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Review Article

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IL-15 in T-Cell Responses and Immunopathogenesis

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Conflict of Interest
The authors declare no potential conflicts of interest.

ABSTRACT

IL-15 belongs to the common gamma chain cytokine family and has pleiotropic immunological functions. IL-15 is a homeostatic cytokine essential for the development and maintenance of NK cells and memory CD8$^+$ T cells. In addition, IL-15 plays a critical role in the activation, effector functions, tissue residency, and senescence of CD8$^+$ T cells. IL-15 also activates virtual memory T cells, mucosal-associated invariant T cells and γδ T cells. Recently, IL-15 has been highlighted as a major trigger of TCR-independent activation of T cells. This mechanism is involved in T cell-mediated immunopathogenesis in diverse diseases, including viral infections and chronic inflammatory diseases. Deeper understanding of IL-15-mediated T-cell responses and their underlying mechanisms could optimize therapeutic strategies to ameliorate host injury by T cell-mediated immunopathogenesis. This review highlights recent advancements in comprehending the role of IL-15 in relation to T cell responses and immunopathogenesis under various host conditions.

Keywords: Interleukin-15; T-lymphocytes, immunopathogenesis

INTRODUCTION

IL-15 is a cytokine composed of four alpha-helical bundles (1) and is well-known as a common gamma chain (γc, CD132)-dependent cytokine (2), a class that also includes IL-2, IL-4, IL-7, IL-9, IL-21, and TSLP (3). IL-15 is frequently referred to as a pleiotropic cytokine due to its mediation of multiple functions in various types of immune cells. Since its discovery nearly 30 years ago (1,4), IL-15 has emerged as a pivotal cytokine with well-established functions in mediating lymphoid homeostasis, most notably in compartments of NK cells and memory CD8$^+$ T cells (5). However, the functions of IL-15 are not only limited to homeostasis, but are also closely associated with a range of contexts, including the activation, effector functions, tissue residency, and senescence of CD8$^+$ T cells. IL-15 has been recognized as a potent stimulatory cytokine that enhances T-cell immune responses with potential for cancer treatment (6). Dysregulated expression of IL-15 has been also demonstrated in various types of diseases (7). Moreover, IL-15 activates diverse types of unconventional T cells and triggers NK-like cytotoxicity, which could contribute to immunopathogenesis in diverse diseases (8,9). This emphasizes the need for a better understanding of the IL-15-mediated T-cell

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Abbreviations

CAR-T, chimeric Ag receptor T cell; $CD44^{s\text{-}hi}CD49d^{lo}$, CD44 super-high CD49d low; CMV, cytomegalovirus; EBV, epstein-Barr virus; FOXO1, forkhead box O1; γc, common gamma chain; HAV, hepatitis A virus; IAV, influenza A virus; IEL, intraepithelial lymphocyte; IL-15Rα, IL-15 receptor alpha; IRF1, IFN regulatory factor 1; KIR, killer cell immunoglobulin-like receptor; MAIT, mucosal-associated invariant T cells; MR1, class I-related molecule 1; NASH, non-alcoholic steatohepatitis; NKR, NK receptor; NSCLC, non-small cell lung cancer; SOCS, suppressor of cytokine signaling; T_{RM}, tissue resident memory $CD8^+$ T cells; T_{SCM}, stem cell-like memory T cells; T_{VM}, virtual memory T cells.

Author Contributions

Conceptualization: Lee H, Park SH, Shin EC; Data curation: Lee H, Park SH, Shin EC; Investigation: Lee H; Methodology: Lee H, Park SH, Shin EC; Supervision: Shin EC; Writing - original draft: Lee H, Shin EC; Writing - review & editing: Lee H, Park SH, Shin EC.

response in various contexts. Although IL-15 is also indispensable in shaping NK cell biology, as comprehensively reviewed elsewhere (10), this review focuses on recent advancements in understanding the role of IL-15 in relation to T-cell responses under varying host conditions.

EXPRESSION OF IL-15 AND ITS SIGNAL TRANSDUCTION

Despite the abundant expression of IL-15 transcripts in a wide variety of tissues and both hematopoietic and non-hematopoietic cells (11-15), IL-15 protein is mainly produced by monocytes, dendritic cells, and epithelial cells (12,14,16). IL-15 primarily operates in a cell contact-dependent manner through the trans-presentation of membrane-bound complexes comprised of IL-15 and IL-15 receptor alpha (IL-15Rα) on the producing cells to IL-2/IL-15 receptor-β chain (CD122) and γc on the responding cells (17). This process begins with the preassembly of IL-15 with IL-15Rα in a complex within the endoplasmic reticulum/Golgi, followed by its subsequent transportation to the cell surface. IL-15 has also been reported to signal as soluble IL-15-IL-15Rα complexes or IL-15 alone, but trans-presentation has been demonstrated to be the dominant mechanism eliciting potent IL-15 signals (18-20).

IL-15 production is triggered by inflammation, infection, or prolonged cellular stress (7). Various types of inflammatory stimuli have been shown to trigger IL-15 expression. Treatment with polyinosinic:polycytidylic acid or LPS, either *in vivo* or *in vitro*, enhances the expression of IL-15 and IL-15Rα on dendritic cells (14,21). Type I IFNs, including IFNα and IFNβ, have also been shown to upregulate IL-15 mRNA and protein expression in dendritic cells, monocytes, macrophages, and epithelial cells (14,22-25). In addition, IFNγ, a type II IFN, can elevate the expression of IL-15 and IL-15Rα in monocytes, endothelial cells, and epithelial cells (12,25-27). More recently, in epithelial cells, IFNγ was shown to upregulate the expression of IL-15 and IL-15Rα more potently, promoting the effector functions of NK cells via IL-15 trans-presentation compared to type I IFNs (25). This previous study showed that IFN regulatory factor 1 (IRF1) plays a critical role in IL-15 expression induced by IFNγ and type I IFNs (**Fig. 1**). This result suggests that the IFNs-IRF1-IL-15 axis may serve as a regulatory target for the treatment of diseases in which the expression of IL-15 is dysregulated.

IL-15 activates three main downstream signaling pathways, including the JAK/STAT, PI3K/AKT/mTOR, and Ras/Raf/MAPK pathways (10). Upon binding to IL-15, the IL-2/15Rβγ receptors recruit and activate JAK1, leading to the subsequent phosphorylation of STAT3 via the β chain (28,29). Simultaneously, JAK3 is recruited to the γ chain, where it phosphorylates STAT5. This cascade of reactions results in the formation of phosphorylated STAT3/STAT5 heterodimers, which subsequently translocate to the nucleus, leading to the activation of anti-apoptotic (Bcl-2 and Mcl-1) and oncogenic (c-Myc) transcription factors (30-32). In the second signaling pathway, activated adaptor protein, Shc is recruited to a phosphorylated site on the β chain and triggers phosphorylation of GAB2 through the adaptor Grb2, which in turn activates the PI3K/AKT/mTOR signaling pathway crucial for cell proliferation and survival (33). This pathway leads to accumulation of mTORC1 in the nucleus, which induces E4 promoter-binding protein 4 (E4BP4)-mediated upregulation of Eomes (34,35). Subsequently, Eomes binds to the *il2rb* promoter, increasing CD122 expression and establishing a positive feedback loop of IL-15 signaling. A recent study demonstrated that IL-15-mediated phosphorylation of AKT accumulates X-box binding protein 1 (XBP1) in the nucleus, where it recruits T-bet to induce the transcription of genes encoding effector molecules, such as IFNγ and granzyme B (36). In addition to the PI3K/AKT/mTOR signaling

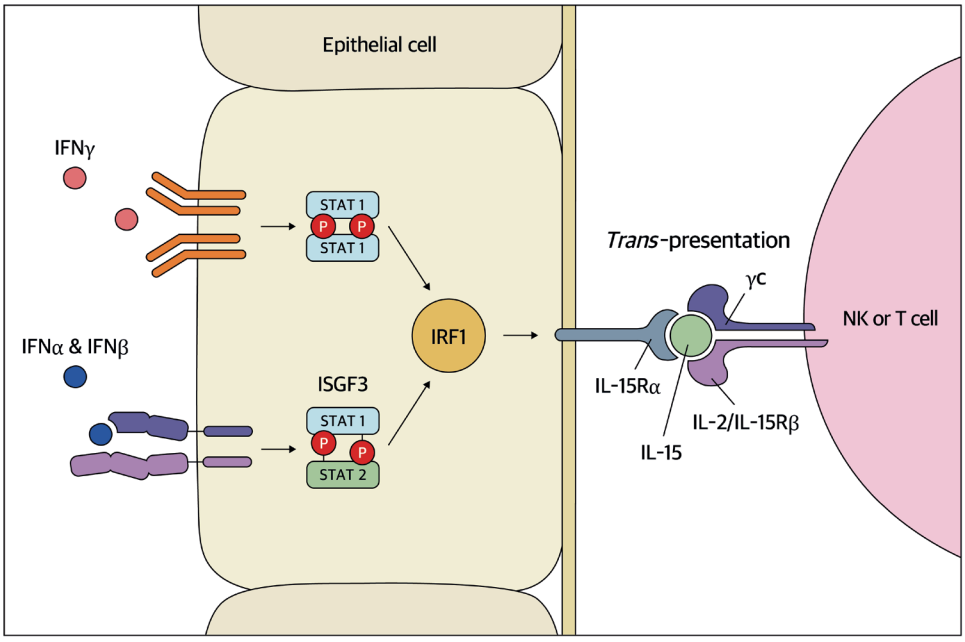

Figure 1. IFNγ- and type I IFN-mediated IL-15 trans-presentation.
IFNγ and type I IFNs activate distinct signaling pathways leading to the upregulation of IL-15. However, these pathways eventually converge at IRF1. IFNγ signaling primarily depends on STAT1 homodimers for the activation of IRF1. In type I IFN signaling, the ISGF3 complex is formed by a phosphorylated STAT1 and STAT2 heterodimer, which subsequently activates IRF1.
ISGF3, IFN-stimulated gene factor 3.

pathway, IL-15-induced activation of Grb2 also triggers the Ras/Raf/MAPK signaling pathway, which subsequently activates c-Fos, c-Jun, and c-Myc, which are responsible for cell proliferation (37,38).

The IL-15 signaling pathways can be negatively regulated by intracellular checkpoints, namely, suppressor of cytokine signaling (SOCS) family members. STAT5 has been shown to upregulate genes that encode SOCS proteins (39,40). Cytokine-inducible SH2 protein (CIS) is a member of the SOCS family that inhibits the enzymatic activity of JAK1, thereby suppressing JAK-STAT signaling (41). Similarly, SOCS3 suppresses IL-15-induced STAT5 phosphorylation, thereby inhibiting the IL-15 responsiveness of cells (42). Furthermore, zinc fingers and homeoboxes 2 (ZHX2), OTU domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1), tumor necrosis factor-α-induced protein 8-like 2 (TIPE2), and forkhead box protein O1 (FOXO1) have been reported to be transcription repressors that negatively regulate the IL-15-induced transcriptional activity of STAT5 (43), AKT (44), mTOR (45), and T-bet (46), respectively.

IL-15 AND T-CELL RESPONSES

Memory CD8$^+$ T cells

IL-15 has been demonstrated to play a significant role in homeostatic proliferation of memory CD8$^+$ T cells. Previous studies have demonstrated that the absence of IL-15 results in a reduction in the memory CD8$^+$ T-cell population (5,47). Moreover, IL-15 induces the proliferation of stem cell-like memory T cells (T_{SCM}) (48) and prevents attrition of the pre-existing memory CD8$^+$ T-cell population (49). CD8$^+$ T cells are activated upon TCR-mediated recognition of cognate peptides presented by MHC-I (50). Notably, IL-15 promotes

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TCR-mediated activation of CD8⁺ T cells by reducing the TCR activation threshold. This was demonstrated by upregulation of TCR-mediated ERK phosphorylation and Nur77 expression in CD8⁺ T cells in the presence of concurrent IL-15 stimulation (51,52). IL-15 also contributes to TCR-mediated proliferation and IFNγ production by CD8⁺ T cells (53,54). Correspondingly, IL-15 significantly augments Ag-specific memory CD8⁺ T-cell responses and provides protective immunity to viral infection (47, 55-57) and bacterial and parasitic infections (58-60).

Senescent CD8⁺ T cells

Memory CD8⁺ T cells in an advanced stage of differentiation present senescent-like features, including the expression of senescence-associated cell surface (CD57 and KLRG1) and intracellular (p38 and γH2AX) molecules (61), low telomerase activity (62), and shortened telomeres (63). In addition, senescent CD8⁺ T cells are hypo-responsive to TCR stimulation and exhibit impaired TCR-mediated proliferation (64,65). On the other hand, compared to their non-senescent counterparts, senescent CD8⁺ T cells have a greater responsiveness to IL-15. IL-15 induces more robust proliferation in highly differentiated and senescent CD8⁺ T cells than their less differentiated counterparts (66). Therefore, IL-15 contributes to the generation and expansion of the senescent CD8⁺ T-cell population (64,67).

Recently, CD5 was shown to function as a negative regulator of the IL-15 response in memory CD8⁺ T cells (66). The expression of CD5 on human CD8⁺ T cells progressively decreases during cellular differentiation and senescence (68,69). Consequently, highly differentiated and senescent memory CD8⁺ T cells with low expression of CD5 exhibit a heightened responsiveness to IL-15, revealing an inverse correlation between the level of CD5 expression and IL-15 responsiveness. Further analysis showed that CD5 directly suppresses the IL-15-induced proliferation of human memory CD8⁺ T cells by inhibiting mTOR pathways (66).

Upon exposure to IL-15, memory CD8⁺ T cells typically acquire NK cell-like phenotypes and functions, including the upregulation of various NK receptors (NKRs) and cytotoxic molecules (70-72). IL-15 was shown to activate promyelocytic leukemia zinc finger (PLZF) transcription factor, which upregulates NKRs on memory CD8⁺ T cells (72). Senescent CD8⁺ T cells are characterized by enhanced NK cell-like functions mediated by NK-activating receptors (73). Sestrins are stress-sensing proteins produced in response to glucose deprivation, oxidative stress, or cellular senescence (74). Sestrins have been shown to promote senescence-associated features in CD8⁺ T cells, such as down-regulation of TCR-induced intracellular signaling molecules, including LAT, Zap70, and Lck (75). Moreover, sestrins upregulate the expression of NKG2D and its adaptor molecule DAP12, which trigger cytokine secretion and NKG2D-mediated cytotoxicity without TCR stimulation. This indicates that senescent CD8⁺ T cells are reprogrammed by sestrins as they differentiate and exert NK-like cytotoxic activity. Thus, the poor sensitivity to TCR signals and enhanced responsiveness to IL-15 render senescent CD8⁺ T cells sensitive to TCR-independent, IL-15-induced activation. This may explain the loss of immunity to previously encountered pathogens, decreased vaccine efficacy, and enhanced immunopathological tissue injury often demonstrated in aged individuals (73). Further work is required to elucidate the molecular mechanisms underlying IL-15 hyper-responsiveness and the resulting NK-like functions of senescent CD8⁺ T cells.

Virtual memory T cells (T_{VM})

Memory CD8⁺ T cells develop from naïve CD8⁺ T cells after encountering their cognate Ags (50). CD8⁺ T cells exhibiting memory-like characteristics can also develop during routine

T-cell homeostasis, referred to as T_{VM} cells (76). T_{VM} cells originate from naïve $CD8^+$ T cells and acquire memory-like characteristics without prior exposure to Ags (77). The development and maintenance of T_{VM} cells significantly depend on IL-15-mediated stimulation through CD122 (78). The transcription factor Eomes upregulates expression of CD122, which is essential for the T_{VM} cell response to IL-15. Notably, a significant reduction of T_{VM} cells was found in mice with a T cell-specific conditional deletion of Eomes (78). Moreover, IL-15 induces TCR-independent protective immunity mediated by NKG2D and granzyme B expression in T_{VM} cells, as demonstrated in a mouse model of *Listeria monocytogenes* infection (79).

In humans, the expression of inhibitory NKRs, killer cell immunoglobulin-like receptors (KIRs) and/or NKG2A, on $CD8^+$ T cells defines T_{VM} cells (79-81). $CD8^+$ T cells expressing KIR/NKG2A exhibit NK-like effector functions following stimulation with IL-12/IL-18 and/or IL-15, without TCR stimulation (80). The mutually exclusive expression of KIRs or NKG2A on human T_{VM} cells has been identified as an indicator of different functionalities (82). Specifically, KIR^+CD8^+ T cells express high levels of NKRs, such as 2B4, CD16, CD56, and NKG2C, compared to $NKG2A^+CD8^+$ T cells, together with perforin and granzyme B. In addition, KIR^+CD8^+ T cells exhibit enhanced responsiveness to IL-15 with higher levels of STAT5 phosphorylation compared to $NKG2A^+CD8^+$ T cells (81,82). IL-15 stimulation leads to the upregulation of CD107a, perforin, granzyme B, and CD16 and promotes the antibody-dependent cellular cytotoxicity of KIR^+CD8^+ T cells. These findings demonstrate that the IL-15 responsiveness differs among heterogenous human T_{VM} cells recognized by KIRs or NKG2A.

Tissue-resident memory $CD8^+$ T cells (T_{RM})

T_{RM} cells are a long-lasting, non-circulating population that establishes residence in the tissue (83). T_{RM} cells have the capacity to rapidly provide on-site immune responses against invading pathogens by not only degranulating perforin and granzyme B, but also producing cytokines, such as IFNγ and TNF, that effectively coordinate both local innate and adaptive immune cells (84,85). T_{RM} cell formation begins with the initial induction of T_{RM} precursor cells into epithelial tissues. The local cytokine environment consists of TGFβ and IL-15, promoting the residence and development of these cells into long-lived T_{RM} cells (86). IL-15 plays a crucial role in preserving T_{RM} cells across diverse tissues, including the skin, liver, salivary glands, lungs, and kidneys (87-90). However, certain T_{RM} subsets located in non-lymphoid tissues, such as the female reproductive tract, pancreas, and small intestines, can persist without IL-15 (89). Nevertheless, though some T_{RM} populations may not depend on IL-15 for their maintenance, these cells still undergo proliferation in response to IL-15 (91).

NKR-expressing $CD8^+$ T cells

Subpopulations of $CD8^+$ T cells express NKRs such as NKG2C (92). The expansion of NKG2C-expressing $CD8^+$ T cells have been observed in response to various pathological conditions, including cytomegalovirus (CMV) infection, Stevens-Johnson syndrome, toxic epidermal necrolysis, and celiac disease (92). $NKG2C^+CD8^+$ T cells expressing high levels of cytotoxic molecules have been shown to effectively lyse target cells upon co-stimulation with anti-CD94 and anti-CD3 Abs (71,93). However, another study reported that, even in the absence of TCR stimulation, the ligation of NKG2C alone can trigger T cells to proliferate and eliminate HLA-E-transfected target cells lacking expression of other MHC-I molecules (94). This suggests that NKG2C signaling may serve as a potential alternative to TCR-mediated activation of $CD8^+$ T cell cytotoxicity.

NKR-expressing $CD8^+$ T cells exist at a higher frequency in the liver than the peripheral blood (95). Recent advancements in multi-omics analysis have investigated the diverse subgroups of liver sinusoidal $CD8^+$ T cells that express NKRs. A specific NK-like $CD8^+TCR\alpha\beta^+$ liver sinusoidal T-cell population characterized by high expression of CD56 without CD161 expression ($CD56^{hi}CD161^-CD8^+$ T cells) was found to express various NKRs, including CD94, KIRs, and NKG2C (96). In addition, this population exhibits hyper-responsiveness to IL-15, IL-12, and IL-18 but weak responsiveness to TCR stimulation. Upon stimulation with IL-15, in addition to both IL-12 and IL-18, these $CD56^{hi}CD161^-CD8^+$ T cells expand and exert NK-like effector functions through NKG2D and NKG2C in a TCR-independent manner (96). Further investigation is required to elucidate the precise role and regulatory mechanisms of $CD56^{hi}CD161^-CD8^+$ T cells in various types of disease, particularly in relation to IL-15.

Innate-like, unconventional T cells

Beyond its role in conventional $CD8^+$ T cells, IL-15 also plays a critical role in homeostasis and effector functions of innate-like unconventional T cells including mucosal-associated invariant T cells (MAIT) and γδ T cells (97). MAIT cells recognize intermediates of riboflavin (microbial vitamin B2 metabolites) biosynthesis, presented on class I-related molecule 1 (MR1) on Ag-presenting cells, through semi-variant TCRs composed of Vα 7.2-Ja33, 12, or 20 with limited TCR Vβ diversity (98). IL-15 activates mTORC1 and upregulates T-bet, inducing proliferation and maintenance of MAIT cells (99). In addition, IL-15, in combination with IL-12 or IL-18, can activate MAIT cells to produce IFNγ and granzyme B in a STAT5-dependent manner (100,101).

The γδ T cells express lineage-specific γδ TCR and share numerous characteristics with αβ T cells in terms of cytotoxic effector functions and pro-inflammatory cytokine production (102). However, γδ T cells do not rely on MHC molecules. This MHC-independent property involves the recognition of both exogenous and endogenous Ags, encompassing both foreign and self-Ags (103,104). IL-15 plays a pivotal role in proliferation and homeostasis of γδ T cells (105). γδ T cells sensitized by IL-15 were shown to maintain the expression of Mcl-1 following the activation of STAT5 and ERK for promoting cell survival against apoptosis (106). Moreover, IL-15 has been shown to activate γδ T cells and enhance their anti-tumor immune response (102,106,107).

IL-15 PROMOTES $CD8^+$ T CELL-MEDIATED ANTI-TUMOR IMMUNE RESPONSES

IL-15 can enhance the anti-tumor immune response of $CD8^+$ T cells (108). Previous studies in mouse tumor models demonstrated that IL-15 treatment increases the number of tumor-infiltrating $CD8^+$ T cells and their IFNγ production (109,110). In addition, IL-15 has been shown to improve the $CD8^+$ T-cell response to immune checkpoint blockade. IL-15 reinvigorated tumor-infiltrating $CD28^-PD\text{-}1^+CD8^+$ T cells that are unresponsive to PD-1 blockade in non-small cell lung cancer (NSCLC) (111). IL-15 also plays a crucial role in the self-renewal of progenitor exhausted $TCF\text{-}1^+PD\text{-}1^+CD8^+$ T cells, which are characterized by stem-like properties and associated with a more favorable response to PD-1 blockade (112).

Various forms of IL-15 have been developed as immunotherapeutic agents and are presently undergoing clinical trials in combination with anti-PD-1 Abs for the treatment of cancer patients (113-115). N-803 (formerly known as ALT-803) is a superagonist complex consists

of an IL-15 mutant bound to a bivalent IL-15Rα sushi domain and IgG1-Fc fusion protein (116). N-803 has been recognized as a potent inducer of the activation, proliferation and cytotoxicity of $CD8^+$ T cells and NK cells, thereby conferring anti-tumor efficacy in preclinical models including breast cancer (117), colon cancer (116) and glioblastoma (110). N-803 is currently being evaluated in several ongoing clinical trials (118). Results from the recent clinical trials demonstrated that N-803 yielded promising responses with a tolerable safety profile when used in patients with NSCLC (113) and bladder cancer (119). IL-15 has also been integrated in chimeric Ag receptor T cell (CAR-T) engineering for the treatment of cancer through adoptive cell therapy. CAR-T cells expanded *ex vivo* with IL-15 exhibit a less differentiated phenotype, reduced expression of exhaustion and pro-apoptotic molecules, and enhanced mitochondrial metabolism, with administration resulting in a stronger anti-tumor response (120-123).

IL-15 has been shown to activate tumor-infiltrating bystander memory $CD8^+$ T cells. A considerable portion of memory $CD8^+$ T cells present within tumor infiltrates is specific for tumor-unrelated viruses, such as CMV and Epstein-Barr virus (EBV) (124). Though tumor-specific $CD8^+$ T cells typically express CD39, bystander $CD8^+$ T cells within tumor tissues lack CD39 expression. IL-15-induced activation of memory $CD8^+$ T cells has been shown to contribute to the anti-tumor immune response via an NKG2D-dependent mechanism, enhancing tumor control even in the absence of cognate Ag recognition (125).

IL-15-INDUCED T CELL-MEDIATED IMMUNOPATHOGENESIS

Viral infection

IL-15 has been shown to activate memory $CD8^+$ T cells to proliferate and exert effector functions in the absence of TCR stimulation (126). During viral infection, the upregulation of IL-15 triggers bystander activation of memory $CD8^+$ T cells (8,127). IL-15 induces polyclonal expansion of bystander memory $CD8^+$ T cells with a highly diverse TCR repertoire (128). Though several studies have reported a protective effect (129-131), a significant number of studies have demonstrated a detrimental effect of IL-15-induced bystander activation of memory $CD8^+$ T cells, leading to host tissue damage during microbial infections (95,132-137).

The pathological contribution of IL-15-drvien bystander-activated memory $CD8^+$ T cells is well described in acute hepatitis A virus (HAV) infection (**Fig. 2**). In adults, acute HAV infection often causes severe liver injury (138). During acute HAV infection, independent of TCR, elevated IL-15 activates pre-existing memory $CD8^+$ T cells specific for HAV-unrelated viruses, such as human CMV, EBV, influenza A virus (IAV), respiratory syncytial virus, and vaccinia virus (133). These bystander-activated memory $CD8^+$ T cells express increased levels of NK cell-activating receptors (NKG2D and NKp30) and cytotoxic molecules (perforin and granzyme B), as well as activation markers (CD38 and HLA-DR) and proliferation marker Ki-67. In addition, IL-15 upregulates chemokine receptor CCR5 via ERK signaling pathway, facilitating the migration of bystander-activated memory $CD8^+$ T cells to the infected liver during acute HAV infection (134). This finding aligns with previous studies indicating that IL-15 promotes the migration of memory $CD8^+$ T cells to the infection site without antigenic stimulation (139-141). In the HAV-infected liver, bystander-activated memory $CD8^+$ T cells exert NKG2D-dependent NK-like cytotoxicity and kill hepatocytes expressing NKG2D ligands (133). This NK-like cytotoxicity significantly correlates with liver damage in patients with acute HAV infection, indicating the presence of IL-15-induced immunopathological mechanisms

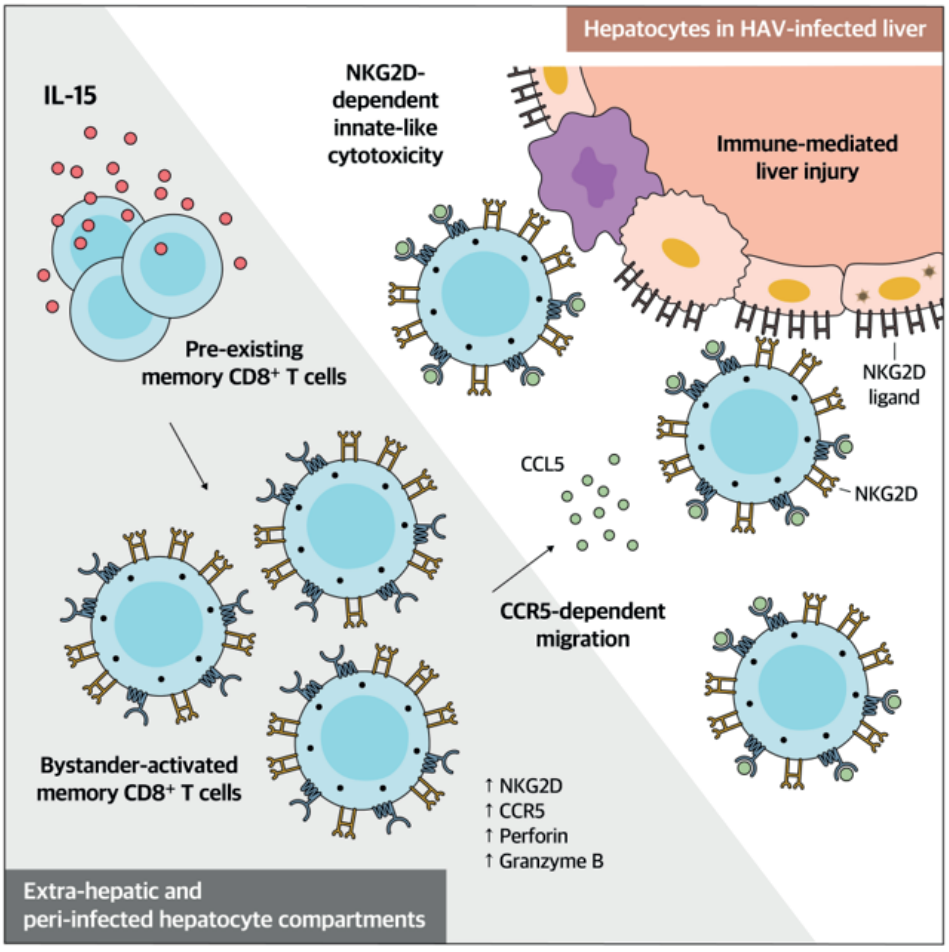

Figure 2. Bystander-activated memory CD8⁺ T cells induced by IL-15 contribute to liver damage during acute HAV infection.
During acute HAV infection, elevated IL-15 activates pre-existing memory CD8⁺ T cells that are specific for HAV-unrelated viruses, independent of TCR engagement. This IL-15-induced bystander activation of memory CD8⁺ T cells occurs both outside the liver and in the areas surrounding infected hepatocytes (left). These bystander-activated memory CD8⁺ T cells express upregulated NKG2D and CCR5. Bystander-activated memory CD8⁺ T cells migrate into the HAV-infected liver via a CCR5-dependent mechanism (right). Within the HAV-infected liver, NKG2D triggers NK-like cytotoxicity against hepatocytes expressing NKG2D ligands. Notably, in patients with acute HAV infection, the NK-like cytotoxicity of bystander-activated memory CD8⁺ T cells significantly correlates with liver injury, as reflected by the level of ALT in serum.
ALT, alanine transaminase.

performed by bystander-activated memory CD8⁺ T cells. Similarly, this NK-like cytotoxic attribute driven by IL-15 has been also observed in MAIT cells (142), the most prevalent innate-like T cells in human liver (100). In the absence of a TCR-MR1 interaction, the combination of IL-15 with IL-12 and IL-18 upregulates of NKG2D, granzyme B, and CD2 in a PI3K-mTOR signaling-dependent manner (142). Subsequently, MAIT cells kill hepatocytes through NK-like cytotoxicity which is associated with severe liver damage in patients with acute HAV infection.

Importantly, though IL-15 upregulates surface expression of NKG2D and CCR5 on memory CD8⁺ T cells, TCR stimulation has no impact on these markers (133,134). Interestingly, concurrent TCR stimulation abrogates the IL-15-induced upregulation of NKG2D and CCR5. Therefore, the upregulation of NKG2D and CCR5 serves as a marker of IL-15-induced bystander activation of memory CD8⁺ T cells (143). Consistent with this, IFN-induced transmembrane protein 3

(IFITM3) has been recognized as an indicator of IL-15-induced bystander activation of memory $CD8^+$ T cells in a murine model of IAV infection (144). This suggests that IL-15 promotes innate-like features, whereas TCR stimulation is responsible for preserving the intrinsic adaptive nature of memory $CD8^+$ T cells. However, the regulatory mechanisms underlying IL-15-induced bystander activation in memory $CD8^+$ T cells have not been fully elucidated yet.

Chronic inflammatory diseases

Overexpression of IL-15 is associated with pathology in various chronic inflammatory diseases (7). The pathological contribution of TCR-independent, IL-15-induced upregulation of NKG2D on $CD8^+TCR\alpha\beta^+$ intraepithelial lymphocytes (IELs) has been demonstrated in celiac disease (145). In celiac disease, intestinal epithelial cells overexpress IL-15 and the NKG2D ligand MHC class I polypeptide-related protein (MICA) (146). Dysregulated IL-15 production upregulates NKG2D on $CD8^+TCR\alpha\beta^+$ IELs in the absence of TCR stimulation, and they contribute to intestinal-tissue damage through NK-like killing activity (145).

The intestinal mucosa serves as a primary site for extrathymic lymphopoiesis of γδ T cells, often referred to as γδ intestinal IELs (147). The homeostatic proliferation of γδ IELs is mainly induced by the IL-15 produced by adjacent epithelial cells (148). γδ IELs exhibit NK-like features, responding rapidly and consistently to tissue alarmins and stress-induced ligands of NKRs without requiring Ag recognition (149). Although γδ IELs play a critical role in mucosal protection, dysregulated activation of γδ IELs can exacerbate inflammation and contribute to the progression of intestinal diseases (150,151). Interestingly, the Ikaros zinc finger (IKZF) transcription factor Aiolos has been identified as a regulator that suppresses expression of NKRs, cytotoxic molecules, and chemokines in γδ IELs (9). This Aiolos-induced regulatory mechanism involves a partial attenuation of IL-15 signaling in γδ IELs and has been shown to ameliorate colitis in a mouse model. As unrestricted IL-15 production can lead to T cell-mediated tissue damage, the Aiolos-mediated regulation of IL-15 signaling is crucial for maintaining intestinal homeostasis. Further investigation into other regulatory factors suppressing IL-15 signaling, as well as the expression of NKRs and cytotoxic mediators (43-46,66) that may contribute to tissue damage and disease pathogenesis, is warranted. These could serve as promising therapeutic targets for alleviating IL-15-induced T cell-mediated immunopathological tissue damage.

The TCR-independent, IL-15-induced NK-like cytotoxicity of effector memory $CD8^+$ T cells was also shown to contribute to the pathogenesis of alopecia areata (152). IL-15 was shown to expand T_{VM} cells expressing remarkably high levels of CD44 and lacking CD49d ($CD44^{s\text{-}hi}CD49d^{lo}$), which cause alopecia areata in a mouse model (153). IL-15 upregulated NKG2D and cytotoxic molecules in $CD44^{s\text{-}hi}CD49d^{lo}$ T_{VM} cells and facilitated their migration to the cutaneous tissues. Here, the local expression of IL-15, IL-12, and IL-18, as well as NKG2D ligands, leads to the damage of hair follicles by $CD44^{s\text{-}hi}CD49d^{lo}$ T_{VM} cells through their NKG2D-dependent killing activity. This finding was further supported by effectively controlling disease progression through the administration of blocking Abs targeting CD122, IL-12, and IL-18 or NKG2D in the mouse model (153).

Interestingly, a study reported that germline STAT3 gain-of-function mutations in mice induce CD122-dependent expansion of $CD8^+$ T cells, which contribute to the autoimmune-like pathology (154). These expanded $CD8^+$ T cells were characterized by the upregulation of NKG2D and effector molecules (IFNγ, granzymes, and perforin), and their accumulation significantly correlated with the development of autoimmune-like pathology.

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In non-alcoholic steatohepatitis (NASH), IL-15 drives hepatic accumulation of CXCR6^{+}CD8^{+} T cells, which cause liver damage (155). During NASH, uncontrolled production of IL-15 in the liver down-regulates FOXO1, rendering liver-resident CXCR6^{+}CD8^{+} T cells susceptible to metabolic stimuli, including acetate and extracellular ATP. Upon exposure to acetate, liver-resident CXCR6^{+}CD8^{+} T cells upregulate granzyme B expression and TNF production to become auto-aggressive CD8^{+} T cells. With subsequent exposure to extracellular ATP, which signals through P2X7 purinergic receptor, auto-aggressive CD8^{+} T cells kill hepatocytes in an MHC-I-independent, Fas ligand-dependent manner, contributing to the liver damage in NASH (155). Further research to elucidate the mechanisms underlying uncontrolled IL-15 production and how IL-15 reprograms T cells to acquire pathological functions could support the identification of therapeutic targets for ameliorating T cell-mediated tissue injury.

CONCLUSION

In summary, IL-15 is essential for the homeostasis and effector functions of T cells. However, dysregulated IL-15 production can trigger TCR-independent, NK-like activation of T cells that contributes to immunopathological tissue damage (**Fig. 3**). Although significant progress has been made in demonstrating the pathological contribution of IL-15, further investigations are

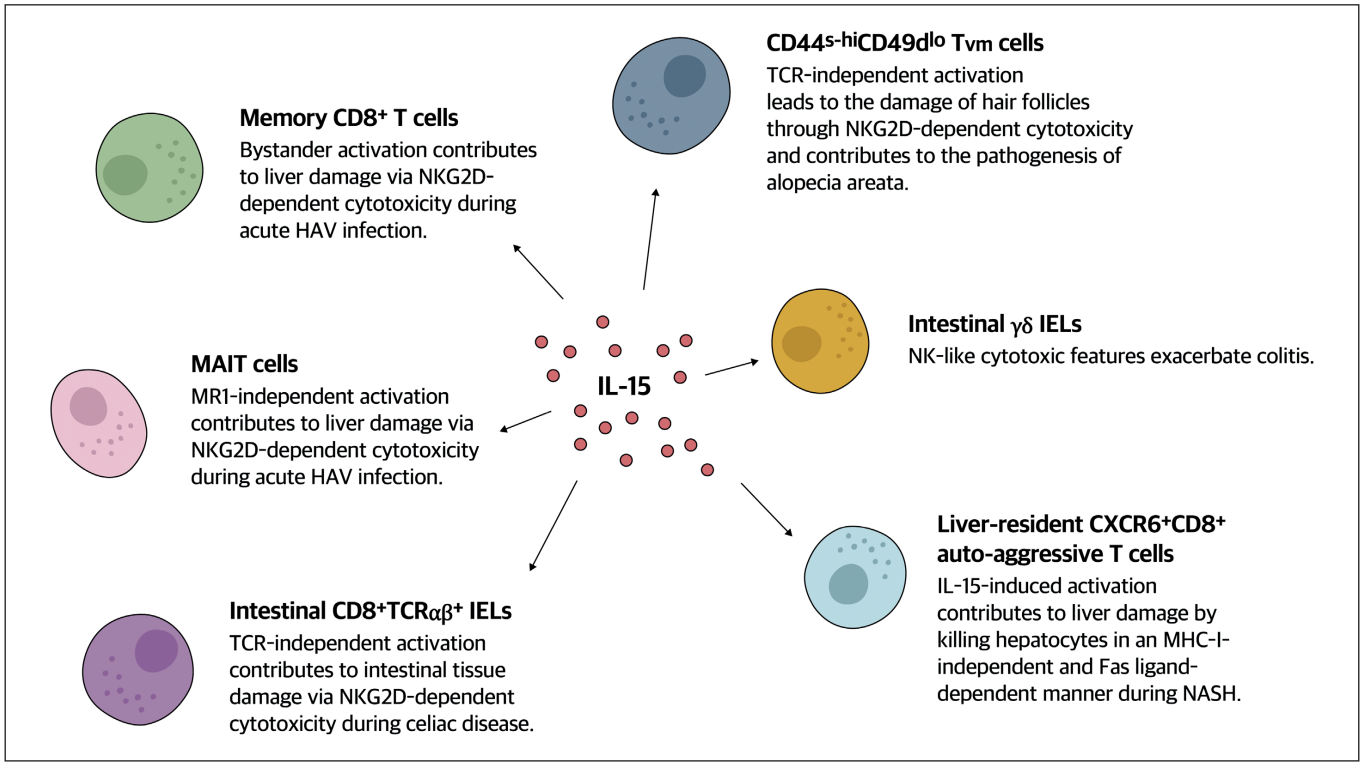

Figure 3. IL-15-induced T cell-mediated immunopathogenesis in various diseases.
Dysregulated production of IL-15 triggers TCR-independent and NK-like cytotoxicity of T cells that contributes to immunopathological tissuse damage in various diseases. IL-15 activates bystander memory CD8^{+} T cells to kill hepatocytes in an NKG2D-dependent manner, leading to severe liver injury during acute HAV infection. This IL-15-induced immunopathological liver injury was also induced by MR1-indpendent activation of MAIT cells during acute HAV infection. IL-15 activates intraepithelial intestinal CD8^{+} T cells independenly of TCR signaling to exert inestinal tissue damage through NKG2D-dependent cytotoxicity during celiac disease. IL-15 activates CD44$^{s\text{-}hi}$CD49d^{lo} T_{VM} cells to damage hair follicle cells through NKG2D-dependent cytotoxicity, contributing to alopecia areata pathogenesis. IL-15 upregulates NK-like feuatures of γδ intestinal intraepithelial lymphocytes that contribute to the pathogenesis of colitis. IL-15 drives hepatic accumulation of CXCR6^{+}CD8^{+} auto-aggressive T cells, which contribute to liver damage by killing hepatocytes in an MHC-I-independent and Fas ligand-dependent manner during NASH.

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required to explore T cell-mediated immunopathogenesis in various diseases, encompassing those not yet thoroughly examined. Moreover, it is necessary to determine the specific types of T cells that exhibit the most pronounced responsiveness to IL-15 and play a significant role in inducing immunopathology in each distinct disease. Furthermore, the molecular mechanisms underlying IL-15-induced T cell-mediated immunopathogenesis remain poorly understood. Therefore, it is crucial to gain further insights into the regulatory mechanisms involved in IL-15-induced T-cell activation. These insights will shed light on therapeutic targets to alleviate immunopathology observed in various infectious diseases and chronic inflammatory diseases.

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