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IL-15 functions as a danger signal to regulate tissue-resident T cells and tissue destruction

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Abstract

In this Opinion article, we discuss the function of tissues as a crucial checkpoint for the regulation of effector T cell responses, and the notion that interleukin-15 (IL-15) functions as a danger molecule that communicates to the immune system that the tissue is under attack and poises it to mediate tissue destruction. More specifically, we propose that expression of IL-15 in tissues promotes T helper 1 cell-mediated immunity and provides co-stimulatory signals to effector cytotoxic T cells to exert their effector functions and drive tissue destruction. Therefore, we think that IL-15 contributes to tissue protection by promoting the elimination of infected cells but that when its expression is chronically dysregulated, it can promote the development of complex T cell-mediated disorders associated with tissue destruction, such as coeliac disease and type 1 diabetes.

The integrity of our tissues is regularly challenged by intracellular infection, in particular by viruses. In response, T helper 1 (T_H1) cell-mediated immunity, which is characterized by the production of interferon-γ (IFNγ) by T cells and a concomitant increase in the number of tissue-resident cytotoxic T cells, is thought to have a key role in tissue protection by promoting the elimination of infected cells[1–3]. However, concurrent T_H1 cell-mediated immunity and cytotoxic T cell responses are also associated with autoimmunity and tissue destruction[4–6]. Thus, how tissues control the initiation of T_H1 cell responses and regulate cytotoxic T cells is key to maintaining their integrity.

Interleukin-15 (IL-15) is a member of the four α-helix bundle family of cytokines that includes IL-2, IL-4, IL-7, IL-9 and IL-21. IL-15 shares the common cytokine receptor γ-chain (γc; also known as CD132) of its heterodimeric receptor with the receptors for IL-2, IL-7, IL-4, IL-9 and IL-21, and it shares the β-chain (IL-2/IL-15Rβ; also known as CD122) with the receptor for IL-2 (REFS 7,8). IL-15 functions mainly in a cell contact-dependent manner through the *trans*-presentation of membrane-bound IL-15–IL-15Rα (IL-15 receptor

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α-subunit) complexes to responding cells that express IL-2/IL-15Rβ–γc[8]. Signalling by *cis*-presentation or through soluble complexes of IL-15–IL-15Rα[9–11] also contributes, but to a lesser extent, to IL-15-induced responses. By contrast, IL-2, which also signals through IL-2/IL-15Rβ–γc, is mainly produced as a soluble factor by activated T cells[12] (FIG. 1a) and, unlike IL-15, *trans*-presentation by the α-chain of the IL-2 receptor may be only a minor mechanism for IL-2-induced signalling[13]. IL-15 receptor signalling induces JAK1 (Janus kinase 1)–STAT3 (signal transducer and activator of transcription 3) and JAK3–STAT5 activation via the β-chain and γc, respectively[14]. IL-15 is notable among cytokines for being produced by a wide range of cells[14], including non-myeloid cells such as epithelial and stromal cells, antigen-presenting cells and other myeloid cells such as mastocytes, and B cells and T cells of the adaptive immune system. Furthermore, IL-15 can be induced in response to innate microbial triggers[15,16] and under conditions of sterile inflammation, reflecting the presence of ongoing cellular distress[17,18]. Notably, most — if not all — organ-specific autoimmune disorders are associated with IL-15 overexpression in the affected tissue[19–26], whereas the opposite holds true for the related cytokine IL-2, deficiency of which leads to autoimmunity[27,28]. The absence of IL-15 in solid tumours is associated with defective lymphocyte activation in the tumour environment and decreased patient survival, which further supports a role for IL-15 in tissue immunity and destruction[29].

Considerable effort has focused on deciphering the role of IL-15 expressed by myeloid cells in the survival and proliferative expansion of natural killer (NK) cells, memory $CD8^+$ T cells and innate-like intestinal intraepithelial lymphocytes (IELs)[7,8,30] (BOX 1). However, the role of IL-15 expressed by non-haematopoietic and haematopoietic tissue-resident cells in the regulation of tissue effector T cell responses and tissue immunity in general is less well recognized. In this Opinion article, we suggest that tissues constitute a crucial checkpoint for the initiation and execution of destructive T cell responses and that IL-15 should thus be recognized as a master regulatory cytokine with regard to tissue immunity. More specifically, we propose that IL-15 is a cytokine that communicates the health status of the tissue to the immune system and has a key role in promoting immune responses that drive tissue destruction through its effects on dendritic cells (DCs) and tissue-resident effector cytotoxic T lymphocytes (CTLs). Finally, we discuss our belief that IL-2 cannot fulfil the same role as IL-15 in tissue immunity and the possible mechanisms that underlie the postulated opposing roles of IL-15 and IL-2 in tissue immunopathology.

Tissue-specific regulation of CTL responses

It has long been thought that the nature of the infectious agent and the innate pathways activated in DCs in response to infection determine which type of immune response (for example, a T_H1, T_H2, T_H17 or regulatory T (T_{Reg}) cell response) is generated, based on the level of co-stimulatory molecules expressed and the types of cytokines produced by DCs[31]. However, different tissues have different challenges and requirements for ensuring their survival. For example, the eye lacks self-renewal properties and, by impeding T_H1 cell responses while promoting T_H2 cell and T_{Reg} cell responses, it promotes immune responses that effectively eliminate ocular pathogens while minimizing tissue damage that can cause blindness[32–34]. In the gut, T_H17 cell responses and peripherally derived T_{Reg} cell responses are promoted to enable the maintenance of intestinal immune homeostasis through the

production of secretory IgA and antimicrobial peptides[35], while still allowing for protective immune responses against pathogens. Although the cellular and molecular mechanisms underlying the role of tissues in directing T cell differentiation are still being uncovered, known examples have been linked to the functional properties of tissue DCs imparted by the tissue environment. For example, intestinal DCs, which are in an environment rich in retinoic acid, transforming growth factor-β (TGFβ) and IL-6, tend to induce gut-homing receptors on T cells[36–38] and to promote T_{Reg} cell[39–41] and T_H17 cell[35,39,42] responses. Furthermore, oral but not systemic infection with the pathogen *Yersinia enterocolitica* triggers the selective induction of T_H17 cell responses instead of T_H1 cell responses through engagement of Toll-like receptor 1 (TLR1) in the presence of TGFβ and retinoic acid[43].

However, although the role of the tissue environment in guiding the early differentiation of T cells is now well recognized, the role of the tissue in controlling the activation status of existing effector T cells — which encompass both tissue-resident effector memory T cells (T_{RM} cells) and recently differentiated effector T cells that have emigrated from lymph nodes[44,45] — is less well understood. Effector CTLs contain granules that are armed with cytolytic molecules (such as granzyme and perforin) and pro-inflammatory molecules (such as IFNγ). A prototype of T_{RM} cells are IELs, which express CD69 and CD103 (also known as integrin αE), are located between epithelial cells in the intestine and have an important role in immune protection against pathogens[17]. Such tissue-resident effector memory CTLs must provide rapid protection against infection while preventing indiscriminate tissue destruction. Classical immunology textbooks teach us that whereas naive T cells and central memory T cells require co-stimulation (also known as signal 2) in addition to T cell receptor (TCR) stimulation (signal 1) for their activation (FIG. 1b), effector T cells require only signal 1 to mediate their effector function. We propose that this notion is only partially correct because although effector CTLs do have the potential to induce cytolysis and produce cytokines in response to TCR stimulation in the absence of co-stimulation, their activity in these circumstances is largely suboptimal as shown by the very high levels of TCR stimulation that are required *in vitro* and the low levels of cytolysis and cytokines produced[46–48].

We therefore suggest that the tissue environment functions as a second checkpoint for effector CTL activation but that this role for the tissue has frequently been overlooked because most studies are not designed to address it. In our view, the best controlled *in vivo* experiment to address this issue showed that forced migration of effector CTLs in a healthy tissue that expressed the cognate antigen was not sufficient to induce tissue destruction — and, more specifically, diabetes — using a TCR- and β-islet-transgenic mouse model[49]. Moreover, there are several examples of mouse models in which the induction of an inflammatory adaptive immune response specific for dietary antigens is insufficient to cause tissue damage when it takes place in an intestine where epithelial cells are originally healthy[50–53]. In humans, two disease examples support this concept. One is latent autoimmune diabetes in adults (LADA), in which the presence of adaptive immunity against antigens expressed by β-islet cells is predictive of but not sufficient for the development of type 1 diabetes[26]. The other is potential coeliac disease[54], in which the presence of an adaptive immune response specific for gluten does not result in the activation of intraepithelial CTLs or villous atrophy in the absence of epithelial stress (as measured by the

expression of heat shock proteins and IL-15)[55]. The proposed tissue-specific second checkpoint for effector CTL activation has a teleological foundation in that it ensures that tissues are not unnecessarily destroyed in response to microorganisms that can activate pattern recognition receptors on DCs and hence induce T cell responses but that are not harmful to the tissue. Furthermore, this checkpoint would provide an evolutionary advantage by allowing tissues to overcome pathogen evasion strategies that depend on MHC class I downregulation leading to defective TCR activation. Based on these observations and the functional properties of IL-15 described below, we propose that IL-15 and stress inducible non-classical MHC class I molecules expressed by distressed tissue cells provide co-stimulatory signals to cytotoxic T_{RM} cells that license them to become killer cells and destroy tissue cells (FIG. 1b).

Comparing roles of IL-2 and IL-15 *in vivo*

The contrasting associations of IL-15 overexpression and IL-2 deficiency with autoimmunity[27,28], which have led to the development of therapies for autoimmune disorders based on selectively blocking IL-15 signalling[18] but on providing low doses of IL-2 (REF. 56), suggest that even though IL-2 and IL-15 signal through a common receptor and share some important biological functions[8,12], they have distinct roles *in vivo*. We first present evidence suggesting that there are key similarities between IL-2 and IL-15 biology, before discussing in greater depth the underlying mechanisms that may explain their apparent opposing *in vivo* roles in autoimmunity.

Similar functions of IL-2 and IL-15 include stimulating the generation, proliferation and activation of NK cells, promoting the proliferation of activated T cells and facilitating the induction of CTLs, as well as inducing the proliferation of, and immunoglobulin synthesis by, pre-activated B cells[8]. In addition, IL-2 and IL-15 induce a similar gene expression profile in peripheral blood $CD8^+$ T cells, in particular when saturating concentrations of each cytokine are used[57]. However, strikingly, IL-2-deficient mice develop autoimmune and inflammatory disorders, whereas IL-15-deficient mice do not. Conversely, IL-15 overexpression has been reported in numerous organ-specific autoimmune disorders[19–26], whereas to our knowledge there are no reports suggesting a link between IL-2 overexpression and autoimmunity in humans. Furthermore, IL-15-deficient mice have a reduction in the number of NK cells, central memory $CD8^+$ T cells and resident IELs[58], whereas IL-2-deficient mice develop major hyper-lymphoproliferative disorders[27,28]. These *in vivo* differences suggest that, although IL-15 and IL-2 exert some common *in vivo* functions, they also have key distinct functions, as illustrated by the following observations. Although IL-15 was reported to enhance the proliferative expansion of forkhead box P3 $(FOXP3)^+$ T_{Reg} cells[59–63] and to have a role in the development of $CD25^-FOXP3^+$ T cells[62], the development of $CD25^+FOXP3^+$ T_{Reg} cells is acknowledged to be strictly IL-2 dependent, and IL-2 deficiency is overall associated with a major defect in the homeostatic maintenance of T_{Reg} cells[62,64–66]. Furthermore, IL-15 was shown to block the differentiation of peripherally derived T_{Reg} cells, especially in the presence of retinoic acid[51]. Finally, IL-2 promotes the elimination of potentially harmful self-reactive T cells through activation-induced cell death (AICD)[67], whereas IL-15 is an anti-apoptotic factor in several systems and inhibits AICD[68,69]. The opposing roles of IL-15 and IL-2 *in vivo* in terms of AICD are

in particular illustrated by a report showing that blocking IL-2 enhances the rate of appearance of dividing $CD8^+$ memory T cells, whereas the absence of IL-2/IL-15Rβ decreases it[70].

To explain the apparent paradox that IL-2 and IL-15 have distinct roles *in vivo* yet they signal through a common receptor, investigators in the field have relied on the explanation that IL-2 mainly functions as a soluble factor, whereas IL-15 mainly functions in a cell contact-dependent manner and hence induces signalling in the presence of other co-stimulatory signals provided by the cell *trans*-presenting IL-15 (REF. 8). The main mechanisms by which IL-2 and IL-15 interact with their receptors *in vivo* are *cis*-presentation and *trans*-presentation, respectively (FIG. 1a), although IL-15 signalling by *cis*-presentation or through soluble complexes of IL-15Rα–IL-15 (REFS 9–11) and IL-2 signalling by *trans*-presentation[13] have also been described.

Ultimately, we propose that, in addition to the fact that IL-15, but not IL-2, mainly functions in a cell contact-dependent manner, two crucial differences drive the apparent paradoxical opposing roles of IL-15 and IL-2 in tissue immunopathology. First, IL-2 is typically not produced by antigen-presenting cells or non-haematopoietic cells such as epithelial or stromal cells, and thus it cannot function in a similar manner to IL-15 as a first messenger relaying tissue distress. Second, because IL-2 is secreted transiently and at low levels by tissue-resident effector CTLs[45], and the produced IL-2 is rapidly consumed by the activated effector T cells and T_{Reg} cells residing in the tissue[12], we suggest that IL-2 fails to reach sufficient levels in tissues to allow for signalling through the constitutively expressed dimeric IL-2/IL-15Rβ–γc receptor that is shared with IL-15. Consequently, IL-2-mediated signalling by effector T cells in these environments would mainly, if not selectively, take place through the high-affinity trimeric IL-2Rα–IL-2/IL-15Rβ–γc receptor, which is upregulated only in response to TCR signalling. This is in contrast to IL-15, which achieves much higher concentration levels locally because it is *trans*-presented by the distressed cell to the responder cells[71,72] and which has the ability to signal selectively through the dimeric receptor because of its tenfold higher affinity than IL-2 for this receptor[57]. If correct, IL-2 and IL-15 would thus signal in T cells that have different activation statuses. Furthermore, the presence or absence of IL-2Rα (also known as CD25) in combination with the different affinity of the two cytokines for their receptors would lead to differences in the physical engagement and signalling of the IL-2/IL-15Rβ chain and γc. This may explain why, although IL-2 and IL-15 regulate a very large set of common genes (that is, 4,284 genes) in peripheral blood $CD8^+$ T cells *in vitro*, there are 406 and 492 genes that are uniquely regulated by IL-2 and IL-15, respectively[57], suggesting that the two cytokines also have unique transcriptional properties. This difference might be even more pronounced if studies were carried out on peripheral blood effector CTLs and cytotoxic T_{RM} cells, rather than on global peripheral blood $CD8^+$ T cells, which mainly include central memory and naive T cells.

Future functional and transcriptional profiling studies that compare the effects of different concentrations of IL-2 and IL-15 in resting and TCR-activated memory T cells and T_{RM} cells in the absence or presence of a blocking IL-2Rα-specific antibody will help to further dissect the mechanisms underlying the differential roles of IL-2 and IL-15 *in vivo*. Similar

studies carried out with different DC and innate lymphocyte subsets would also help to delineate the functional impact of these cytokines on tissue DCs and innate lymphocytes. Finally, when analysing the roles of IL-15 and IL-2 *in vivo*, it is important to take into account where these cytokines are actually expressed and can signal to responder cells under physiopathological conditions. This is illustrated, for example, by the observation that whereas IL-2 and IL-15 can both prevent FOXP3$^+$ T_{Reg} cells from exerting their suppressive functions on effector T cells *in vitro*[73,74], IL-15 but not IL-2 was shown to be present in the joint fluid of patients with juvenile arthritis *in vivo*, and therefore it can be suggested that IL-15 and not IL-2 is responsible for the T_{Reg} cell-inhibitory effect in this case[74]. Furthermore, there is some evidence that IL-15 overexpression in the intestinal epithelium[68], but not in the lamina propria[51,55], promotes the acquisition of activating NK receptors by IELs, and IL-15 (but not IL-2) was reported to be expressed by intestinal epithelial cells[55,75,76].

Role of IL-15 in tissue immunity

Where IL-15 is upregulated and in which cell type it signals have a defining impact on its role in tissue immunity. Here, we discuss in detail the regulation of IL-15 and its immuno pathological effects on DCs and T cells. IL-15 also affects NK cells and group 1 innate lymphoid cells (ILC1s). ILC1s were shown to produce large amounts of IFNγ in response to IL-15 stimulation and are thought to have a role in the early protection of tissues against pathogens and potentially in intestinal inflammatory disorders[77] (FIG. 2).

IL-15 regulation

IL-15 has a uniquely wide cellular distribution compared with other cytokines and can be expressed by both haematopoietic and non-haematopoietic cells. More specifically, IL-15 can be expressed by monocytes and macrophages[15,78,79], DCs[15,80,81], mast cells[82], B cells and T cells[83,84], endothelial cells[78], bone marrow and lymph node stromal cells[78,85], and tissue cells such as fibroblasts[86], intestinal and respiratory epithelial cells[75,76,87–89], hair follicles[90] and keratinocytes[91]. Bacterial and viral infections associated with innate signals such as type I IFN, double-stranded RNA and TLR signalling through MYD88 have been reported to induce IL-15 upregulation[15,16]. Intriguingly, however, IL-15 has also been reported to be induced in tissues under conditions of sterile inflammation, such as in autoimmune disorders[19–26,92], coeliac disease[75,76,93], inflammatory bowel disease[94–96], alopecia areata[90] and sarcoidosis[97], although the mechanisms underlying these observations remain poorly understood. Key transcription factors that are induced under inflammatory conditions and that regulate *IL15* transcription are nuclear factor-κB (NF-κB; in particular p50) and IFN regulatory factor 1 (IRF1), the binding motifs for which are found in the promoter region of *IL15* (REF. 98). Whether other factors associated with tissue stress, such as oxidative stress, DNA damage, endoplasmic reticulum stress or metabolic alterations, are associated with IL-15 upregulation remains to be determined. Interestingly, many of the susceptibility genes for coeliac disease and, more generally, for autoimmune and inflammatory disorders have a functional connection with IL-15, which suggests that IL-15 dysregulation in these diseases may result from alterations of this network. Whatever the mechanisms underlying IL-15 overexpression, the fact that it functions in a cell contact-

dependent manner has major implications because the location of IL-15 upregulation will determine its biological effect.

Effect on DCs and the development of T_H1 cells

Because of the importance of T_H1 cell-mediated immunity in the protection against intracellular microorganisms and as a pathological mediator of autoimmunity, the factors that are required to promote DC production of IL-12p70, a major cytokine involved in T_H1 cell differentiation, are of major interest. Importantly, the lack of IL-2/IL-15Rβ expression by DCs has been shown to affect IL-12 production and signalling in DCs *ex vivo* and *in vitro*[99]. In addition, IL-15-deficient mice but not IL-2-deficient mice mimic this defect in IL-12 production, which indicates a crucial role for IL-15-induced signalling in DCs for the induction of T_H1 cell-mediated immunity through IL-12 production[99] (FIG. 2). Furthermore, it has been demonstrated that IL-15 promotes T_H1 cell-mediated immune responses in the intestinal environment by synergizing with retinoic acid to induce the differentiation of inflammatory DCs in a JUN N-terminal kinase 2 (JNK2; also known as MAPK9)-dependent manner[51]. Finally, the acquisition of an inflammatory phenotype by DCs upon stimulation with IL-15 is also made evident by the increased ability of IL-15-stimulated DCs to secrete IFNγ, to stimulate the proliferation of antigen-specific $CD8^+$ T cells and to activate NK cells[81,100]. This ability of IL-15 to promote DC-mediated T_H1 cell responses led to efforts to use IL-15-treated DCs as a potential vaccine for cancer therapy[101,102]. In addition, IL-15 was shown to promote IL-23 secretion by intestinal DCs and T_H17 cell differentiation in the presence of IL-6 (REFS 51,103). Thus, a role for IL-15 has also been uncovered in diseases such as psoriasis[22,23] and autoimmune encephalomyelitis[103], in which IL-17 is thought to have a more important role in immunopathology than IFNγ.

Licensing of effector CTLs to mediate tissue destruction

The focus of this Opinion is not to discuss the largely reviewed effects of IL-15 on the homeostasis of NK cells, invariant NKT cells and $CD8^+$ T cells[8,14,104] but to address its role in the regulation of effector CTL responses in tissues. Here, we discuss the ability of IL-15 to reduce the TCR activation threshold of CTLs by providing co-stimulation, to promote lymphokine-activated killer activity (LAK activity) in CTLs (defined as the ability of a cytokine to enable a CTL to mediate cytolysis independently of the TCR and in the absence of MHC restriction) and to render CTLs resistant to T_{Reg} cells.

The ability of IL-15 to promote the cytolytic functions of effector CTLs and their production of IFNγ was first suggested by studies looking at the effect of IL-15 on IELs, which are a prototypical example of cytotoxic T_{RM} cells[105,106]. Follow-up studies showed that IL-15 increased TCR-mediated cytolysis in IELs[48]. This is made possible because, similarly to CD28, IL-15 can activate phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) signalling pathways[107–109] and thereby functions as a co-stimulatory molecule for the TCR (FIG. 3). The ability of IL-15 to reduce the TCR activation threshold for effector CTLs may provide a mechanistic basis to explain the ability of $CD8^+$ T cells to recognize self-antigens *in vitro* in a TCR-dependent process[46] and to mediate *in vivo* the destruction of solid tumours lacking expression of cognate antigen in a TCR-dependent manner[47] when IL-15 is present.

In addition to directly functioning as a co-stimulatory signalling molecule for the TCR, IL-15 promotes the expression of the NK receptors NKG2D (natural killer group 2, member D)[48,107,110] and CD94 (REFS 75,111), which themselves can function as co-stimulatory receptors for the TCR in effector CTLs[5]. Importantly, human tissue cells can upregulate expression of the non-classical MHC class I or class I-like molecules HLA-E and MICA (MHC class I polypeptide-related sequence A) under conditions of stress or activation, which are ligands for CD94–NKG2 receptor family and NKG2D receptors, respectively[107,112,113]. NKG2D, like CD28, associates with the adaptor molecule DNAX-activation protein 10 (DAP10), which contains a PI3K motif[114,115]. Shortly after its discovery, NKG2D was shown to co-stimulate the TCR in virus-specific T cells[116] and in cytolytic IELs[48]. Furthermore, NKG2D was proposed to have a key role in the regulation of tissue-resident effector T cells[48]. This is particularly relevant for human physiopathology because cytotoxic T_{RM} cells generally lack expression of the co-stimulatory receptor CD28 (REFS 48,117), and human tissue cells lack expression of its B7 ligands (also known as CD80 and CD86).

Finally, IL-15 has been shown to increase the expression of cytotoxic effector molecules such as TNF-related apoptosis-inducing ligand (TRAIL; also known as TNFSF10) and perforin[118], and to endow effector CTLs with LAK activity — in other words, to enable NKG2D–DAP10 signals to mediate TCR-independent cytolysis[48,107]. This property of IL-15 is linked to its ability to function as a co-stimulatory molecule for the NKG2D-mediated cytolysis signalling pathway by synergizing with NKG2D to promote the activation of PI3K, JNK, extracellular signal-regulated kinase (ERK) and cytosolic phospholipase A2 (cPLA2)[107,109,119] (FIG. 3). By promoting the activation of cPLA2, IL-15 also induces the release of arachidonic acid to promote tissue inflammation together with cell lysis[48,107,109]. Whether and how STAT3 and STAT5 (which are downstream of the IL-15 receptor) are involved in the regulation of NK receptor expression and function in CTLs remain to be determined.

In summary, we propose that IL-15 has the ability to enable effector CTLs to kill damaged tissue cells based on the recognition of stress and inflammatory signals rather than a cognate antigen through two distinct, but not mutually exclusive, mechanisms: by decreasing the TCR activation threshold of effector CTLs and by inducing TCR-independent LAK activity in CTLs (FIG. 2). In the absence of specific antigen recognition, the targeting of tissue cells by effector CTLs remains highly specific as it involves receptor–ligand interactions that direct CTLs exclusively against cells that upregulate expression of IL-15 and non-classical MHC class I or class I-like molecules. Furthermore, IL-15 confers such properties to effector but not central memory CTLs — in other words, only to T cells that have undergone recent activation through their TCR, which further helps to contain and restrict the potent effects of IL-15.

Rendering CTLs resistant to T_{Reg} cells

Following the discovery that T_{Reg} cells have an important role in preventing autoimmunity[120], it was surprising to find that the number of T_{Reg} cells is increased in tissues of patients with autoimmune diseases[121]. In particular, studies have shown that there

is an increase in the number of $CD4^+CD25^{hi}$ T cells that have suppressive functions and express cytotoxic T lymphocyte-associated antigen 4 (CTLA4), glucocorticoid-induced TNFR-related protein (GITR; also known as TNFRSF18) and OX40 (also known as TNFRSF4) — the classical T_{Reg} cell phenotype — in patients with rheumatoid arthritis[122,123] and inflammatory bowel disease[124,125]. This suggests that, at least in these cases, the increase in the number of $FOXP3^+$ T cells that is observed in humans is probably not due to a failure to discriminate between effector and regulatory T cells. This led to further analysis of the ability of T_{Reg} cells to exert their regulatory functions and to the discovery that several cytokines of the γc family, including IL-15, IL-7 and IL-2, could prevent T_{Reg} cells from exerting their suppressive effect on effector $CD4^+$ T cells *in vitro*. However, only IL-15 and IL-7 were present in the synovial fluid, suggesting that these cytokines, but not IL-2, limit the suppressive effect of T_{Reg} cells in patients with juvenile arthritis[74]. Later, it was shown that IL-15 renders human peripheral blood-derived $CD4^+$ and $CD8^+$ T cells resistant to the suppressive effects of thymus-derived $CD4^+CD25^+FOXP3^+$ T_{Reg} cells by activating the PI3K pathway in the effector T cells[73] (FIG. 2). These direct effects of IL-15 on T_{Reg} cells and their suppressive functions, together with the ability of IL-15 to inhibit IL-2-induced AICD of effector lymphocytes[126], underline the ability of IL-15 to interfere with immune tolerance.

Hence IL-15, a cytokine that is induced in distressed tissues, profoundly changes the functional phenotype of differentiated immune cells, favouring the development of T_H1 cell responses, decreasing the TCR activation threshold of effector CTLs and endowing them with LAK activity, and rendering effector T cells insensitive to the suppressive effects of T_{Reg} cells. All of these properties are tailored towards favouring the destruction of tissue cells (FIG. 2), which may be beneficial in the context of intracellular infection but is deleterious in the context of autoimmunity.

Role of IL-15 in health and disease

Taking into account the proposed role of IL-15 in the tissue-specific regulation of effector T cell responses, here we discuss its role in protection against infection and in autoimmunity. Conversely, we suggest that the lack of IL-15 and stress signals in solid tumours may have a crucial role in the inability of CTLs to eliminate such tumours (FIG. 4).

Protection of tissues against pathogens

Protection against intracellular microorganisms is primarily mediated by CTL-mediated destruction of infected cells. A key immune evasion strategy used by intracellular pathogens is to downregulate MHC class I expression by infected cells to prevent TCR-mediated recognition by CTLs[127]. However, the host has evolved mechanisms to counteract pathogen immune evasion and ensure protective immunity that involve upregulation of the expression of IL-15 and non-classical MHC molecules. Intracellular pathogens such as mycobacteria[128], listeria[129], *Cryptosporidium parvum*[130] and a wide range of viruses[89,131–133] have been reported to induce IL-15 expression, probably downstream of the activation of various innate immune receptors such as TLR4 (REFS 81,133). Furthermore, intracellular pathogens have been reported to upregulate the expression of non-classical

MHC class I ligands for activating NK receptors on host cells. For example, the NKG2D ligands MICA and MICB and their mouse counterpart RAE1 (retinoic acid early transcript 1) have been shown to be upregulated on stressed infected cells[89,130,134]. Of note, induction of these non-classical MHC class I molecules is not directly mediated by IL-15 (REF. 135) and occurs in response to heat shock factor 1, hyper proliferation and DNA damage[136,137]. The ability of IL-15 to function as a co-stimulatory signalling molecule for the TCR (see earlier) and to induce the expression of NK receptors enables CTLs to bypass the effects of downregulation of MHC class I molecules and to kill infected cells based on the recognition of danger signals. In agreement, IL-15 was shown to promote the upregulation of activating NK receptors on CTLs and the induction of NK receptor-dependent cytotoxic mechanisms in several infectious contexts[130,134,138–140]. Interestingly, viruses have developed several strategies to prevent the expression of NK receptor ligands on the surface of infected cells[141], which indicates that this is an effective host strategy and must be countered by viruses for them to survive.

In summary, in response to an infection with intracellular pathogens, IL-15 activates key immune cell types and effector functions that are crucial for the destruction of infected cells. Furthermore, because IL-15 functions in a cell contact-dependent manner and the upregulation of its expression ends with the clearance of the pathogen, CTLs are only activated in a transient manner and specifically target infected cells. This mechanism provides protection for tissues against pathogens while avoiding indiscriminate tissue destruction.

Autoimmune responses

The same properties that we believe enable IL-15 to mediate protection against pathogens are probably responsible for its role in the pathogenesis of organ-specific autoimmune disorders in which its expression is dysregulated. IL-15 expression is stringently regulated at the levels of transcription, translation and intracellular trafficking to avoid excessive protein production and secretion[98] (BOX 2). However, for unknown reasons, IL-15 has been found to be constitutively upregulated in tissue cells that are targeted by a wide variety of autoimmune processes, such as rheumatoid arthritis[19,20], multiple sclerosis[21,142], psoriatic arthritis or psoriasis[22,23], systemic lupus erythematosus[24,25], type 1 diabetes[26], inflammatory bowel disease[94–96] and coeliac disease[75,76,93].

The chronic overexpression of IL-15 in tissues is also often associated with the upregulated expression of ligands for activating NK receptors. For example, coeliac disease is characterized by the induction of stress-inducible MIC molecules[107,112] and of the non-classical MHC class I molecule HLA-E[113] on epithelial cells, which are ligands for NKG2D and CD94–NKG2C, respectively. IL-15 promotes the expression of these activating NK receptors by IELs[107,113], which acquire cytotoxic properties and the ability to kill epithelial cells based on the recognition of stress signals[48,107,109]. IL-15 also upregulates NKG2D and DAP10 expression on peripheral blood $CD4^+NKG2D^+$ T cell clones from patients with Crohn disease[143]. Furthermore, IL-15 upregulation in patients with Crohn disease[94–96] is associated with increased expression of NKG2D on $CD4^+$ T cells in the lamina propria and of MICA on epithelial cells, which suggests that tissue damage in these patients could be

mediated by the interaction between $CD4^+NKG2D^+$ T cells and $MICA^+$ epithelial cells[143]. The severity of rheumatoid arthritis pathology is also associated with the degree of expansion of a population of $CD4^+CD28^-$ T cells that express NKG2D upon stimulation with IL-15 and tumour necrosis factor (TNF) and with the expression level of stress-inducible MIC ligands by rheumatoid synoviocytes[144]. Finally, IL-15 endows these $CD4^+CD28^-$ T cells with the ability to lyse microvascular endothelial cells in patients with Wegener granulomatosis[145], increases the cytotoxic properties of $CD8^+$ T cells from patients with multiple sclerosis[84] and is associated with NKG2D upregulation in patients with alopecia areata[90].

Inhibition of JAK1 and JAK2 in patients with alopecia areata who overexpress IL-15 in their hair follicles leads to a near-complete restoration of hair growth[90], which suggests that IL-15 has a pathogenic role, although it cannot be excluded that JAK inhibition could affect signalling induced by other cytokines such as IL-2. Other strong evidence in support of a role for IL-15 in tissue destruction in the context of autoimmune disorders is provided by observations in patients with LADA or potential coeliac disease who maintain normal tissue integrity despite having developed an adaptive T cell response specific for β-islet cells or gluten, respectively (FIG. 5). Indeed, IL-15 is upregulated in the serum and β-islet cells of patients with type 1 diabetes but not with LADA[26,146]. Similarly, patients with active coeliac disease, but not potential coeliac disease, overexpress IL-15 in their epithelium[55]. Moreover, and in support of a primary role for IL-15 in mediating tissue destruction, we found that a subset of family members of patients with active coeliac disease had normal intestinal architecture and no signs of adaptive anti-gluten immunity but had epithelial cells expressing high levels of IL-15. Strikingly, IL-15 overexpression was absent in patients with potential coeliac disease. In accordance with IL-15 having a role in the licensing of cytotoxic T_{RM} cells to kill, only IELs from family members with high levels of IL-15 expression had upregulated expression of NKG2D and activating CD94 NK receptors[55]. The absence of villous atrophy in these individuals correlated with the presence of IELs with high levels of inhibitory CD94–NKG2A receptors[55] and of epithelial cells that failed to upregulate expression of MICA (B.J., unpublished observation). These observations in humans are consistent with reports in transgenic mouse models showing that antigen-specific CTLs fail to mediate tissue destruction despite the presence of cognate antigens when the tissue is healthy and hence fails to provide stress signals to the immune system[49].

These observations in the context of autoimmunity suggest that the inability of tumour-specific CTLs to eliminate solid tumours may not only be due to the expression of TGFβ[147] and ligands for the inhibitory receptor PD1 (programmed cell death protein 1)[148,149] but also due to the lack of expression of stress signals and IL-15 overexpression by tumour cells. In particular, it was shown that loss of IL-15 expression in solid tumours such as colorectal cancers was associated with decreased inflammation in the tumour environment and poor clinical prognosis[29]. Conversely, in head and neck cancer, in which inflammation promotes tumour growth, it was shown that a high level of expression of IL-15 was associated with increased inflammation and poor clinical outcome[150]. More systematic analysis of IL-15 in tumours is of high interest and warrants further investigation. Furthermore, studies in mice have suggested that IL-15 overexpression in solid tumours can lead to their effective elimination by CTLs even in the absence of a cognate antigen[47]. IL-15 should therefore be

considered for cancer therapy[101,102] in patients with tumours for which inflammation does not constitute a selective advantage. Delivery to the tumour of soluble IL-15 complexes that have been shown to stimulate potent NK cell and $CD8^+$ T cell responses *in vivo*[151,152] may be especially effective in patients with cancer and may not have the high toxicity reported for high-dose IL-2 therapy[153].

Concluding remarks

Individual tissues have unique challenges and needs; therefore, endowing tissues with the ability to control the type of immune response that is generated and whether T_{RM} cells should exert their effector functions has a clear advantage for maximal tissue protection. It enables the immune response to be tailored to the individual requirements of the tissue and ensures that effector T cells exert their functions locally only if there is ongoing active tissue distress that requires control of an infectious agent. Type I IFN[154], IL-33 and thymic stromal lymphopoietin (TSLP)[155] are cytokines that, similarly to IL-15, are inducibly expressed by non-haematopoietic epithelial and stromal cells and have the capacity to relay the health status of the tissue to the immune system and modulate the immune response accordingly. Whereas type I IFN and IL-15 drive mostly T_H1 cell-mediated immunity, IL-33 and TSLP promote T_H2 cell-mediated immunity. These cytokines could thus also be considered to be master regulatory cytokines of tissue immunity. Interestingly, IL-15 has been found in all mammals sequenced so far, as well as in many reptiles and birds, which shows that this cytokine has been conserved for more than 250 million years of evolution and indicates that it is likely to have an important role in survival. The role of IL-15 and all of its pleiotropic immunological properties can be summarized in terms of its ability to promote the destruction of infected tissue cells. More generally, we propose that tissue destruction by cytotoxic T_{RM} cells only occurs when tissue cells provide them with a `kill me' signal. Furthermore, additional cytokines associated with complex immune disorders[156,157], such as IL-21, could synergize or, to some extent, have redundant functions with IL-15 to promote tissue destruction by licensing effector CTLs to kill[158]. Stratifying patients on the basis of tissue expression levels of IL-15, type I IFN and IL-21, determining the level of redundancy of IL-15 with type I IFN and IL-21, and understanding the mechanisms underlying IL-15 dysregulation and how IL-15 reprogrammes differentiated cells to acquire new functional properties will aid in the design of new therapeutic strategies aimed at modulating tissue immunity.

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Glossary

Activation-induced cell death (AICD)

A phenomenon in T cells, in which activation through the T cell receptor results in apoptosis. CD95 (also known as Fas) and its ligand (CD95L) are the main regulators of

AICD, and the engagement of CD95 ultimately leads to DNA cleavage by caspase-activated DNase (CAD).

Latent autoimmune diabetes in adults (LADA)
A disorder characterized by the presence of diabetes-associated autoantibodies and islet-reactive T cells in the absence of β-cell destruction and overt diabetes.

Lymphokine-activated killer activity (LAK activity)
The ability of T cells to lyse target cells in the absence of specific antigenic stimuli and MHC restriction. LAK cells can be generated *in vitro* in the presence of interleukin-15 (IL-15) or high concentrations of IL-2.

Potential coeliac disease
A form of coeliac disease defined by the presence of transglutaminase- and gluten-specific antibodies and compatible HLA molecules in the absence of villous atrophy.

Tissue-resident effector memory T cells (T_{RM} cells)
A population of non-circulating memory T cells with an effector-like phenotype that have entered tissues during the effector phase of immune responses and can permanently reside in tissues.

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Box 1 | Role of IL-15 in the homeostasis of NK, NKT and CD8$^+$ T cells

The generation of mice deficient in interleukin-15 (IL-15) or in IL-15 receptor α-subunit (IL-15Rα) revealed important roles for IL-15 in the development, maintenance and proliferation of memory CD8$^+$ T cells, natural killer (NK) cells and invariant NKT (iNKT) cells[8,14,104]. IL-15 receptor signalling contributes to cell proliferation and survival through the phosphorylation and activation of Janus kinase 1 (JAK1) and JAK3, which subsequently recruit and phosphorylate signal transducer and activator of transcription 5 (STAT5) and STAT3 (REF. 8). The STAT proteins dissociate from the IL-15 receptor and translocate to the nucleus, where they promote transcription of the gene encoding the anti-apoptotic factor BCL-2 and of the proto-oncogenes *MYC*, *FOS* and *JUN*[14]. IL-15 can also trigger the RAS–RAF–MEK–mitogen-activated protein kinase (MAPK) and the phosphoinositide 3-kinase (PI3K)–AKT signalling pathways, which induce mitogenic signals and BCL-2- and BCL-X$_L$-mediated anti-apoptotic signals, and can limit the production of the pro-apoptotic proteins BIM (also known as BCL-2L11) and PUMA (also known as BBC3)[14].

In addition, IL-15 induces iNKT cell and NK cell activation and increases the cytotoxicity of NK cells by enhancing the production of perforin and granzymes A and B[14]. Macrophage- and dendritic cell-derived IL-15 supports the development and maturation of memory CD8$^+$ T cells, hepatic iNKT cells and NK cells[104]. The *trans*-presentation of IL-15 by intestinal epithelial cells is also crucial for the homeostasis of innate-like T cells such as CD8αα$^+$ TCRαβ$^+$ T cells and TCRγδ$^+$ T cells[30,58,104]. IL-15 supports the survival of unconventional intraepithelial lymphocytes through the activation of JAK–STAT, PI3K–AKT and ERK signalling pathways that lead to the upregulation of BCL-2 and MCL1 expression[14].

Box 2 | Post-transcriptional regulation of IL-15

To tightly control the function of this potent pro-inflammatory cytokine, interleukin-15 (IL-15) expression is tightly regulated at several levels to limit its translation and secretion. First, IL-15-mediated signalling requires that the IL-15 receptor α-subunit (IL-15Rα) is expressed on the cell surface through a mechanism known as *trans*-presentation (FIG. 1b). More specifically, IL-15 is transported through the Golgi apparatus to the cell surface as a complex bound to IL-15Rα. The complex is then presented by membrane-bound IL-15Rα in *trans* to responder cells expressing the IL-2/IL-15 receptor β-chain (IL-2/IL-15Rβ) and the common cytokine receptor γ-chain (γc) of the IL-15 receptor[8]. In addition, IL-15 associated with IL-15Rα can be cleaved into soluble complexes to mediate IL-15 responses[9,10]. Second, IL-15 expression is regulated post-transcriptionally by several distinct mechanisms. Unlike the 5′ untranslated regions (UTRs) of effectively translated mRNAs, which are short and devoid of AUGs, the 5′ UTR of *IL15* is long and contains many AUG sites upstream of the initiation AUG, thus restricting the translation of *IL15* mRNA[98]. The presence of a carboxy-terminal negative regulatory element in the IL-15 mature protein also contributes to control translation[98]. Finally, IL-15 exists as two isoforms generated by alternative splicing. Both produce mature proteins that are associated with alternative signal peptides[98]. The long signal peptide is associated with the secreted soluble form of IL-15, whereas the short signal peptide is associated with a cytoplasmic or nuclear form of IL-15, the intracellular localization of which could be consistent with a role as a transcriptional regulator[98]. Therefore, not only do these signal peptides contribute to the regulation of IL-15 translation, but they also influence the intracellular trafficking of the protein. However, the exact roles of those isoforms are unclear, as is whether their expression and regulation are tissue specific.

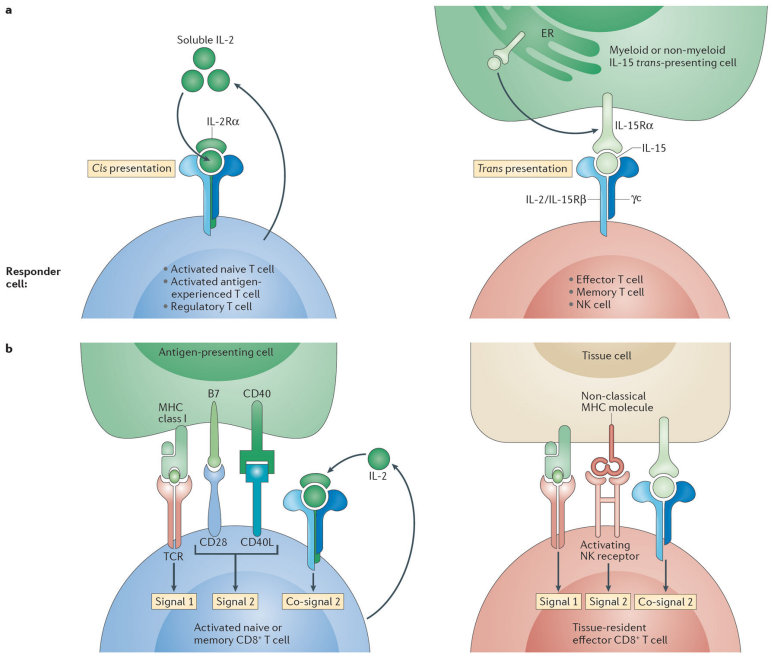

Figure 1. Models contrasting IL-15 and IL-2 signalling and the regulation of naive versus tissue-resident effector memory T cells

a | Interleukin-15 (IL-15) signalling compared with IL-2 signalling. The main mechanism by which IL-15 interacts with its receptor *in vivo* is *trans*-presentation. IL-15 is assembled as an IL-15–IL-15 receptor α-subunit (IL-15Rα) complex intracellularly in the endoplasmic reticulum (ER), then shuttled to the cell surface and presented by distressed cells in *trans* to responder cells expressing a heterodimer of the IL-2/IL-15 receptor β-chain (IL-2/IL-15Rβ) and the common cytokine receptor γ-chain (γc). This receptor is constitutively expressed by effector and memory T cells, as well as by natural killer (NK) cells. Unlike IL-15, IL-2 is mainly secreted as a soluble factor by T cells in response to co-stimulation. IL-2 can bind the IL-2/IL-15Rβ–γc receptor with low affinity and interacts with high affinity in an autocrine manner with the trimeric receptor IL-2Rα–IL-2/IL-15Rβ–γc. This trimeric receptor is only transiently expressed on all activated T cells and NK cells. **b** | Regulation of naive versus effector cytotoxic T lymphocytes (CTLs). Naive or memory $CD8^+$ T cells require, in addition to T cell receptor (TCR) signals (signal 1), co-stimulation (signal 2) provided by CD28 and CD40 ligand (CD40L) — which recognize B7 and CD40, respectively, expressed by dendritic cells — to become activated and undergo differentiation. In the absence of co-stimulation, very little IL-2 is produced by T cells, and cells that receive a TCR signal die or become anergic. IL-2, which is induced in response to signal 2, promotes T cell proliferation and prevents anergy[159], and it therefore functions as a co-signal. By contrast, tissue-resident effector memory $CD8^+$ T cells classically do not express CD28 and do not require signal 2 for survival. Furthermore, tissue cells do not express B7. However, we propose that a different form of co-stimulation is required for tissue effector CTLs to exert their effector function: signal 2 and co-signal 2 are provided by activating NK receptors recognizing non-classical MHC class I molecules and by IL-15, respectively, that are induced on tissue cells under conditions of stress and infection.

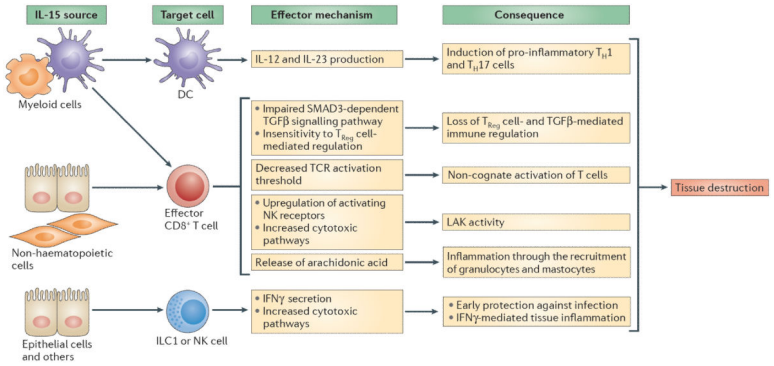

Figure 2. IL-15 has pleiotropic effects on tissue-resident cells that promote T_H1 cell-mediated responses and tissue destruction

Interleukin-15 (IL-15), produced by cells of haematopoietic or non-haematopoietic origin, can act on dendritic cells (DCs) — possibly in an autocrine manner if the source of IL-15 is a DC — and endow them with the ability to secrete IL-12 and IL-23 and to promote the differentiation of T helper 1 (T_H1) and T_H17 cells. In addition, IL-15 blocks the ability of transforming growth factor-β (TGFβ) to suppress the activation of T cells by impairing SMAD3-dependent TGFβ-induced signalling. By activating the phosphoinositide 3-kinase (PI3K) pathway, IL-15 renders effector $CD8^+$ T cells unresponsive to the suppressive effect of forkhead box P3 $(FOXP3)^+$ regulatory T (T_{Reg}) cells. In addition to its ability to upregulate the expression of activating natural killer (NK) receptors such as natural killer group 2, member D (NKG2D), which endows cytotoxic T cells with lymphokine-activated killer (LAK) activity, IL-15 lowers the T cell receptor (TCR) activation threshold. IL-15 synergizes with the NKG2D cytolytic signalling pathway, leading to the activation of cytosolic phospholipase A2 (cPLA2), which in turn crucially regulates NKG2D-mediated degranulation and cytolysis and induces the release of arachidonic acid. Arachidonic acid can promote inflammation and the recruitment and activation of granulocytes. Finally, IL-15 promotes interferon-γ (IFNγ) production by group 1 innate lymphoid cells (ILC1s) and NK cells and cytotoxic pathways in NK cells. All of these IL-15-mediated immunological effects are directed towards promoting protection against intracellular pathogens but can also lead to tissue destruction.

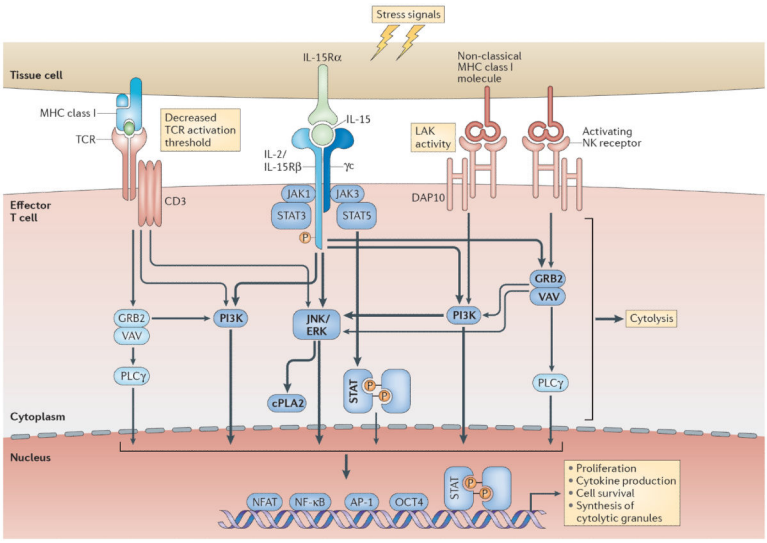

Figure 3. IL-15, NKG2D and the TCR function in synergy to enable CTLs to kill distressed target cells

Interleukin-15 (IL-15) and non-classical MHC class I molecules are induced on tissue cells by cellular stress. IL-15-induced signalling in T cells activates phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase (ERK), JUN N-terminal kinase (JNK) and cytosolic phospholipase A2 (cPLA2). Natural killer group 2, member D (NKG2D), which associates with the adaptor molecule DNAX-activation protein 10 (DAP10; containing a PI3K activation motif), additionally activates VAV–growth factor receptor-bound protein 2 (GRB2) and phospholipase Cγ (PLCγ)[119]. Both IL-15 and NKG2D can hence co-stimulate T cell receptor (TCR) signalling and enhance TCR-mediated effector functions and cell survival. As a result, IL-15-induced signalling in cytotoxic T lymphocytes (CTLs) substantially reduces the TCR activation threshold, enabling CTLs to recognize low-avidity antigens and acquire the potential for autoreactivity. Furthermore, by functioning as a co-stimulatory molecule for the NKG2D-mediated signalling pathway, IL-15 enables NKG2D to mediate direct cytolysis (that is, lymphokine-activated killer (LAK) activity), independently from signalling through the TCR. In addition, IL-15 activates the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, leading to the phosphorylation of STAT3 and STAT5 and the formation of STAT dimers that traffic to the nucleus for transcriptional activation. How the JAK–STAT pathway intersects with TCR and NKG2D signalling remains to be determined. Arrows and words in bold highlight pathways and molecules activated by IL-15. γc, common cytokine receptor γ-chain; IL-2/IL-15Rβ, IL-2/IL-15 receptor β-subunit; IL-15Rα, IL-15 receptor α-subunit; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; NK, natural killer.

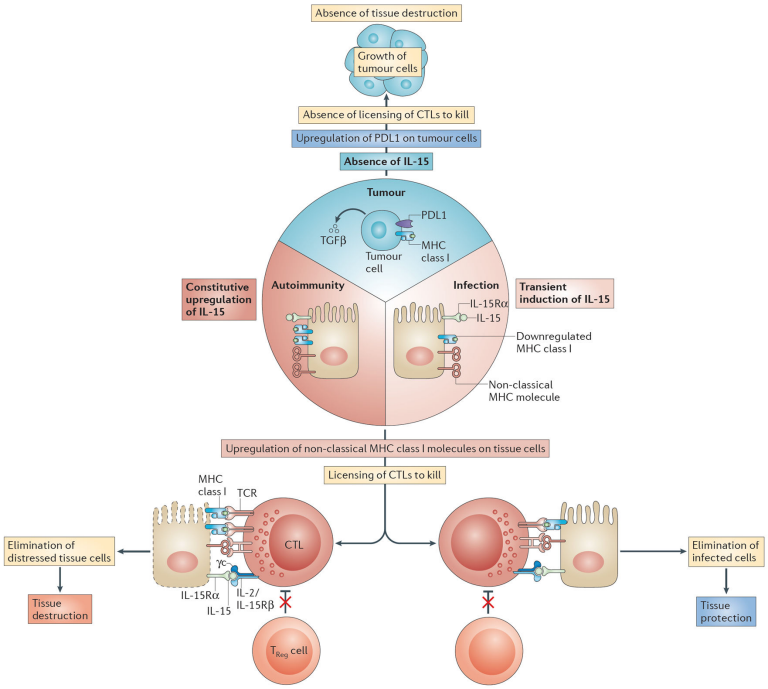

Figure 4. Proposed roles of IL-15 in tissue protection and tissue destruction

Intracellular microorganisms, in particular viruses, cause the downregulation of expression of MHC class I molecules as a mechanism of immune evasion to prevent the destruction of infected cells by cytotoxic T lymphocytes (CTLs). The host, in turn, upregulates expression by infected cells of interleukin-15 (IL-15) and the non-classical MHC class I molecules such as MHC class I polypeptide-related sequence A (MICA), which is recognized by the activating natural killer (NK) receptor NKG2D (natural killer group 2, member D). Together, this leads to a reduced T cell receptor (TCR) activation threshold and to lymphokine-activated killer (LAK) activity in CTLs. CTLs can hence destroy infected cells despite low levels of or absent MHC class I expression. Furthermore, effector CTLs are rendered resistant to the effects of forkhead box P3 $(FOXP3)^{+}$ regulatory T (T_{Reg}) cells and transforming growth factor-β (TGFβ) in the presence of IL-15. Once the infected cells are eliminated and replaced by healthy cells, CTLs return to a `resting state' and again become sensitive to immune regulation. In the context of autoimmunity, MHC class I molecules are not downregulated, and the expression of IL-15 and MICA is constitutive for unknown reasons. This leads to the chronic activation of CTLs and ongoing tissue destruction. By contrast, tumours — in addition to expressing TGFβ and PDL1, which is the ligand for the inhibitory receptor PD1 (programmed cell death protein 1) — also lack surface expression of IL-15 and MICA. Hence, CTLs lack the necessary activating signals as well as being sensitive to the inhibitory signals present in the tumour environment, resulting in a lack of CTL-mediated killing of tumour cells. γc, common cytokine receptor γ-chain; IL-2/IL-15Rβ, IL-2/IL-15 receptor β-subunit; IL-15Rα, IL-15 receptor α-subunit.

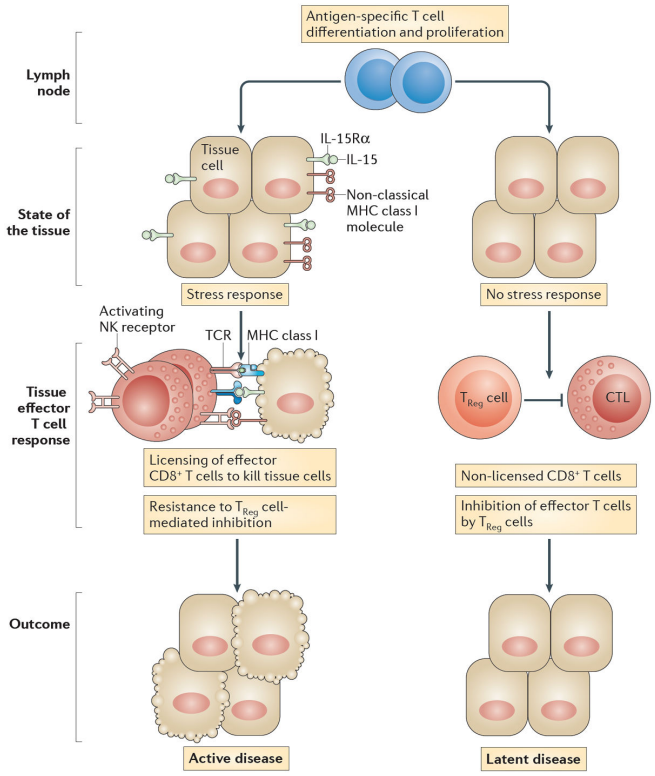

Figure 5. Lack of IL-15 expression by tissue cells is associated with latent autoimmunity

Effector cytotoxic T lymphocytes (CTLs) residing in healthy tissue fail to receive the necessary signals to exert their effector functions and mediate tissue destruction. Only when these effector CTLs are in contact with non-haematopoietic tissue cells that upregulate expression of interleukin-15 (IL-15) and non-classical MHC class I molecules do they become licensed to kill the distressed tissue cells. Latent autoimmune diseases such as potential coeliac disease and latent autoimmune diabetes in adults (LADA) are characterized by the presence of a dysregulated immune response to gluten and β-islet self-antigens, respectively, with the preservation of functional tissue. Conspicuously, IL-15 upregulation is absent in the intestinal epithelial cells and β-islet cells of these patients, which supports the hypothesis that, to mediate tissue destruction, CTLs require signals that license them to kill their target cells. IL-15 upregulation in intestinal epithelial cells and β-islet cells is associated with the licensing of CTLs to promote tissue destruction and the development of active coeliac disease and overt type 1 diabetes, respectively. Licensing of CTLs comprises a reduction in the T cell receptor (TCR) activation threshold, the acquisition of lymphokine-activated killer activity and resistance to immune regulation. IL-15Rα, IL-15 receptor α-subunit; NK, natural killer; T_{Reg} cell, regulatory T cell.