR4). More recently, trials of IL-15 in combination with anticancer monoclonal antibodies have been initiated in patients with chronic lymphocytic leukemia, renal cell cancer, adult T-cell leukemia, and mycosis fungoides. It is hoped that with the expanding understanding of the role of IL-15Rα/IL-15 trans-presentation in the life, function, and death of normal and malignant lymphoid cells is providing a new perspective for the treatment of autoimmune disorders and malignancies.

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