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IL-15: a central regulator of celiac disease immunopathology

Valérie Abadie¹ and Bana Jabri^{2,3}

¹Sainte-Justine Hospital Research Centre, Department of Microbiology and Immunology, Faculty of Medicine, University of Montreal, Montreal, Canada

²Department of Pediatrics, University of Chicago, Chicago, IL, USA

³Department of Medicine and Department of Pathology, University of Chicago, Chicago, IL, USA

Summary

Interleukin-15 (IL-15) exerts many biological functions essential for the maintenance and function of multiple cell types. Although its expression is tightly regulated, IL-15 upregulation has been reported in many organ-specific autoimmune disorders. In celiac disease, an intestinal inflammatory disorder driven by gluten exposure, the upregulation of IL-15 expression in the intestinal mucosa has become a hallmark of the disease. Interestingly, because it is overexpressed both in the gut epithelium and in the *lamina propria*, IL-15 acts on distinct cell types and impacts distinct immune components and pathways to disrupt intestinal immune homeostasis. In this article, we review our current knowledge of the multifaceted roles of IL-15 with regards to the main immunological processes involved in the pathogenesis of celiac disease.

Keywords

IL-15; celiac disease; tissue; autoimmunity; cytotoxic T cells; loss of oral tolerance

Introduction

Since its discovery in 1994 (1–3), the role of IL-15 has expanded tremendously from a T-cell growth factor to pleiotropic cytokine that acts on virtually each cell type of the innate and adaptive immune system. For a long time, IL-15 was viewed as a cytokine that primarily plays a role in immune homeostasis, namely in NK cell and memory CD8⁺ T-cell homeostasis. However, the fact that multiple reports depict the overexpression of IL-15 in tissues targeted by autoimmune processes poses the question of whether IL-15 may play a role in tissue immunity and be implicated in the development of organ-specific autoimmune disorders. Celiac disease (CD) is a T-cell-mediated intestinal disorder induced by dietary gluten that is a unique disease model to study the pathogenesis of autoimmune disorders in humans. Since IL-15 was first proposed to play a key role in CD pathogenesis (4–6), numerous studies have confirmed its role in multiple phases of the disease and expanded its impact on multiple cell types and immunological responses. In this review, we discuss the

Correspondence to: Bana Jabri, Departments of Medicine, Pathology and Pediatrics, University of Chicago, KCBD, 900 East 57th Street, MB#9, Chicago, IL 60637, USA, Tel: + 1 773 834 8670, Fax: +1 773 702 2281, bjabri@bsd.uchicago.edu.

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role of IL-15 in the pathogenesis of organ-specific autoimmunity using CD as a model, but first we highlight some general key features of IL-15 biology and CD pathogenesis.

Overview of IL-15 biology

IL-15 signaling and expression

IL-15 belongs to the family of Type I cytokines encompassing IL-2, IL-4, IL-7, IL-9, IL-21, and IL-15 (7–9). It shares the γ c chain (CD132) of its heterotrimeric receptor with all members of the γ c family cytokines (10) and the β chain (IL-2/15R β or CD122) with IL-2 (11). The interaction of IL-15 with IL-2/15R β chain and γ c chain leads to the phosphorylation of Jak1 and Jak3, respectively, and to the activation of STAT5 (12–14). The Jak-STAT signaling pathway supports T-cell and natural killer (NK) cell homeostasis and expansion. In addition, IL-15 triggers other signaling pathways in T lymphocytes by promoting the phosphorylation of the Src family cytoplasmic tyrosine kinases, Lck and Syk (15–17), and by activating the phosphatidylinositol-3-kinase (PI3K), the kinase AKT (18, 19) and the Ras/Raf/MEK/mitogen-activated protein kinase (MAPK) (20–23) pathways that lead to mitogenic and anti-apoptotic signals (reviewed in 24). Unlike IL-2, IL-15-driven proliferation of T lymphocytes requires FKBP12 (12-Kda FK506-binding protein)-mediated p70S6 kinase (25). In addition, the recruitment of TRAF2 and Syk to the cytoplasmic tail of IL-15R α chain has been shown to mediate IL-15 signaling in fibroblasts and neutrophils (26, 27).

IL-15 is a unique cytokine, because it is not secreted and can be upregulated on the surface of all cell types under conditions of inflammation and stress. Its expression on the cell surface requires the ‘private’ IL-15R α chain. IL-15 is bound to IL-15R α intracellularly during synthesis in the endoplasmic reticulum, shuttled to the surface, and is presented in *trans* to responder cells expressing the other IL-15R subunits, IL-15R β and γ c; thus, IL-15 signaling acts in a cell contact-dependent manner (28–30). IL-15R α stabilizes binding and greatly enhances the affinity of IL-15 for IL-2R β (31). Although IL-15 transpresentation represents the main mechanism by which IL-15 interacts with its receptor *in vivo*, alternative mechanisms have been proposed. For instance, *cis*-presentation represents another mechanism that involves soluble IL-15 binding to IL-15R α allowing signaling of adjacent IL-2R β / γ c on the same cell (32–34). Murine and human IL-15 and IL-15R α can exist not only in membrane bound but also in a soluble form. Thus, the abundance of soluble IL-15R α /IL-15 complexes that are cleaved from the surface of cells (35–37) suggests that IL-15 complexed to IL-15R α could also mediate IL-15 responses. Nevertheless, it still remains unclear whether *cis*-presentation or stimulation by soluble IL-15R α /IL-15 complexes are active mechanisms *in vivo* (38). Expression of IL-15 is tightly regulated at the level of transcription, translation, and intracellular trafficking, avoiding excessive protein production and secretion (39). The translation of IL-15 mRNA into protein is limited by the presence of multiple AUG initiation sites in the 5'-UTR region, a long signal peptide, and a negative regulatory element in the C-terminus of the IL-15 mature protein coding sequence (39, 40). Alternative splicing also controls IL-15 expression. Distinct IL-15 isoforms encoding the same mature protein that use different signal peptides are generated by alternative splicing. These different signal peptides drive the trafficking of IL-15 to distinct

intracellular compartments where IL-15 isoforms are differentially translated (41–45). However, it is unknown whether expression of IL-15 isoforms contributes to tissue-specific regulatory functions. In addition, multiple isoforms of IL-15R α contribute to IL-15 regulation. Splice variants of IL-15R α in human monocytes and dendritic cells have been shown to determine the mode of action of IL-15, by either preventing the release of IL-15/IL-15R α heterodimers from cell membranes thereby favoring transpresentation, or by promoting the release of IL-15 as a soluble secreted cytokine that can act on neighboring cells in a paracrine fashion (46). Therefore, IL-15 expression is fine-tuned at multiple levels to ensure that the cytokine can undertake its numerous functions. The fact that IL-15 acts mostly in a cell contact-dependent manner and that IL-2 preferentially signals via the high affinity IL2R α -IL2R β - γ c receptor may explain why these two cytokines that share a common signaling model yet promote different, and even opposing, outcomes. For instance, it is striking to note that inflammation and autoimmunity are associated with IL-2 deficiency (47–50) but that a dysregulated increase in IL-15 expression is observed in many inflammatory autoimmune diseases (51).

Both stromal cells and antigen-presenting cells mediate IL-15 transpresentation depending on the tissue of residence, their location within the tissue, and the responder cell (38). IL-15 expression by both hematopoietic cells and non-hematopoietic cells, i.e. medullary thymic epithelial cells, hepatic stellate cells and bone marrow stromal cells, is involved in the development and survival of naive CD8⁺ T cells, invariant NKT cells, and NK cells (52–58). Macrophages and dendritic cells are critically involved in IL-15 transpresentation to memory CD8⁺ T cells, hepatic invariant NKT cells, and differentiated NK cells (35, 52, 59–65). Thus, distinct stages of lymphocyte differentiation require IL-15 transpresentation by different cell types, which include both hematopoietic and non-hematopoietic cells (38).

In the gut, IL-15 expression is influenced by innate immune signaling. Indeed, TLR4 activation was shown to upregulate IL-15 on dendritic cells (35), and intestinal epithelial cells (IECs) require MyD88 for the expression of IL-15 and to promote the maintenance of intraepithelial lymphocytes (IELs) in an IL-15-dependant manner (66). This suggests that the microbiota, in the absence of overt inflammation, could continuously stimulate MyD88 signaling and hence contribute to the constitutive intestinal expression of IL-15 during steady state conditions. Furthermore, it has been suggested that Nod2 signaling might maintain the expression of IL-15 via recognition of the microbiota, as reduced IL-15 expression contributes to the loss of IELs in NOD2-deficient mice (67). Finally, consumption of a diet high in polyunsaturated fat leads to a decrease in IL-15 expression and concomitant reduction in IELs (68). Nevertheless, whether a direct association exists between diet, microbiota, and IL-15 expression has yet to be determined.

Role of IL-15 in immune homeostasis

The critical multifaceted roles of IL-15 during immune homeostasis are well established. IL-15 regulates adaptive memory CD8 $\alpha\beta$ TCR $\alpha\beta$ T cells, as well as innate and innate-like lymphocytes. Its role in B-cell biology under physiological conditions is still under investigation.

Extensive characterization of mice deficient in IL-15 or in its private receptor α chain (IL-15R α) demonstrated that IL-15 is required for the development, maintenance, and expansion of memory CD8 $^{+}$ T cells (38, 69–76), NK cells (77), and invariant NKT cells (49, 63, 70, 72, 78). IL-15 promotes the survival of CD8 $^{+}$ T cells by increasing the expression of the anti-apoptotic molecule Bcl-2 (79). In addition to its extensive role in promoting cell development and survival, it has been shown that IL-15 induces iNKT and NK cells activation (35, 53, 80–84) and increases the cytotoxicity of NK cells (85).

IELs in the small intestine represent a heterogeneous population of T cells composed mainly of TCR $\alpha\beta$ and TCR $\gamma\delta$ CD8 $^{+}$ T cells residing within the intestinal epithelium whose main role is to maintain the integrity of the epithelial layer by eliminating infected cells and promoting epithelial repair (86). In mice, IL-15 and IL-15R α expression on intestinal epithelial cells (IECs) was shown to be critical for the survival and development of innate-like T-cell lymphocytes, i.e. CD8 $\alpha\alpha^{+}$ TCR $\alpha\beta^{+}$ T cells and TCR $\gamma\delta^{+}$ T cells (38, 49, 63, 64, 70, 72, 87–89). Furthermore, TCR $\gamma\delta^{+}$ IELs were also shown to be expanded in transgenic mouse models where IL-15 is overexpressed in IECs (90). The mechanism underlying IL-15-mediated survival of unconventional IELs involves the activation of the Jak3-Jak1-PI3K-Akt-ERK pathway to upregulate Bcl-2 and Mcl-1 (79, 88, 91, 92). Additionally, it has been suggested that IL-15 can regulate the generation of the restricted TCR variable gamma-region gene repertoire of TCR $\gamma\delta^{+}$ IELs (93), yet the exact role that IL-15 plays on $\gamma\delta$ T cells is unclear. IL-15 does not seem to be critical for the survival of TCR $\alpha\beta^{+}$ CD8 $\alpha\beta^{+}$ T cells whose numbers are maintained in the absence of IL-15R α (72, 88). The limited expression of IL-2/15R β expression on CD8 $\alpha\beta$ T cells that reside within the intestinal epithelium could provide an explanation as to why IL-15 is less critical for this subset of IELs in mouse (38), yet the signals required for the survival of this subset of IELs remain to be determined. Nevertheless, it was shown that human CD8 $\alpha\beta^{+}$ IELs respond to IL-15 and its presence increases their cytolytic properties (6, 94, 95) and upregulates the expression of NK receptors (5, 6, 96), suggesting that IL-15 may impact on CD8 $\alpha\beta^{+}$ IELs function under inflammatory conditions. Furthermore, it was shown that TCR $\gamma\delta^{+}$ IELs are expanded in intestinal organ cultures treated with IL-15 (97). IL-15 has also been recently implicated in the activation of human intraepithelial Type 1 innate lymphoid cells by promoting the production of IFN- γ (98). This latter observation is in line with the critical protective role played by IL-15 in defense mechanisms against invading pathogens, especially in the gut (99, 100). Although mice deficient in IL-15 or IL-15R α exhibit normal numbers of B lymphocytes (70, 72, 101), *in vitro* studies also suggest that IL-15 can modulate B-cell activities by promoting the differentiation and proliferation of activated human B cells as well as immunoglobulin production (102, 103). Finally, besides its wide range of activities on lymphocytes, IL-15 has an impact on dendritic cells, neutrophils, and mast cells by preventing their apoptosis (104–107).

IL-15 overexpression in organ-specific autoimmune disorders other than celiac disease

In accordance with its essential role in regards to the control of immune homeostasis, IL-15 expression is tightly regulated at the translational, transcriptional, and intracellular trafficking levels and coordinated with cellular fate in myeloid vs. lymphoid cells (39, 108). Removal of these control mechanisms results in abnormal IL-15 expression in multiple cell

types, whose detrimental impact is exemplified in many autoimmune disorders and chronic inflammatory diseases. More specifically, IL-15 is upregulated in tissue cells that are targeted by an autoimmune process such as rheumatoid arthritis (109–114), multiple sclerosis (115, 116, 120), psoriatic arthritis or psoriasis (117–119), systemic lupus erythematosus (121–123), and type-1 diabetes (124). Furthermore, increased levels of IL-15 and/or IL-15-IL15R α complexes have also been documented in the serum of patients with systemic lupus erythematosus (121, 123) or type-1 diabetes (124, 125). There is also dysregulated expression of IL-15 and IL-15R α in the mucosal tissues of patients with inflammatory bowel disease (IBD) (126–130).

Mechanisms invoked to explain the role of IL-15 in organ-specific autoimmune disorders involve facilitating the maintenance of CD8⁺ memory T-cell survival including that of self-reactive memory T cells (9, 51), bystander activation with secretion of additional inflammatory cytokines by neighboring cells (51), activation of B cells (129), and upregulation of the activating NK receptor on CD8⁺ T cells (5, 6, 96, 131) and CD4⁺ T cells (132, 133).

Overview of celiac disease

CD is an inflammatory disorder with autoimmune features that occurs in genetically susceptible individuals expressing HLA-DQ2 or HLA-DQ8 molecules. CD patients develop inflammatory T-cell and antibody responses against dietary gluten, a protein present in wheat, rye, and barley (134). In addition, CD patients develop autoantibodies specific for the enzyme tissue transglutaminase (TG2). The disease is the ‘tip of an iceberg’ that includes a much larger undiagnosed population with various aspects of dysregulation of adaptive and innate immunity in response to gluten (135). The typical histopathological picture of CD is a small intestine enteropathy that is characterized by crypt hyperplasia, a massive increase in IELs, and villous atrophy as a consequence of surface IEC destruction. CD can be classified as classical or potential, depending on the presence of histological abnormalities in duodenal biopsies (136). Potential CD is defined by the presence of inflammatory anti-gluten immune response and anti-TG2 antibodies in the absence of villous atrophy, and therefore represents an incomplete, less severe form of CD. In contrast, classical active CD is characterized by the presence of villous atrophy (4, 137, 138), even though the identification of mucosal abnormalities upon intestinal biopsy is no longer required for diagnosis when anti-TG2-antibodies are detected (136). Withdrawal of gluten from the diet is classically associated with normalization of serology and progressive recovery of villous structures (139–143). However, while full recovery tends to occur in children with CD, more than 40% of adult CD patients maintain some level of histological anomalies on a gluten free diet (GFD) (144, 145). Furthermore, despite adherence to GFD, adult CD patients can develop a severe complication called refractory celiac disease (RCD), viewed as an early stage of enteropathy-associated T-cell lymphoma and characterized by severe villous atrophy and the presence of IELs with an abnormal phenotype (146–149).

IL-15 expression in celiac disease

The chronic upregulation of IL-15 in the epithelium (5, 150) and in the intestinal *lamina propria* (LP) (150, 151) is a hallmark of the disease and correlates with the degree of mucosal damage (152). Interestingly, the pattern of IL-15 overexpression differs between potential CD patients, active CD patients, and patients undergoing GFD. While most active CD patients have increased levels of IL-15 both in the intestinal LP and in the epithelium (Fig. 1), IL-15 is not upregulated in IECs in potential CD patients (authors' unpublished data), potentially suggesting that it may be required for development of villous atrophy. Conversely, a high number of CD patients on a GFD maintain high levels of IL-15 expression in the epithelium (Fig. 1), suggesting that dysregulated expression of IL-15 in the epithelium is insufficient to induce villous atrophy. We discuss below, how, according to its location, IL-15 impacts distinct immune components and pathways to disrupt intestinal immune homeostasis.

Role of IL-15 in celiac disease pathogenesis

Because it is upregulated both in the epithelium and in the LP, IL-15 acts on distinct cell types and promotes the dysregulation of multiple immune mechanisms in the small intestine that together contribute to CD pathogenesis (Fig. 2).

Role of IL-15 in loss of oral tolerance

Gluten is a unique protein due to its high content in proline and glutamine residues, and therefore it is a very good substrate for TG2. Prolines prevent gluten from being digested by intestinal enzymes (153), and the presence of a high frequency of glutamines and their spacing with proline (154), make the glutamines within gluten a good target for deamidation by TG2. Hence, the unique amino-acid composition of gluten allows for the generation of long peptides with negative charges that have a relatively high affinity for CD-predisposing HLA-DQ2 (155) and HLA-DQ8 (156), when TG2 is activated (157). However, the generation of peptides able to bind to HLA-DQ2 and HLA-DQ8 does not explain why inflammatory and not regulatory T-cell responses are induced. Indeed, unlike in healthy individuals where regulatory mechanisms allow the intestinal immune response to remain unresponsive to innocuous food antigens [an active process called oral tolerance (158)], CD patients exhibit a loss of oral tolerance manifested by HLA-DQ2 or HLA-DQ8-restricted anti-gluten inflammatory CD4⁺ T cells secreting interferon- γ (IFN- γ) and IL-21 in the small intestinal mucosa (159–162). Because IL-15 has pro-inflammatory properties and is highly upregulated in the LP of CD patients (150, 151), where dendritic cells taking up dietary antigens reside (163, 164), we hypothesized that IL-15 signaling in dendritic cells may lead to the induction of inflammatory T cell responses against gluten and the loss of oral tolerance (165, 166). Using an HLA-DQ8 mouse model overexpressing IL-15 in the LP but not in the intestinal epithelium, we showed that IL-15 in combination with retinoic acid altered the tolerogenic phenotype of intestinal dendritic cells, hence preventing the generation of inducible Foxp3⁺ Treg cells to dietary gluten and promoting the development of a T_H1 inflammatory immune response to orally ingested gluten (165). It is important to note, however, that the location of IL-15 overexpression critically determines on which cells it acts and what the pathological impact is. For instance, IL-15 overexpression in the

intestinal epithelium in our hands is not associated with the loss of oral tolerance (165, authors' unpublished data), and potentially explains why ovalbumin-fed mice overexpressing IL-15 in the epithelium but not in the LP show no decrease in Foxp3⁺ T cells expressing the T-cell-receptor specific for ovalbumin (167). Furthermore, a defect in inducible regulatory T cells can be easily missed if one does not strictly control for TCR specificity using RAG-deficient TCR transgenic T cells (167), because regulatory Foxp3⁺ T cells without defined specificity are attracted, as are other effector T cells, to inflamed tissues. This explains why Foxp3⁺ T cells are paradoxically increased in the tissues of autoimmune disorders (168–172) and inflammatory bowel disease (173–179). To which degree Foxp3⁺ T cells recruited to inflamed tissues encounter their (self) antigen and are activated remains to be determined. Finally, in addition to losing oral tolerance, mice overexpressing IL-15 in the LP produce anti-TG2 IgG and IgA antibodies (165). Interestingly, no villous atrophy was observed in these mice, supporting the concept that in absence of the epithelial stress associated with IL-15 overexpression in the epithelium, adaptive anti-gluten immunity is insufficient to induce tissue damage. Hence, events leading to sustained or repetitive IL-15 upregulation in the LP have the potential to lead to the constitution of a growing inflammatory effector and memory pool of gluten-specific T cells that can result in the development of potential, but not active, CD.

Role of IL-15 in blocking the ability Foxp3⁺ regulatory T cells to regulate effector T-cell responses

Sallustro and colleagues (180), looking at effector and Foxp3⁺ T cells in the synovia of juvenile arthritis patients, first proposed that the presence of IL-15 could interfere with the regulatory properties of Foxp3⁺ T cells. It was later shown that IL-15 blocks the ability of transforming growth factor (TGF- β) to suppress activation of human mucosal T lymphocytes by activating c-Jun N-terminal kinase (JNK) and subsequently impairing Smad-3-dependent TGF- β signaling (181). Disruption of TGF- β signaling likely results in increased proliferation and production of inflammatory cytokines, ultimately promoting sustained intestinal inflammation (152). In addition, by activating the PI3K pathway, IL-15 renders effector CD8⁺ T cells unresponsive to the suppressive effect of Foxp3⁺ regulatory T cells (182). This may be by the same mechanism that IL-15 impairs the ability of regulatory T cells isolated from the blood and intestinal biopsies of CD patients to block effector CD4⁺ T cells *in vitro* (183). Interestingly, while IL-15 alters the response of effector T cells to regulatory T cells, it does not alter the intrinsic regulatory properties of Foxp3⁺ T cells (184). Altogether, this may explain why despite the increase in Foxp3⁺ T cells in inflamed tissues of patients with CD, autoimmune disorders, and IBD, effector T cells are highly effective at promoting tissue damage.

Role of IL-15 in the licensing of cytotoxic T cells to kill epithelial cells and induce active celiac disease

The induction of non-classical MHC class I molecules and the upregulation of IL-15 on IECs, as well as the dysregulated activation of IELs that acquire cytotoxic properties, are a hallmark of CD and were shown to be critically involved in the development of villous atrophy. Cytotoxic IELs are not gluten-specific but rather kill epithelial cells based on the recognition of stress signals (4, 6, 166). In healthy individuals, IELs mainly express the

inhibitory CD94/NKG2A receptor (5, 131) and only low levels of the activating NKG2D receptor (6). In contrast, IELs from CD patients lack the inhibitory CD94/NKG2A receptor (185) and express high levels of the activating NKG2D and CD94/NKG2C receptors (96, 185). Concomitantly, IECs in the inflamed mucosa of CD patients express high levels of the stress-inducible MIC molecules (96, 186), and non-classical MHC class I molecule HLA-E (185), which are the main ligands for NKG2D and CD94/NKG2C, respectively. IL-15 was shown to upregulate the activating NKG2D receptor, endowing cytotoxic IELs with the ability to kill IECs expressing the stress-induced MIC molecules (6, 96, 187). IL-15 stimulation induces CD94 expression in IELs by increasing CD94 transcription and its expression on the cell surface (5). However, it does not affect the expression of NKG2A, NKG2C, or DAP12 (5, 185). Moreover, IL-15 induces the expression of NKG2D (6, 96) by increasing NKG2D and DAP10 transcription (96). Furthermore, IL-15 acts as a costimulatory molecule for the NKG2D cytolytic pathway (96, 187), hence endowing IELs with lymphokine-activated killer (LAK) activity (6, 96), i.e. with the capacity to kill in a T-cell receptor (TCR)-independent manner. In addition to its ability to endow IELs with LAK activity, IL-15 lowers the overall activation threshold of IELs (6, 94, 186). This could result in the recognition of low affinity epithelial self-antigens and the ability to kill epithelial cells in absence of cognate antigens but in a TCR-dependent manner. This scenario is supported by studies in mice showing that CD8⁺ T cells can reject solid tumors expressing IL-15 in a TCR-dependent manner despite the fact that they do not express the cognate antigen for the CD8⁺ T cells mediating their rejection (188).

In our view, it is very likely that the destruction of epithelial cells by IELs involves both the TCR and NK receptors. Importantly, only epithelial cells expressing IL-15 and ligands for activating NK receptors will be destroyed. Hence, despite the fact that IELs in the presence of IL-15 act as innate-like lymphocytes that kill epithelial cells based on stress signals, this destruction is highly specific. This led us to propose that IELs in CD are autoreactive and that CD is a model for organ specific autoimmunity (189). This concept is further supported by the presence of autoantibodies specific for TG2, which are required for the diagnosis of CD.

Role of IL-15 in promoting survival of abnormal intraepithelial lymphocytes and promoting refractory celiac disease

In the case of RCD, sustained expression of high levels of IL-15 in the epithelium (150, 190) leads to the expansion of a subset of CD3⁺ cytotoxic IELs that have undergone profound genetic reprogramming of their NK functions, ultimately acquiring an aberrant and highly activated NK cell-like phenotype (148). IL-15 is thought to contribute to the expansion and survival of these IELs with an aberrant phenotype by exerting anti-apoptotic action on IELs (150, 190, 191). Indeed, IL-15 is able to activate an anti-apoptotic cascade, involving phosphorylation of Jak3 and STAT5 and the increased expression of the anti-apoptotic B cell lymphoma-extra large (Bcl-xL) protein (190). In addition to playing a critical role in the sustained survival of these abnormal IELs, IL-15 also increases their cytolytic capacities (186). Refractory sprue is mimicked in an IL-15 transgenic mouse model where human IL-15 is expressed in intestinal epithelial cells. This upregulation of IL-15 is associated with the expansion of activated NK-like cytotoxic IELs and villous atrophy (190, 192). The link

between IL-15, the increase in NK-like cytotoxic IELs and villous atrophy, is supported by the finding that blocking IL-15 signaling prevents villous atrophy (192), suggesting that neutralizing IL-15 or blocking its signaling may be a treatment for RCD.

IL-15 and genetic risk factors of celiac disease

Because of its large contribution to CD immunopathogenesis, one would have expected the identification of *il15* as a CD susceptibility gene by genome wide association studies. However, no genetic association has yet been found for the gene encoding IL-15 (193). This lack of association suggests that the increased levels of IL-15 in patients might be the consequence of the deregulation of genes capable to modulate the levels of the cytokine; that is, *trans* effects. By analyzing the functional interactions among CD susceptibility genes and IL-15, we found that several of the genes were associated with IL-15, suggesting that the increased levels of IL-15 observed in CD patients probably results from functional variation in this CD-susceptibility network (Fig. 3). Interestingly, among the genes that have direct associations with IL-15 in this network are the γ c cytokines IL-21 and IL-2, which share many common structural and functional properties with IL-15. More generally, the genes associated with IL-15 are strongly enriched for key pathways that are central for the pathogenesis of CD such as IgA production, T-cell receptor signaling, or antigen processing and presentation. We also observed a significant enrichment for genes belonging to the autoimmune thyroiditis and Type 1 Diabetes pathways, an observation in accordance with several reports showing that IL-15 upregulation is associated with increased risk for such diseases (124, 125, 194, 195).

Functional redundancy between IL-21, type-1 IFN, and IL-15 in celiac disease

Due to shared receptor components and signaling pathways, γ c cytokines theoretically present a high degree of redundancy. In fact, IL-15 and IL-21 exert many overlapping activities in regards to CD immunopathogenesis (Fig. 4) including the ability to render effector CD4⁺ T cells resistant to the suppressive effects of regulatory T cells (196), the ability to drive the production of IFN- γ (160), and the ability to upregulate cytotoxic activity in IELs (197). Although *in vitro* studies have demonstrated that IL-21 by itself has very little effect, if any, on the proliferation of CD8⁺ T cells, IL-21 synergizes with IL-15 to promote CD8⁺ T-cell activation and expansion, production of IFN- γ , and upregulation of granzyme B and perforin (198). The fact that IL-15 enhances the production of IL-21 suggests the establishment of an amplification loop that could foster the ongoing inflammatory response (199). In agreement with the hypothesis that IL-21 could contribute to the induction of inflammation and tissue damage in CD is the finding that potential CD patients not only lack IL-15 overexpression in the LP, but also fail to express IL-21 (200). Although they do not share structural components and signaling pathways, Type I interferon (IFN) is another cytokine that could exert redundant effects with IL-15 (Fig. 4). IFN- α expression is dysregulated in the small intestine mucosa of CD patients (201–203). In addition, clinical observations of the development of CD in hepatitis C patients treated with IFN- α (204) as well as the induction of inflammatory anti-gluten responses and the generation of TG2 antibodies following rotavirus infections (205) suggest that IFN- α likely plays a critical role in the induction of inflammatory T-cell responses against gluten. However, whether and how Type I IFN contributes to CD pathogenesis remains to be determined.

Conclusions and future directions

Overall, the involvement of IL-15 in multiple steps of the NKG2D cytolytic pathway, together with its confirmed roles in abrogating oral tolerance to dietary gluten and interfering with the suppressive activity of intestinal regulatory T cells, makes this cytokine a key player involved in the dysregulation of immune responses in CD. Future studies will also better delineate the role of IL-15 in other organ-specific autoimmune disorders. In particular, it will be important to determine whether IL-15 is critical in the development of autoreactive T-cell responses and the destruction of the tissues targeted by the autoimmune process. In this regard, it is interesting to note that LADA (latent autoimmune diabetes in adults) patients, unlike type-1 diabetes patients, lack IL-15 overexpression in islet β -cells (124), suggesting that, as observed in potential CD, upregulation of IL-15 in tissue cells is critical to license cytotoxic T cells to kill the tissue targeted by the autoimmune process.

Although the exact factors and mechanisms responsible for triggering IL-15 upregulation have yet to be defined, it has been suggested that gliadin peptides could promote IL-15 expression by IECs (186, 206). However, this effect is likely indirect, due to the upregulation of multiple inflammatory mediators as a consequence of T-cell activation. Because IL-15 can be induced by many inflammatory stimuli, including cytokines and TLR ligands (207, 208), other factors, notably microbial components that are enriched in the intestinal compartment, could promote sustained IL-15 expression. However, it is important to acknowledge that we know very little about the mechanisms underlying IL-15 dysregulation in CD and when this dysregulation occurs.

Due to the central role of IL-15 in the immunopathogenesis of CD, there is a growing interest in developing novel therapies able to dampen the actions of IL-15. To inhibit IL-15 activity and to prevent its deleterious effect on oral tolerance and IELs activation, several agents have been developed, including antibodies specific for IL-15 or IL-2/15R β , and Jak inhibitors. The humanized antibody (Hu-Mik- β -1) directed towards IL-2/15R β prevents the transpresentation of IL-15 by antigen-presenting cells to neighboring NK cells and CD8⁺ T cells (9, 209). The administration of TM β -1 (the anti-mouse equivalent of Hu-Mik- β -1) to IL-15 transgenic mice results in the abrogation of inflammatory cytokine production and in the reversal of intestinal damages (165, 192). The Food and Drug Administration has authorized the usage of Hu-Mik- β -1 to treat CD patients with the type II form of RCD (210), who develop enteropathy-associated T-cell lymphoma with a two year survival of less than 30% (146, 211). Another approach consists of interfering with the IL-15 signaling pathway. It involves the administration of the Jak2/3 inhibitor tofacitinib that has been shown to completely reverse the intestinal pathological changes observed in the T3^b-hIL-15 transgenic mouse model (212). Finally, *ex vivo* experiments have demonstrated the capacity of the humanized anti-IL-15 monoclonal antibody AMG714 to inhibit the activation of Jak3 and STAT5 in the mucosa of type II RCD patients. In addition, the administration of AMG714 to IL-15 transgenic mice restores IELs apoptosis and consequently inhibits their accumulation (190). Thus, these anti-IL-15 therapies represent promising therapeutic approaches, especially for patients with refractory disease. However, because of the potential redundancy with IL-21, type-1 IFN and yet undefined cytokines, we cannot

exclude that combination therapies or therapies targeting common signaling pathways may be necessary to achieve a therapeutic effect.

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Fig. 1. Patients with active celiac disease have high IL-15 expression both in the intestinal *lamina propria* and epithelium, while patients on a gluten free diet only maintain high expression in the epithelium

Representative pictures of IL-15 immunohistochemistry staining are shown. Duodenal formalin fixed paraffin embedded sections were obtained from control non celiac subjects (control, left panel), untreated (active CD, middle panel), and treated celiac disease patients (GFD, right panel). Epithelial expression was assessed semi-quantitatively looking at staining intensity and localization (typically being stronger at the villous tip and then reducing its intensity going towards the crypts). The rate of IL-15 positive cells on the total number of infiltrating mononuclear cells in the *lamina propria* was assessed by two independent investigators in a double-blind set. Upregulation of IL-15 can be observed in both the small intestinal epithelium and lamina propria of active CD patients. Interestingly, celiac patients on a gluten-free diet (GFD) seem to retain only the epithelial but not the *lamina propria* IL-15 overexpression.

Fig. 2. Multifaceted roles of interleukin-15 (IL-15) in celiac disease pathogenesis

IL-15 impacts distinct cell types to mediate its pathogenic effects. (i) In the *lamina propria*, IL-15 endows mucosal dendritic cells with inflammatory properties in a c-Jun N-terminal kinase (JNK)-dependent manner, and subsequently with the ability to prevent the differentiation of regulatory T cells and to promote inflammatory Th1 cell responses leading to the loss of oral tolerance. (ii) IL-15 renders effector T cells resistant to the suppressive functions of regulatory T cells through a mechanism involving JNK and phosphatidylinositol 3 kinase (PI3K). (iii) IL-15 impacts on intraepithelial lymphocytes by inducing the expression of NKG2D. The synergy between IL-15 and NKG2D cytolytic signaling pathway promotes the binding of the NKG2D-DAP10 complex to distinct adaptor proteins including PI3K whose activation promotes the phosphorylation of the mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase (ERK), and JNK. This leads to cPLA₂ activation, which in turn critically regulates NKG2D-mediated degranulation and cytolysis, and induces the release of arachidonic acid, a precursor of the pro-inflammatory compounds called leukotrienes. (iv) In patients with refractory sprue, IL-15 leads to the expansion and survival of an abnormal subset of CD3⁺ intraepithelial lymphocytes by activating an anti-apoptotic cascade involving the phosphorylation of Jak3 and STAT5.

Fig. 3. Interactions between IL-15 and celiac disease susceptibility genes

(A). Network of known interactions between celiac disease (CD)-associated genes and IL-15. We used the STRING database to look for known functional interactions among CD susceptibility genes, as well as functional interactions between CD susceptibility genes and IL-15 (red). The figure only shows CD-associated genes that are directly or indirectly connected with IL-15. STRING database assembles information about both known and predicted protein-protein interactions on the basis of numerous sources, including experimental repositories, computational prediction method, and public text collections. We grouped genes based on the distance matrix obtained from the String global scores. We used the KMEANS algorithm setting the number of groups to three. Proteins pairs with a higher global core (i.e. stronger evidence that they interact together) are grouped together on the same cluster. The three clusters are represented by different colors (yellow, purple, and blue). IL-15 is directly connected with the ‘yellow cluster’. The thickness of the lines connecting the genes is proportional to String global scores supporting the evidence of an interaction. Solid and dashed lines represent intra- and inter-cluster connections, respectively. (B). KEGG pathway enrichment analysis for the CD-associated genes shown in panel A. The y-axis reports the fold enrichments observed for genes in a particular pathway (named in y-axis) using all human genes as our background expectation.

Fig. 4. Overlapping functions of IL-15, IL-21, and Type I interferon

Both IL-15 and IL-21 render effector $CD4^+$ T cells resistant to the suppressive functions of regulatory T cells. Both IL-15 and Type I interferon endow dendritic cells with inflammatory properties and have been shown to mediate loss of oral tolerance and to promote Th1 immunity. All three cytokines have the ability to confer cytotoxic properties to $CD8^+$ T cells.