

## Review article

## Interleukin-15 in autoimmunity



Hugues Allard-Chamard<sup>a,b,\*</sup>, Hemant K. Mishra<sup>c</sup>, Madhuparna Nandi<sup>d</sup>, Marian Mayhue<sup>d</sup>, Alfredo Menendez<sup>b,e</sup>, Subburaj Ilangumaran<sup>b,d</sup>, Sheela Ramanathan<sup>b,d,\*</sup>

<sup>a</sup> Division of Rheumatology, Department of Medicine, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, QC, Canada

<sup>b</sup> Centre de Recherche Clinique, Centre Hospitalier d'Université de Sherbrooke, Sherbrooke, QC, Canada

<sup>c</sup> Vet & Biomedical Sciences, University of Minnesota, Minneapolis, MN, USA

<sup>d</sup> Department of Immunology and Cell Biology, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, QC, Canada

<sup>e</sup> Department of Microbiology and Infectious Diseases, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, QC, Canada

## ARTICLE INFO

## Keywords:

IL-15  
Autoimmunity  
Rheumatoid arthritis  
Type 1 diabetes  
Immunotherapy

## ABSTRACT

Interleukin-15 (IL-15) is a member of the IL-2 family of cytokines, which use receptor complexes containing the common gamma ( $\gamma_c$ ) chain for signaling. IL-15 plays important roles in innate and adaptative immune responses and is implicated in the pathogenesis of several immune diseases. The IL-15 receptor consists of 3 subunits namely, the ligand-binding IL-15R $\alpha$  chain, the  $\beta$  chain (also used by IL-2) and the  $\gamma_c$  chain. IL-15 uses a unique signaling pathway whereby IL-15 associates with IL-15R $\alpha$  during biosynthesis, and this complex is 'trans-presented' to responder cells that expresses the IL-2/15R $\beta\gamma_c$  receptor complex. IL-15 is subject to post-transcriptional and post-translational regulation, and evidence also suggests that IL-15 *cis*-signaling can occur under certain conditions.

IL-15 has been implicated in the pathology of various autoimmune diseases such as rheumatoid arthritis, autoimmune diabetes, inflammatory bowel disease, coeliac disease and psoriasis. Studies with pre-clinical models have shown the beneficial effects of targeting IL-15 signaling in autoimmunity. Unlike therapies targeting other cytokines, anti-IL-15 therapies have not yet been successful in humans. We discuss the complexities of IL-15 signaling in autoimmunity and explore potential immunotherapeutic approaches to target the IL-15 signaling pathway.

## 1. Background

IL-15 belongs to the four  $\alpha$ -helix family of cytokines that includes IL-2, IL-4, IL-7, IL-9 and IL-21 [1]. The receptors for IL-4, IL-7, IL-9 and IL-21 are heterodimeric consisting of a ligand-specific  $\alpha$  chain that binds the cytokine and the common  $\gamma$  ( $\gamma_c$ ) chain as the signaling component [2]. The receptors for IL-2 and IL-15 share an additional  $\beta$  chain (IL-2/15R $\beta$ ) to form the heterotrimeric IL-2R and IL-15R receptor complexes [3]. Even though both IL-15 and IL-2 can sustain the proliferation of IL-2 dependent cell lines, the cellular source of IL-15 and IL-2 are different and they serve non-redundant functions in the immune system. IL-2 is produced mainly by activated T cells and plays an important role in T cell expansion during immune responses and in the

maintenance of regulatory T cells [4]. On the other hand, IL-15 is produced by a variety of immune and non-immune cells and is essential for the homeostasis of CD8 $^+$  T cells, NK, NKT,  $\gamma\delta$  T cells and intestinal intraepithelial lymphocytes (IEL) [5–9]. One of the major differences in the manner in which IL-15 signaling is initiated is through a process called 'trans-presentation' [10]. Unlike IL-2, which is secreted and associates with IL-2R $\alpha$  followed by binding to the  $\beta\gamma$  complex on target cells, functional IL-15 signaling in most instances requires the association of IL-15 with IL-15R $\alpha$  during bio-synthesis and the presentation of this ligand-receptor complex to cells that expresses the IL-2/15R $\beta\gamma$  chain complex (Fig. 1). IL-15 complexed to IL-15R $\alpha$  is considered as 'heterodimeric complex'. Reflecting the necessity for trans-presentation, *Il15ra* $^{-/-}$  mice phenocopies *Il15* $^{-/-}$  mice as both harbor reduced

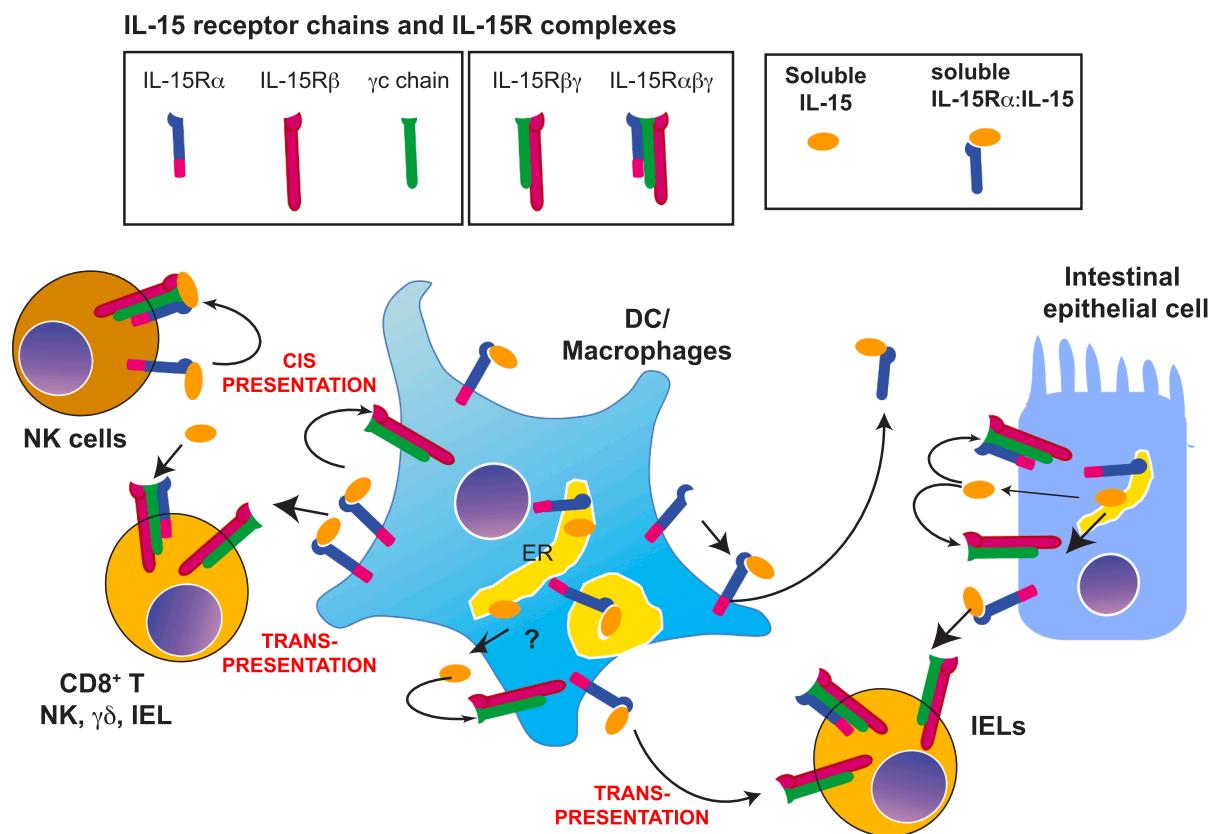
**Abbreviations:** DC, dendritic cells; LSP, long signal peptide; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; mIL-15R $\alpha$ , murine; SCID, severe combined immunodeficient; sIL-15R $\alpha$ :IL-15, soluble IL-15R $\alpha$ :IL-15; SSP, short signal peptide; T1D, type 1 diabetes; Tg, transgenic; Treg, regulatory T cells; UTR, untranslated region

\* Corresponding authors at: Division of Rheumatology, Department of Medicine, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, QC J1H 5N4, Canada (H. Allard-Chamard). Department of Immunology and Cell Biology, Faculty of Medicine and Health Sciences, Université de Sherbrooke, 3001 North 12th Avenue, Sherbrooke, QC J1H 5N4, Canada (S. Ramanathan).

E-mail addresses: [Hugues.Allard-Chamard@USherbrooke.ca](mailto:Hugues.Allard-Chamard@USherbrooke.ca) (H. Allard-Chamard), [Sheela.Ramanathan@usherbrooke.ca](mailto:Sheela.Ramanathan@usherbrooke.ca) (S. Ramanathan).

<https://doi.org/10.1016/j.cyto.2020.155258>

Received 10 August 2020; Accepted 13 August 2020  
1043-4666/ © 2020 Elsevier Ltd. All rights reserved.



**Fig. 1.** Schematic representation of IL-15 synthesis and bioavailability to myeloid and epithelial cells and lymphocytes. IL-15 forms a complex with IL-15R $\alpha$  during biosynthesis and is trans-presented to responder cells expressing IL-15R $\alpha\beta\gamma$  or IL-15R $\beta\gamma$ . Even though soluble IL-15 can act on lymphoid cells (in orange), studies on *Il15ra* $^{-/-}$  mice indicate that the bioactivity of endogenously produced IL-15 is critically dependent on IL-15R $\alpha$  mediated trans-presentation for lymphoid cells. Most of the soluble IL-15 is complexed with sIL-15R $\alpha$  that is cleaved from the cell surface *in vivo*. At high concentrations IL-15 can signal directly via IL-15R $\beta\gamma$ . NK - Natural killer cells, IEL - intra-epithelial lymphocytes.

numbers of memory CD8 $^+$  T cells, NK cells, NKT cells and IEL [11,12]. As the genes coding for IL-15 and IL-15R $\alpha$  are expressed by most cell types, the requirement for trans-presentation of IL-15 by IL-15R $\alpha$  suggests that the bio-availability of IL-15 is tightly regulated *in vivo*. Moreover, it also implies that under physiological conditions, the site of action of IL-15 is limited to the vicinity of the producer cells and that IL-15 cannot easily diffuse to reach distant sites of action. The reader is referred to excellent reviews on the topic of IL-15 trans-presentation to T cells and NK cells for more details [5,13–15]. Here, we focus our discussion on the role of IL-15 in autoimmune diseases and the complexities of IL-15 and its receptor expression.

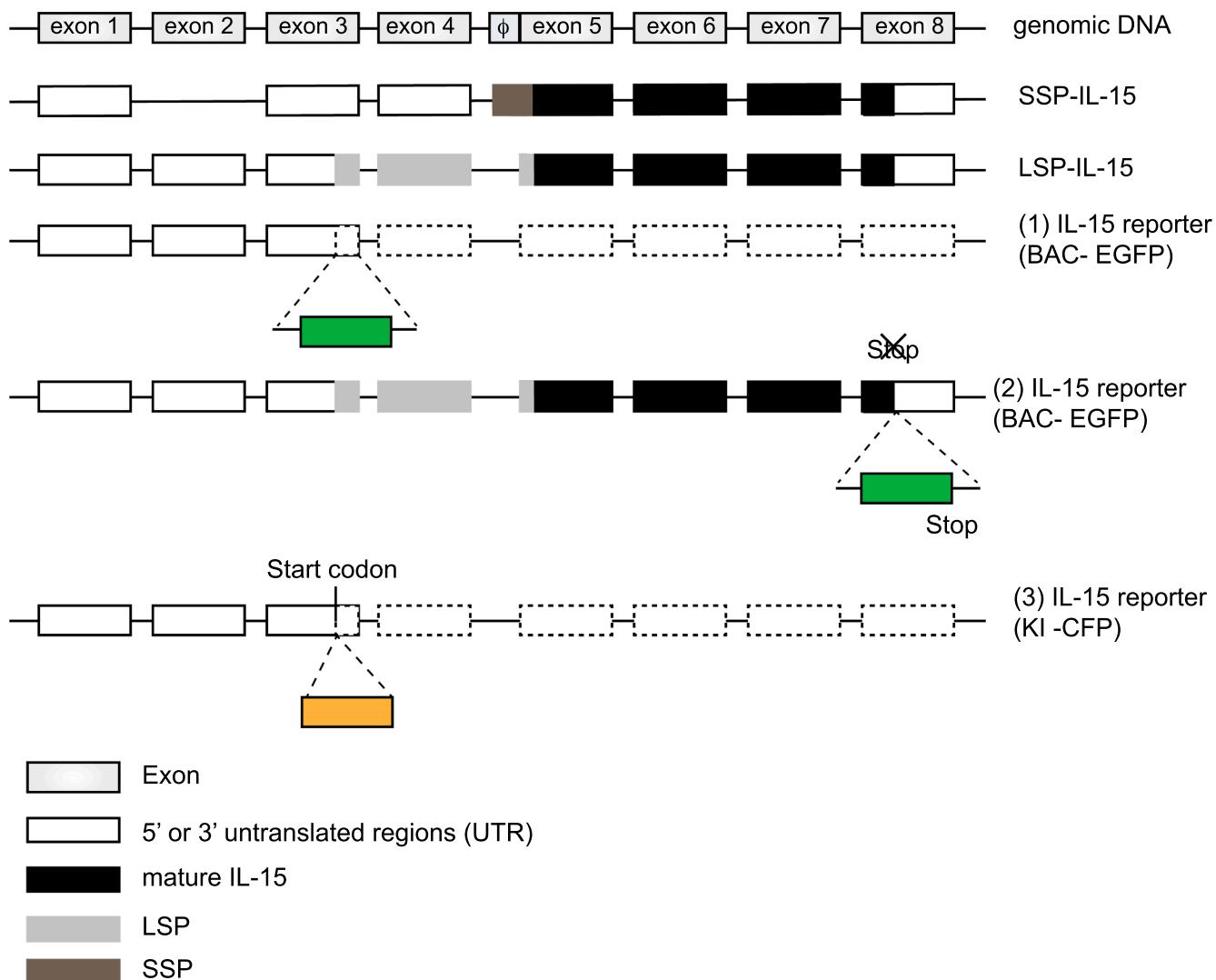
## 2. IL-15 and autoimmunity

IL-15 is broadly expressed by hematopoietic and non-hematopoietic cells [16] and influences various aspects of the innate and adaptive immune system [17] and plays a key role in the pathogenesis of various autoimmune disorders [17–20]. IL-15 can indeed be a treacherous cytokine as it could limit self-tolerance mediated by AICD if not regulated properly [21]. The mechanisms through which IL-15 promotes chronic inflammation and tissue-specific autoimmune diseases have been studied in detail in rheumatoid arthritis, inflammatory bowel disease, autoimmune diabetes and celiac disease [1,22–29], however the exact role of IL-15 in the cytokine cascade remains obscure. Chronic inflammation associated with autoimmunity in turn, can upregulate IL-15 expression and sustain the inflammatory processes. IL-15 and other inflammatory cytokines that are upregulated following viral infections have been associated with autoimmunity [30,31]. One of the potential side effects of using IL-15 along with checkpoint inhibitors for cancer

immunotherapy is the reactivation of autoreactive T cells [32,33]. Disease susceptibility mapping studies have identified polymorphisms in *IL15* and/or *IL15RA* in psoriasis, rheumatoid arthritis and celiac disease thus highlighting the putative roles of IL-15 in activating different subsets of innate and adaptive immune cells [29,34,35]. It also strongly suggests that IL-15 contributes to sustaining the pathological processes in autoimmunity.

## 3. IL-15 isoforms and their expression

IL-15 was cloned in 1994 independently by 2 groups as a soluble factor produced by a simian epithelial kidney cell line and HTLV-1-transformed T-cell leukemia cells (HuT-102) [36,37]. *Il15* transcripts can be easily detected at high levels in placenta, skeletal muscles, kidney and LPS-activated monocytes and to a lesser extent in lungs, liver, heart and pancreas under steady-state conditions [16,36]. Human IL-15 is expressed in two isoforms, one with a short signal peptide (SSP; 1.2 kb) of 21 aminoacids and the other with a long signal peptide (LSP; 1.5 kb) of 48 aa upstream of the IL-15 coding region [38] (Fig. 2). The SSP-IL-15 is detected at a basal level in most of the tissues tested but is very low in lymphocytes, skeletal muscle, ovary and brain [38] whereas the LSP-IL-15 is primarily expressed in skeletal muscles and kidney. The signal peptide of SSP-IL-15 does not resemble a typical signal peptide as it does not target the mature protein to the endoplasmic reticulum and is not secreted outside the cell [38]. Besides, translation of the SSP-IL-15 is inefficient due to the weak Kozak sequence preceding the initiation codon [38]. The LSP sequence regulates the rate of IL-15 synthesis and targets it for secretion [38,39]. Intriguingly, deletion of the LSP domain increases the quantity of the intra-cytosolic and secreted IL-15



**Fig. 2.** Schematic representation of genomic organization of IL-15. Genomic Organization of the murine IL-15 gene is shown. Two alternately transcribed mRNAs (SSP-IL-15 and LSP-IL-15) are generated. They differ in the signal peptide sequences while the sequence of the mature IL-15 generated remains the same. The organization of the (BAC constructs) and knockin reporter is indicated. The diagram is not to scale. 1- Ref#48; 2- Ref#50; 3- Ref #49. Human IL-15 also shows a similar functional organization; Ref # 3, 40.

[39]. The difficulty of detecting IL-15 protein and the existence of two different signal peptides is not unique to humans as similar genomic organization and alternate isoforms of the transcribed IL-15 are observed in mice [40–42]. Similar to human IL-15, murine LSP-IL-15 is produced in greater quantity and is secreted while SSP-IL-15 remains intracellular [38,42].

Despite the presence of abundant IL-15 transcripts in many tissues the detection of intracellular or secreted protein is often difficult [42–46], indicating that post-translational mechanisms play an important role in regulating protein levels. The 5' UTR of IL-15 mRNA contains up to 10 AUG sequences that impede efficient translation in mammalian cells [46]. Thus IL-15 is expressed at high levels by HuT-102 cells as this inhibitory 5' UTR is lost in the fusion between long terminal repeat of HTLV-1 and *IL15* gene [46]. In addition to the above-mentioned translational controls, sequences at the 3' end of the IL-15 mRNA also diminish the translational efficiency [39]. Following translation, LSP-IL-15 may undergo three different fates [38,42]. The majority of the translated protein is unglycosylated and is degraded by proteasomes in the cytosol. A fraction of LSP-IL-15 translocate to the ER where following glycosylation, multiple species of LSP-IL-15 are generated by alternative cleavage of the LSP. The fully processed glycosylated 16–17 kDa IL-15 protein is secreted through the conventional

ER-Golgi pathway [47]. Nishimura *et al.* [42] compared the abundance and translational efficiency of IL-15 transcripts isolated from LPS and IFN $\gamma$  activated peritoneal macrophages. Of the three mRNA isoforms, the SSP isoform that generates a 16 kDa protein was efficiently translated *in vitro*. Analysis of lysates of peritoneal macrophages stimulated with a combination of IFN $\gamma$  and LPS (LPS/IFN $\gamma$ ) also revealed the presence of 16 kDa protein associated with SSP-IL-15. Despite the relatively higher efficiency of the LSP-IL-15 transcripts to undergo translation, the tissue distribution pattern and the observed upregulation of the SSP-IL-15 in macrophages, suggest that the SSP-IL-15 may be of physiological significance during immune responses. However, additional studies are needed to compare the regulation of the two isoforms in different cell types and tissues during immune responses to pathogens and in autoimmunity.

In order to follow the expression of IL-15 in different tissues, three different IL-15 reporter mice were generated using the LSP-IL-15 isoform [48–50] (Fig. 2). Colpitts *et al.* [48] generated a transcriptional reporter by replacing the first 4 aa of the LSP-IL-15 sequence with EGFP and 42 kb upstream sequences in a bacterial artificial chromosome. Sosinowski *et al.* [50] constructed a similar BAC vector but cloned the EGFP downstream of the IL-15 coding sequence such that the EGFP expression was also a reflection of translation. Both groups showed

transcriptional upregulation of IL-15 to varying levels in DC subsets following infections. Cui et al [49] generated a translational reporter for IL-15 by replacing the LSP-IL-15 sequence with CFP (IL-15-CFP KI mice) to identify the different cell types and the tissues where IL-15 protein is expressed. Within the thymus, MHC class-II<sup>hi</sup> medullary thymic epithelial cells (mTEC) expressed higher levels of IL-15 when compared to MHC class-II<sup>lo</sup> mTEC, cortical TEC, vascular endothelial cells and pericytes. These observations suggest that IL-15 can influence the development of CD8<sup>+</sup> T cells in the thymus as reported previously [51–53]. IL-15 expression was also high in a subset of CXCL12-abundant reticular (CAR) cells in the bone-marrow and fibroblastic reticular cells (FRC) in the T cell zones of peripheral lymph nodes excluding mesenteric lymph nodes. In addition to DC, liver macrophages expressed high levels of IL-15 [49]. LPS administration to IL-15-CFP mice upregulated the expression of IL-15 in lymphatic and vascular endothelial cells in addition to DC and liver macrophages. In the intestine, endothelial cells in the lamina propria expressed higher levels of IL-15 than intestinal epithelial cells (IEC). However, conditional deletion of IL-15 in IEC affects the maintenance of intestinal IELs, indicating that the low level of IL-15 expression is sufficient for biological function [54]. As a corollary, IL-15R $\alpha$  in DC, macrophages, hepatocytes and IEC is required for the maintenance of CD8<sup>+</sup> T cells, NK and NKT cells in different organs [55–58]. Thus, despite the low expression, IL-15 expressed in non-hematopoietic tissues contributes to the homeostasis of immune cells responsive to IL-15.

#### 4. IL-15R $\alpha$

IL-15R $\alpha$  is the exclusive ligand binding chain for IL-15 similarly to IL-2R $\alpha$  for IL-2. Both IL-2R $\alpha$  and IL-15R $\alpha$  lack signaling competent protein motifs in their cytoplasmic tail. The former contains two sushi domains and the later one domain that are involved in cytokine binding [59]. Unlike IL-2R $\alpha$ , which is mainly expressed by antigen stimulated T cells, IL-15R $\alpha$  shows a wide tissue distribution. While IL-2 binds IL-2R $\alpha$  with moderate affinity and the heterotrimeric receptor complex with high affinity [4], IL-15 binds IL-15R $\alpha$  with a very high affinity that is not enhanced by its interaction with IL-15R $\beta\gamma$  chains. Human IL-15 can bind to murine IL-15R $\alpha$  (mIL-15R $\alpha$ ) with high affinity ( $10^{-11}$ M), which is greater than that of mIL-15 [59–61]. Thus, the use of mIL-15 in experiments with murine cells can alter the inherent biological outcome pertinent to the species and this may underlie the differences observed between *in vitro* and *in vivo* situations. Additional receptors for IL-15 have been characterized in mast cells, but the details of the signaling mechanisms have not been characterized [62].

The functional significance of IL-15 trans-presentation by IL-15R $\alpha$  became obvious following the observations that *Il15ra*<sup>-/-</sup> lymphocytes respond to IL-15 as long as IL-15R $\alpha$  was expressed on stromal cells [55,56,63,64]. Tissue-specific deletion of IL-15R $\alpha$  revealed the requirement for trans-presentation by specific cell subsets to maintain IL-15-dependent lymphocytes *in vivo* [55–58]. Similarly, IL-15 expression in any given tissue is required for the survival of tissue-resident IL-15-dependent lymphocyte subsets locally [54,57,65]; for example, the absence of IL-15R $\alpha$  or IL-15 in the intestinal epithelium negatively impacts the development of intestinal IELs. These observations strongly suggest that the availability of circulating IL-15 does not replace the membrane bound IL-15:IL-15R $\alpha$  in the maintenance of lymphoid populations in tissues.

##### 4.1. Biological activity of IL-15 requires association with IL-15R $\alpha$

Unlike other cytokines of its family, IL-15 and IL-15R $\alpha$  function as a heterodimeric complex. Duitman et al. [66] used cloned human IL-15 mature protein with human IL-15R $\alpha$  in COS7 and PC3 cell lines and the expression of these proteins in primary human monocytes to study the trafficking of IL-15. IL-15 and IL-15R $\alpha$  associate with each other during the transit from the ER to Golgi complex prior to being expressed on the

cell surface [66]. Presence of IL-15R $\alpha$  protects IL-15 from proteasomal degradation [66]. The study by Bergamaschi et al. [67] used human IL-15 and IL-15R $\alpha$  constructs with optimised codon usage in 293 cells *in vitro* and hydrodynamic injection of plasmids in mice for *in vivo* analysis. In this study they showed that IL-15R $\alpha$  associates with LSP and SSP isoforms of IL-15, leading to cell surface expression of these heterodimeric complexes. SSP-IL-15, which is usually localized intracellularly, is also detected on the cell surface after interaction with IL-15R $\alpha$  [67]. Hydrodynamic delivery of plasmids expressing SSP-IL-15 or LSP-IL-15 with IL-15R $\alpha$  in mice resulted in increased levels of plasma IL-15 and an increased expansion of NK cells and CD8<sup>+</sup> T cells in circulation [67]. However, when increasing amount of plasmids expressing SSP-IL-15 was injected with constant amounts LSP-IL-15 and IL-15R $\alpha$ , there was a reduction in plasma IL-15 levels with little increase in the cell numbers in the spleen, suggesting that SSP-IL-15 may be a competitive inhibitor of IL-15 activity as it is inherently less stable than the LSP-IL-15 isoform [67]. In this context, it is noteworthy that Nishimura et al. [42] reported more efficient translation of the transcripts of SSP-IL-15 isoform compared to the LSP-IL-15 isoform in cell-free systems. On the other hand, the two isoforms of IL-15 were equally upregulated in a J744A.1 murine macrophage cell line and peritoneal macrophages following stimulation with LPS/IFN $\gamma$ . In contrast, the SSP-IL-15 isoform was predominant in *Salmonella* infected peritoneal macrophages. Reflecting this difference, the lysates of IFN $\gamma$ /LPS activated macrophages contained detectable amount of SSP-IL-15 protein but not LSP-IL-15. These observations suggest that despite being inefficiently expressed at steady state, the SSP-IL-15 may play an important role during immune responses [67–69]. It is possible that the expression of IL-15 is regulated by the differential expression of the 2 isoforms in autoimmunity, even though there are no studies supporting this possibility. Similarly, despite the low level of expression of IL-15 in various tissues, conditional deletion of IL-15 in IEC affects the maintenance of intestinal IELs, indicating that the low level of IL-15 expression is necessary and sufficient for biological function of IELs [54]. As a corollary, IL-15R $\alpha$  in DC, macrophages, hepatocytes and IEC is required for the maintenance of CD8<sup>+</sup> T cells, NK and NKT cells in different organs [55–58].

Bone marrow chimeras with WT, *Il15*<sup>-/-</sup> and *Il15ra*<sup>-/-</sup> mice indicated the necessity for IL-15 and IL-15R $\alpha$  to be expressed by the same cell for bioactivity [67,70,71]. To characterize endogenous IL-15:IL-15R $\alpha$  interactions *in vivo* under homeostatic conditions, different groups analyzed the kinetics of IL-15 and IL-15R $\alpha$  expression in dendritic cells (DC) and the requirement of the IL-15R $\alpha$ :IL-15 complex in activating NK cells [72,73]. Similar to the observation in the overexpression systems discussed above, IL-15R $\alpha$ :IL-15 complex in DC is formed before it is transported from the Golgi to the plasma membrane. Upregulation of transcripts for *Il15* in *Il15ra*<sup>-/-</sup> mice or for *Il15ra* transcripts in *Il15*<sup>-/-</sup> mice indicated that their transcription is not dependent on each other [73]. However, in the absence of IL-15R $\alpha$ , IL-15 protein was not stable. While TLR ligands induced the formation of the IL-15R $\alpha$ :IL-15 complex in WT DCs that are capable of activating NK cells, co-culture of IL-15 deficient and *Il15ra*<sup>-/-</sup> DC did not result in the formation of the complex following TLR stimulation, indicating either that IL-15 is not secreted in the milieu or that the IL-15 secreted by *Il15ra*<sup>-/-</sup> DC is unable to interact with IL-15R $\alpha$  present on *Il15*<sup>-/-</sup> DC. These observations which recapitulate the observations made in overexpression systems discussed above, highlight the importance of coordinated expression of IL-15 and IL-15R $\alpha$  by the same cell in order to form biologically active cell-bound IL-15R $\alpha$ :IL-15 complexes [72,73].

In contrast to trans-presentation where IL-15R $\alpha$ :IL-15 complex on the IL-15 producing cell activates responding cells that express IL-15R $\beta\gamma$  complexes, there are certain situations where IL-15R $\alpha$ :IL-15 complex expressed on the cell surface can activate IL-15R $\beta\gamma$  on the same cell and this process is referred to as *cis*-presentation. *Cis*-presentation has been observed in DC *in vivo* [74]. Following stimulation

through TLR ligand, IL-15 expression that is upregulated in DC acts in an autocrine fashion to activate DC and macrophages. Treatment of NK cells with fused IL-15R $\alpha$ :IL-15 complexes can also initiate signaling by interacting directly with the IL-15R $\beta\gamma$  present on the same cell [75–79]. Thus different constructs of IL-15 fused to IL-15R $\alpha$  sushi domain with or without a Fc region for membrane anchoring are undergoing various phases of clinical trials as immunotherapeutic agents to treat cancer [80–85].

The role of soluble IL-15 and sIL-15R $\alpha$ :IL-15 complex in lymphocyte homeostasis is not very well known. It is well-established that membrane-bound IL-15R $\alpha$ :IL-15 complexes is essential for mediating IL-15-dependent functions on lymphocytes [73]. It has been difficult to detect IL-15 in the supernatants or in body fluids as it is present in very low quantity. Very few groups have shown bioactivity of circulating IL-15 or sIL-15R $\alpha$ :IL-15 complex even under conditions of overexpression [67,68,86], while other groups have not been able to detect functional IL-15 *in vitro* or *in vivo* [46,87]. Furthermore, it has been observed that in humans and in mice, the amount of IL-15 detected in circulation corresponds to that of sIL-15R $\alpha$ :IL-15 complex that is shed from the cell surface in a physiological manner and hence may not be bioactive [59,87,88]. sIL-15R $\alpha$ :IL-15 complexes are cleaved from the cell surface by proteases, but this complex lacks biological function [87]. The cleavage of IL-15R $\alpha$  may be part of the physiological process [86] as it is observed even in *Il15*<sup>-/-</sup> mice [73]. Total body irradiation is associated with increased amount of sIL-15R $\alpha$ :IL-15 complexes in circulation [88,89] as the entry of gut-derived LPS and other microbial components into circulation increases the expression of IL-15R $\alpha$ :IL-15 complexes on the surface of macrophages and other cell types with a concomitant increase in circulating complexes [89]. Induction of systemic inflammation presumably underlies this phenomenon as the synthetic TLR3 ligand poly I:C also increases the circulating levels of sIL-15R $\alpha$ :IL-15 [90]. This increase in sIL-15R $\alpha$ :IL-15 is essentially dependent on ADAM17 mediated cleavage, as it did not occur in *Adam17*<sup>-/-</sup> bone marrow derived dendritic cells [90]. While the increase in sIL-15R $\alpha$ :IL-15 following total body irradiation and poly I:C require intact type 1 IFN (IFN-I) signaling, viral infections can release this complex even in the absence of IFN-I signaling [90,91]. Thus, it appears that the shedding of sIL-15R $\alpha$ :IL-15 complexes is generally associated with their increased expression although their shedding could be mediated by transient activation of ADAM17 during inflammation [92].

Soluble IL-15 has been shown to activate NK cells and CD8 $^{+}$  T cells *in vivo* and *in vitro* in various experimental models. As the stability of IL-15 is increased by complexing with IL-15R $\alpha$  thereby increasing its biological activity [77,78,93], it is possible to hypothesize that the sIL-15R $\alpha$ :IL-15 complexes can increase the concentration of IL-15 in the vicinity of the responding cells and result in the ‘exchange of IL-15 from the complex to the IL-15R $\alpha$  on the responding cell’ to mediate activation even though there is no evidence *in vivo* for such a mechanism [73,87]. IL-15R $\alpha$  bound to IL-15 can activate IL-2/15R $\beta\gamma$  expressed on the same cell or on nearby cells [10,75,94]. IL-15 bound to the IL-15R $\alpha$  on the lymphocyte surface can prolong the activation process as the complex is recycled through the endosomal pathway [10]. Alternately, it has been shown *in vitro* that human CD8 $^{+}$  T cells and NK cells can take up the sIL-15R $\alpha$ :IL-15 complexes that is shed from the IL-15 presenting cell by trans-endocytosis to maintain their activation [95–96]. Proof for such mechanisms *in vivo* is not available yet. By virtue of the ability of IL-15 to activate NK cells, the use of IL-15 to boost anti-tumor immune responses has emerged as an active field of research. However, treatment with IL-15 has been associated with high toxicities in humans accompanied by a 50-fold increase in the serum amount of certain cytokines such as TNF $\alpha$ , IL-6 and IFN $\gamma$  as well as a constellation of symptoms highly reminiscent of macrophage activation syndrome (cytopenia, hypotension, liver injury) [97–102]. As conjugating IL-15 with IL-15R $\alpha$  increased its half-life and bioactivity [67,77,78,93], IL-15:IL-15R $\alpha$ -Fc conjugates, anchored to the membrane through the Fc

receptor, have been generated for use in cancer immunotherapy [15,80,103]. Taken together, these observations in humans indicate that presentation of IL-15 by membrane-bound IL-15R $\alpha$  is required for optimal IL-15 mediated activation of lymphocytes.

IL-15 and IL-15R $\alpha$  expression is upregulated in different types of non-lymphoid cells such as synovial fibroblasts, epithelial cells, keratinocytes and myeloid cells to varying degrees during infections through IFN-I dependent and independent pathways [86,89,91,104]. The *Il15* promoter contains interferon regulatory factor motif (IRF-E) and NF- $\kappa$ B binding motifs indicating that viral elements can upregulate the expression of IL-15 directly [105]. While viral infections can trigger type 1 IFNs directly in Mo-DC and plasmacytoid DC, concomitant presence of IL-15, IL-4, IL-7, IL-12 or GM-CSF enhance its production [106]. Similar to DC-lymphocyte interactions, most of the effects of IL-15 in activating DC and macrophage subsets occurs via cell-cell contact [74]. *In vitro* stimulation of human and murine myeloid cells [107–109] with IL-15 induces JNK and NF- $\kappa$ B, but not JAK/STAT pathway [108,110]. Exposure of Mo-DC to IL-15 enhances their tumoricidal potential [111–112]. Additional studies are required to understand the outcome of IL-15 in non-lymphoid cells during immune responses and in autoimmunity.

## 5. IL-15 in autoimmune diseases

### 5.1. IL-15 in Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most prevalent inflammatory arthritis affecting close to 1% of the general population [113]. It results in progressive inflammation and hypertrophy of the joint’s synovial membrane. The altered synovium of RA is called the rheumatoid pannus [114]. It grows in a tumor-like fashion and invades the surrounding tissue eroding both the bone and cartilage in the vicinity of the joint [115–116]. Uncontrolled cell proliferation in the pannus ultimately leads to joint dysfunctions [117]. Although the exact mechanism triggering the initiation and course of RA remains speculative, both innate and adaptive immune cells are at the core of the pathogenic process. Activated lymphoid (B cells, T cells and NK cells) and myeloid (monocytes, macrophages) cells can be found infiltrating the synovia [114]. Many lines of evidence suggest that IL-15 is a crucial player in RA development, progression and bone destruction. For instance, administration of intravenous recombinant IL-15 can trigger joint inflammation and musculoskeletal symptoms [83,100] and IL-15 over-expression in transgenic mice leads to exacerbated collagen-induced arthritis [118]. IL-15 strongly correlates with both rheumatoid factor and anti-cyclic citrullinated peptide (CCP) seropositivity [34]. These two autoantibodies are well established biomarkers of RA, its aggressiveness and joint erosion. Moreover, circulating concentration of IL-15 tightly correlates with RA activity [119] and its expression is highly elevated within the synovial membrane [25,120]. Specifically, expression of IL-15 has been reported in macrophages, endothelial cells and synoviocytes of RA patients [120]. Genetic variations in *Il15* gene are also associated with RA. Pavkova et al. reported increased prevalence of the *Il15*-267C/T (rs2254514) polymorphism in RA patients compared to healthy controls [34]. Five additional SNPs of the *Il15* locus rs7667746, rs7665842, rs2322182, rs6821171, and rs4371699 have been associated with aggressiveness and a more severe course of RA [121]. IL-15, being a pleiotropic cytokine, its exact role in RA has not been fully elucidated. However, it seems to be an early effector of the inflammatory cascade acting upstream of TNF $\alpha$ , a very well-studied pro-inflammatory cytokines with a prominent role in RA [6,122]. IL-15 can also induce TNF $\alpha$  production from macrophages [25]. Nonetheless, TNF $\alpha$  is not strictly downstream of IL-15 and the interplay between the two cytokines is likely more complex as TNF $\alpha$  could also further nurture IL-15 production from synoviocytes [123].

IL-15 produced locally in the pannus not only can activate potentially autoreactive T cells and thus initiate the disease process but also

can perpetuate the inflammatory cascade leading to joint destruction [120]. In support of this notion, in a model of severe combined immune deficient (SCID) mice engrafted with human RA synovial tissue, endothelial cell-derived IL-15 promoted trans-endothelial migration of T cells and invasion of the synovium [124], as IL-15 has been shown to induce the expression of O-glycans and permit the trafficking of memory CD8<sup>+</sup> T cells to inflamed tissues [125]. In addition, explanted human RA synovium in SCID mice exhibits a spontaneous production of TNF $\alpha$ , IL-6 and IL-1 $\beta$ , which can be partially abrogated by treatment with anti-IL-15 antibody [126]. IL-15 expressing synoviocytes can induce TNF $\alpha$ , IFN $\gamma$  and IL-17 production when co-cultured with T cells [127]. IL-15 enhanced the proliferation of CD4<sup>+</sup> T cells in coculture with macrophages from RA patients [128] and altered CD4<sup>+</sup> T cell polarization. IL-15 primed CD4<sup>+</sup> T cells expressed more IL-23R and produce more IL-17 [118]. *In vitro* IL-15 increased the levels of MHC-II on murine macrophages that resulted in enhanced proliferation of co-cultured antigen specific CD4<sup>+</sup> T cells [128]. The exuberant proliferation observed is not strictly dependent on the MHC regulation as, in both CD4<sup>+</sup> and CD8<sup>+</sup> T cells, IL-15 can lower the threshold for TCR activation and enhance signaling through the ERK and PI3K pathways [129]. IL-15 primed T cells can even overcome tolerance against auto-antigens. IL-15 effect on TCR signaling is independent of the JAK pathway and might represent an alternative pathway to target JAK inhibitor resistant RA [129]. Taken together, these observations highlight the role of IL-15 as a key player of RA pathophysiology and a potential therapeutic target to halt the progression of the disease (Fig. 3). Not surprisingly, different groups have targeted IL-15 in pre-clinical models of RA and in RA patients (discussed in Section 6).

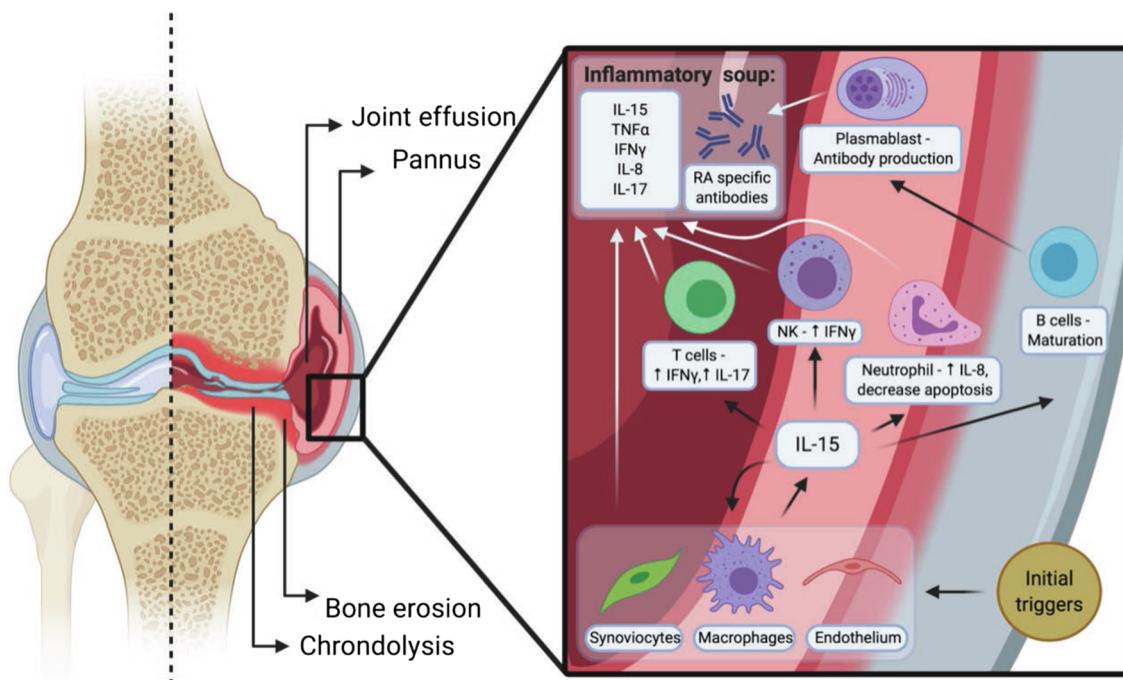
## 5.2. IL-15 in Type 1 diabetes (T1D)

Autoimmune type 1 diabetes (T1D) is a polygenic disease where the insulin producing  $\beta$  cells of the pancreas are destroyed by the immune system [130]. The age of onset ranges from birth to adulthood [131]. Inflammation in the islets initiates the production of islet-specific autoantibodies and progressive T cell-mediated destruction of the islets. While the MHC haplotype predicated the strongest genetic susceptibility

[132], the onset and progression can be modulated by other genetic variations and environmental factors that influence the prognosis of the disease [133]. Various studies have demonstrated an increase in the levels of IL-15 or IL-15R $\alpha$  in the serum and/or in the islets of T1D patients [134–135].

One of the early evidence for a role for IL-15 in the pathogenesis of T1D comes from the observations that treatment of new onset T1D in NOD mice with a combination of IL-2-Fc, mutant-IL-15-Fc along with rapamycin that reduces effector T cell activation [136], prevented further destruction of the few remaining islets and established normoglycemia [137–138]. Whereas IL-2-Fc would have increased the activity of Tregs [139], mutant-IL-15-Fc that competes for IL-15R $\alpha$  would have increased the apoptosis of autoreactive CD8<sup>+</sup> T cells [140]. While the  $\beta$ -cell mass did not show any significant increase, the inflammatory response was attenuated in both cases. Previous work had suggested that targeting  $\gamma_c$  cytokine receptor signaling but not co-stimulatory molecules, was effective in controlling the progression of T1D even after the establishment of the autoreactive T cell repertoire [140–141]. However, survival of islet grafts in mice with T1D required inhibition of co-stimulatory molecules and  $\gamma_c$  signaling [141], indicating that co-stimulation contributed to the priming the naïve repertoire of autoreactive T cells, while the  $\gamma_c$  signaling promotes survival of already primed autoreactive T cells.

The protective effect of the anti- $\gamma_c$  treatment suggests that inhibiting the effector cells that mediate the destruction of islets is more effective than increasing the activity of Tregs as the anti- $\gamma_c$  treatment would also inhibit IL-2 signaling in Tregs. In diabetic patients, allogenic response to the islet grafts during transplantation and the islet-specific T cell response by low avidity and memory CD8<sup>+</sup> T cells contribute to the graft rejection despite immunosuppression [142–143], indicating that antigen specific CD8<sup>+</sup> T cell responses are critical. Additionally, the immunosuppressive T cell depletion regimens used in transplantation increase the production of homeostatic cytokines such as IL-7 and IL-15 to permit the expansion of residual T cells [144]. We have shown previously that exposure of naïve autoreactive CD8<sup>+</sup> T cells to these homeostatic cytokines decreased the TCR threshold and resulted in their activation by low doses of cognate antigen or low affinity altered



**Fig. 3.** IL-15 in rheumatoid arthritis. Contribution of IL-15 to the pathophysiology of rheumatoid arthritis. IL-15 is at the apex of the cytokine cascade triggering rheumatoid arthritis. It can act in an autocrine or a paracrine fashion to promote immune activation, pannus formation and ultimately lead to joint dysfunction and destruction. In the synovium the main sources of IL-15 are the synoviocytes, the macrophages and the endothelial cells. Please refer to the text for details.

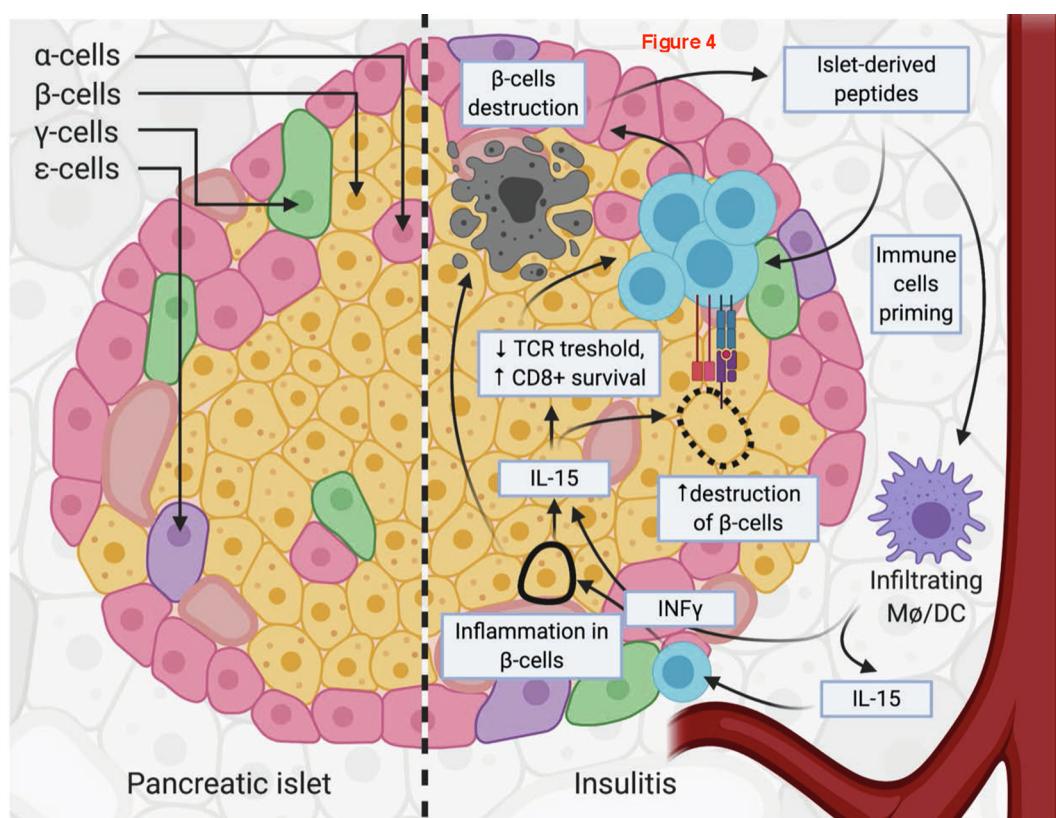
peptide ligands [145]. These findings suggested a potential role for IL-15 in the initial activation of naive autoreactive CD8<sup>+</sup> T cells. Accordingly, we have shown that the incidence and severity of T1D are markedly reduced in NOD mice lacking IL-15 [22]. Furthermore, administration of antibody to IL-2/15R $\beta$  during the insulitis stage [22] or later [146–150] prevented T1D development. These reports suggest that IL-15 acts at all stages of T1D progression and blocking IL-15 signaling presumably targets different cell types at different stages of the disease. Inflammation can upregulate the expression of IL-15 in mouse and rat islets [151–152] and overexpression of IL-15 and IL-15R $\alpha$  in the islets initiates T1D in C57Bl/6 mice [147]. Adoptive transfer of wildtype splenocytes (containing autoreactive T cells) from diabetic mice does not induce T1D in *Il15*<sup>-/-</sup>.NOD.Scid or in NOD.Scid.Gamma mice (NSG) [22]. While it is possible that diabetogenic CD8<sup>+</sup> T cells cannot be maintained in *Il15*<sup>-/-</sup>.NOD.Scid mice, the NSG mice can still trans-present IL-15 to maintain the injected splenocytes, suggesting a role for IL-15 in promoting islet antigen presentation possibly via sustaining inflammation. Additional evidence supports a pathogenic role for IL-15 in T1D that may occur independently of its requirement for the maintenance of lymphocyte subsets. While *Il15*<sup>-/-</sup>.NOD mice are protected from T1D, *Il15ra*<sup>-/-</sup>.NOD mice develop T1D with kinetics similar to that of NOD mice [153]. Thus, T1D development requires IL-15 but does not require its trans-presentation by IL-15R $\alpha$ , whereas both are needed for the maintenance of memory CD8<sup>+</sup> T cells. Therefore, new-onset T1D patients and the T1D patients who receive islet transplantation could benefit from therapies targeting IL-15 signaling by dampening the development and maintenance of diabetogenic T cells (Fig. 4).

### 5.3. IL-15 in Inflammatory Bowel Diseases (IBD)

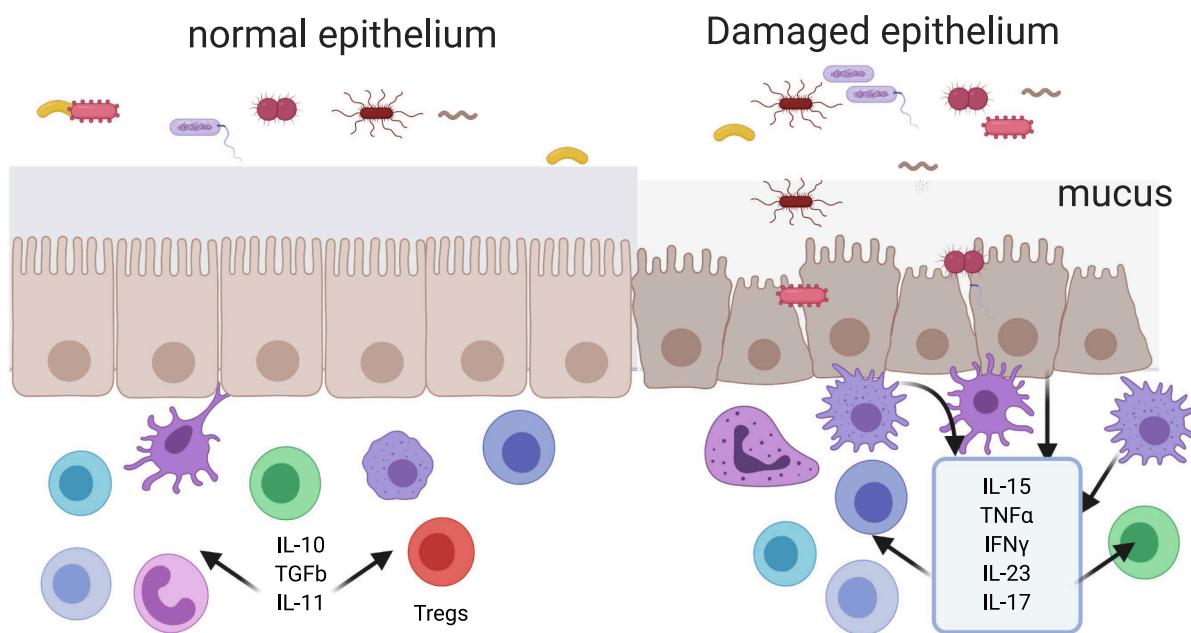
Increasing prevalence of intestinal pathologies in different

geographical locations points towards the important contribution of environmental factors in the pathogenesis of IBD [154]. In a healthy intestine, the immune system maintains the balance between tolerance and immune response to pathogens. For unknown reasons, there is a breakdown of intestinal barrier in IBD leading to inadvertent activation of the innate immune system by the gut microbiota that results in the establishment of chronic inflammation in the gut mucosa. In Crohn's disease (CD), fistulas, ulcers, and granulomas occur in any part of the gastrointestinal tract but are more common in the terminal ileum. In ulcerative colitis (UC) the inflammation is restricted to the mucosa of the colon [155]. Soluble mediators such as cytokines, growth factors and chemokines produced by IEC and the associated immune cells in response to microbial products contribute to the chronic inflammation observed in IBD [156]. Dysregulated immune response to the gut flora causes chronic relapsing inflammation in CD and UC that is characterized by increased production of major pro-inflammatory cytokines such as TNF $\alpha$ , IFN $\gamma$ , IL-1, IL-6, IL-15, IL-17, IL-21 and IL-23 [156–157].

Since 1998 biologics that target TNF $\alpha$  are the gold standard in the treatment of CD and UC [158–163]. Despite the success of targeting TNF $\alpha$ , 30% of the patients do not respond to anti-TNF $\alpha$  therapies (primary non-responders) and 50% of the patients who respond require dose escalation or therapy change are showing promising results in CD and UC [164–168]. IL-12 consists of heterodimer IL-12p40/IL-12p35 and is directly upstream of IFN $\gamma$ -producing Th1/ILC1 subsets. IL-23 is comprised of IL-12p40/IL-23p19 and skews the immune responses towards IL-17 producing Th17/ILC3 subsets [169]. IL-23 signaling may be more relevant to IBD as *IL23R* locus shows the strongest association to CD after *NOD2* [170]. The efficacy of targeting IL-23 will reflect the importance of this pathway in initiating the inflammatory cascade in IBD. Targeting the downstream effector cytokines such as IFN $\gamma$  and IL-17 did not show promising results in IBD clinical trials, while paradoxical IBD induction was noticed after IL-17 blockade [168,171]. Thus,



**Fig. 4.** IL-15 in type 1 diabetes. Contribution of IL-15 to the pathophysiology of type 1 diabetes. IL-15 can act at different stages of insulitis. Increased expression of IL-15 in APC/islet beta cells can activate lymphocytes and contribute to the infiltration of the islets during the early stages of T1D. IL-15 can lower TCR threshold and promotes exuberant CD8<sup>+</sup> T cells survival. Inhibition of IL-15 signaling after the onset of insulitis has been shown to prevent T1D. Please refer to the text for details.



**Fig. 5.** IL-15 in IBD. Contribution of IL-15 to the pathophysiology of IBD. IL-15 produced by the inflamed epithelium or the mucosa associated macrophages and dendritic cells can further promote the production of inflammatory cytokines from myeloid and lymphoid cells and contribute to the dysbiosis observed in IBD. Please refer to the text for details.

identification of additional immunotherapeutic targets will be beneficial in IBD.

IL-15 plays an important role in intestinal homeostasis, as it is required for the maintenance of several lymphoid subsets in the intestine [9]. In fact, the critical role of IL-15 in the intestinal immunological balance is best-known in the context of coeliac disease, an intestinal chronic inflammatory condition in which IL-15 is a critical immunopathogenic factor (reviewed in [20,172]). Multiple lines of evidence suggest that IL-15 also plays an important role in the pathogenesis of IBD [23] (Fig. 5). *Il15*<sup>-/-</sup> mice are protected from DSS (dextran sodium sulphate)-induced colitis with decreased levels of pro-inflammatory cytokines, suggesting an important role for IL-15 in the inflammatory process [173]. In *Toxoplasma gondii*-induced ileitis, IL-15 promotes CCL3 chemokine-mediated recruitment of monocytes [174]. IL-15 can promote the pathogenicity of IL-15-dependent ILC1 subsets in human colitis [7,175]. T cells isolated from the lamina propria (LP) of IBD patients produced more TNF $\alpha$  and IL-12 in response to IL-15 [176]. In the inflamed mucosa of IBD patients, the levels of IL-15 and/or IL-15R $\alpha$  proteins in macrophages and B cells [176–179] and the amount of sIL-15:IL-15R $\alpha$  complexes are increased [177,180]. Moreover, IL-15 expression has been detected by immunohistochemistry in IEC of UC patients [181]. Neutralization of IL-15 in intestinal biopsies from children with UC reduces phagocytic cell activation and IEC proliferation [181]. These observations strongly support a pathogenic role for IL-15 in IBD (Fig. 5).

IL-15 is produced by multiple cell types and requires signaling and responder cells in close proximity for effective trans-presentation. It is thus plausible that IL-15 from different cellular origins contributes differently to the pathogenic process but so far, the relevant cellular origin(s) of IL-15 and signaling partners remain critical missing points. Evidence points to IEC as important mediators of IL-15-driven pathogenesis as transgenic IEC-specific expression of IL-15 increases the susceptibility to DSS colitis [182] and enteroids derived from IBD patients secrete unidentified factor(s) that upregulate IL-15 production by DC [183].

#### 5.4. IL-15 in Psoriasis

In psoriasis, inflammatory infiltrate in the skin triggers marked

parakeratosis, the hyper-proliferation of the epidermal keratinocytes that is associated with retention of nucleated keratinocyte in the stratum corneum and loss of the granular layer of the skin [184]. This disorganization of the skin architecture eventually results in the accumulation of the pathognomonic raised plaques covered with silvery scales. Polymorphisms in *IL15* have been reported in some studies [185–187]. Skin resident memory CD8 $^+$  T cells (CD8 $^+$  T<sub>RM</sub>) have been implicated in the pathology [188]. It remains however a mystery why psoriasis has an exquisite predilection for some area of the body such as the scalp and the extensor surfaces of the limbs. CD8 $^+$  T<sub>RM</sub> are retained in the skin in response to IL-15 expressed by keratinocytes and dermal DC. Thus, inhibition of IL-15 reduced the production of proinflammatory cytokines and the inflammation in xenografts [189]. Application of IMQ (TLR-7 ligand) induces skin thickening in WT and *Il15ra*<sup>-/-</sup> but not in *Il15*<sup>-/-</sup> mice. Selective loss of IL-15R $\alpha$  in the stromal cells increased the inflammatory response as inflamed keratinocytes release sIL-15R $\alpha$  that dampens the inflammation. In support, treatment with sIL-15R $\alpha$  damped the inflammation in the murine models [86]. Serum IL-15 positively correlated with disease severity in psoriasis patients while sIL-15R $\alpha$  showed a negative correlation. More importantly, both IL-15 and sIL-15R $\alpha$  in the sera were bioactive as determined using CTL2 cells, indicating that dampening IL-15 is beneficial in psoriasis. Finally, much interest is emerging for IL-15 as it appears to be genetically linked to IL-17 production by T cells and is even a more potent inducer of IL-17 production than IL-23 in T cells from psoriatic patients [190–191]. Such link is interesting as, so far, as anti-IL-17 therapies, mainly targeting TH17 CD4 $^+$  T cells, are among the most potent therapies available with total clearance of the skin (PASI100) in up to 45.9% of patients at week 52 [192]. Thus, IL-15 could be a potential alternate immunotherapeutic target in psoriatic patients who do not respond to anti-IL-17 therapies [193] or for the subset afflicted with concomitant psoriatic inflammatory arthritis [194].

#### 6. IL-15 as an immunotherapeutic target

The above discussion reiterates the proposition that IL-15 is an obvious target in autoimmune diseases. During the past two decades various groups have documented the beneficial effects of targeting IL-

**Table 1**

Therapeutic approaches to target IL-15 signaling in autoimmunity

Reagent	Target	Species	Pathology	Effect	Refs.
Tmβ1	IL-15Rβ	Mice (NOD)	T1D	Beneficial	[22]
Tmβ1	IL-15Rβ	Mice (NOD)	T1D	Beneficial	[146]
Tmβ1	IL-15Rβ	Mice (NOD)	T1D	Beneficial	[148]
Tmβ1	IL-15Rβ	Mice IL-15/RaTg	T1D	Beneficial	[147]
Tmβ1	IL-15Rβ	Hu-IL-15Tg mice	Refractory CD	Beneficial	[211]
ChMBC7	IL-15Rβ	Mice	Vitiligo	Beneficial	[212]
Small interfering RNA(siRNA) targeting IL-15Rβ	IL-15Rβ	Mice	Arthritis	Beneficial	[196]
Hu-Mik-beta-1	IL-15Rβ	Humans	Large granular leukemia	No change	[213]
Hu-Mik-beta-1	IL-15Rβ	Humans	HAM/TSP	No change	[214]
Hu-Mik-beta-1	IL-15Rβ	Humans	Coeliac disease	Recruitment?	
Anti-CD132	γ <sub>c</sub>	Mice (NOD)	T1D	Beneficial	[141]
BNZ-1	γ <sub>c</sub>	Humans	Leukemia-LGL	beneficial	[215]
Mut-IL-15 Ig	βγ <sub>c</sub>	Mice (NOD)	T1D	Beneficial	[137]
CRB-15	βγ <sub>c</sub>	Mice	Collagen-induced arthritis (CIA)	Beneficial	[195]
Engineered immuno-toxins to IL-15R	IL-15Rα	Mice	Arthritis	Beneficial	[198]
AMG-714	IL-15	Xenograft	Psoriasis	Beneficial	[189]
Soluble decoy IL-15Rα	IL-15	Mice	Arthritis	Beneficial	[196]
AMG-714	IL-15	Humans	RA	Beneficial	[202]
AMG-714	IL-15	Humans	Volunteers	No change	[208]
AMG-714	IL-15	Cynomolgus Monkeys	RA	Beneficial	[208]
AMG-714	IL-15	Humans	Coeliac disease	No change	[206,207]
anti-human IL-15 mAb, CALY-002	IL-15	Hu-IL-15Tg mice	IEL	Beneficial	[208]
anti-human IL-15 mAb 04H04	IL-15	Rhesus Monkeys	Coeliac disease	Beneficial	[210]
Clone # 34593	IL-15	Humans	UC- intestinal biopsies	Beneficial	[180]
IL-15 immunization	IL-15	Macaques	Proof of principle	Beneficial	[216]
Tofacitinib	JAK1, 3	Hu-IL-15Tg mice	Coeliac disease	Beneficial	[217]
Tofacitinib	JAK1, 3	Humans	RA	Beneficial	[204]
Baricitinib	JAK 1, 2	Humans	RA	Beneficial	[204]

15 or its receptors in pre-clinical models of different autoimmune diseases (Table 1). Since the discovery of the pathogenic role of IL-15 in RA, various biologics targeting IL-15 were developed and tested in pre-clinical models of RA. In mouse models of collagen-induced arthritis (CIA), inhibiting IL-15 signaling with CRB-15, an antagonistic IL-15 mutant /Fc2a fusion protein that blocks IL-15R, has been shown to dampen the magnitude of the inflammatory response [195]. CRB-15 markedly improved synovitis and the bone and cartilage destruction, as well as decreased the expression of inflammatory mediators. Several other ways of blocking IL-15 signaling namely, soluble decoy IL-15Rα [196], small interfering RNA(siRNA) targeting IL-15Rβ [197] or engineered immunotoxins eliminating IL-15R-bearing cells [198] were also reported to improve clinical manifestations of experimental arthritis.

Notably, IL-15 blockade in CIA reduces the synovial levels of several inflammatory cytokines such as TNFα, IL-1β, IL-6 and IL-17, affirming the pathogenic role of IL-15 at the apex of the inflammatory cascade in arthritis [195]. Pharmacological targeting of all these downstream cytokines is already used in clinical practice. These include anti-TNFα (Etanercept, Adalimumab, Certolizumab, Golimumab, Infliximab), IL-1R antagonist (Anakinra) anti-IL-1β (Canakinumab), anti-IL-6 (Tocilizumab, Sarilumab) and anti-IL-17 (Secukinumab, Ixekinumab) therapies [199–200]. Therefore, dampening IL-15 signaling is likely to be more effective than individually targeting the inflammatory cytokines. It is noteworthy that IL-15 expression in the synovium is not influenced by blocking TNFα signaling [201]. Hence, anti-IL-15 therapy could be a promising strategy in patients who are refractory to anti-TNF therapy. Indeed, phase I human clinical trials targeting IL-15 in RA have shown promising results. The administration of humanized anti-IL-15 mAb (a human IgG1 anti-IL-15 mAb- 146B7/HuMax-IL15/AMG-714, referred to here as AMG-714) to 30 RA patients resulted in significant clinical improvement [202]. AMG-714 was well tolerated clinically and using

the American College of Rheumatology (ACR) outcome scoring was comparable to anti-TNF therapy, although a little less effective than the JAK inhibitor baricitinib and upadacitinib to improve RA symptoms [203–204]. Numerically, 63% of patients improved by 20% (ACR20), 38% improved by 50% (ACR50), and 25% by 70% (ACR70). No significant effects on circulating T cell subset and NK cell numbers were observed from baseline up to 28 days post-treatment [202]. However, this trend was not observed in subsequent trials. A Phase II clinical trial with AMG-714 did not show any efficacy (ClinicalTrials.gov Identifier: NCT00433875) [205]. AMG-714 also failed in two other trials for coeliac disease or refractory type II coeliac disease, in which treated patients did not show any significant difference in primary endpoint [206–207]. Nonetheless, recruitment will continue for coeliac disease and psoriasis.

AMG-714 has been shown to inhibit IL-15 signalling in human T cells *in vitro* [208], but its efficacy in humans *in vivo* is not clear. Volunteers and patients who received up to 600 mg/dose of AMG-714 did not show any change in the frequency of NK cells or CD8<sup>+</sup> T cells [208]. However, in cynomolgus monkeys AMG-714 was effective at 150 mg/kg in reducing NK cells and humanized anti-IL-15 clone M111 mAb (Hu714MuXHu) was even more potent at 0.1–1.0 mg/kg. These head-to-head comparisons suggest that the affinity of AMG-714 to IL-15 may not be good enough to inhibit IL-15 signaling. It is not clear if the doses used in the recent clinical trials (celiac disease-150 mg or 300 mg per dose [206] or 8 mg/kg per dose [207]) were effective or not.

An alternate approach is to interfere with the binding of IL-15 to its receptors. The anti-huIL-15 mAb CALY-002 [209] from Calypso Biotech interferes with the interaction between IL-15 and IL-15Rβ. CALY-002 has shown promising results in pre-clinical trials and was effective at a range of 0.1–1.0 mg/kg in cynomolgus monkeys, reflecting the dose achieved with Hu714MuXHu [208–209]. Treatment with CALY-002 was efficient at controlling the expansion of IELs in mice that express human IL-15 as a

transgene in the intestinal epithelium. A third anti-human IL-15 mAb 04H04 from Teva Pharmaceuticals was shown to improve symptoms of celiac disease in rhesus monkeys when administered at a dose of 10 mg/kg [210]. The availability of mice that express human IL-15 as a transgene in the intestinal epithelium (hIL-15Tg [211]) can be a valuable tool to compare the efficacy of anti-human IL-15 mAbs. To date only CALY-002 has been tested in hIL-15Tg mice [209].

Another approach to interfere with IL-15 signaling is direct blockade of the signaling competent receptor chain IL-15R $\beta$ . Indeed, inhibition of IL-15R $\beta$  has been shown to be highly effective in different pre-clinical autoimmune models of coeliac disease, T1D and vitiligo [211–212]. Hu-Mik-beta-1 is a humanized IgG1k mAb that binds IL-2/15R $\beta$ . Hu-Mik-beta-1 has been shown to effectively saturate CD122 sites *in vivo*. Phase I clinical trial in a group of celiac patients was completed in December 2019 and the results are awaited (ClinicalTrials.gov Identifier: NCT01893775).

## 7. Conclusions and future directions

The advent of biological therapeutics has markedly improved the disease outcome in RA and other autoimmune diseases to varying degrees. Broad availability of cytokine-targeted drugs such as monoclonal antibodies and decoy receptors has paved the way for a new era of personalized medicine. IL-15 signaling represents a promising target that could be leveraged to treat autoimmune diseases. Targeting IL-15 signaling has a minimal adverse effect profile and has already shown effectiveness. Clearly more studies are needed to carefully evaluate the efficacy of IL-15 targeting therapies and elucidate the underlying mechanisms. Besides, a thorough understanding of the unique properties of IL-15 signaling could help design improved therapeutics.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

Figs. 3–5 were created with BioRender.com.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and materials

Not applicable.

## Funding

This work was supported by Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery grant of SR. MN is the recipient of FRQS post-doctoral fellowship.

## Authors' contributions

SR and HAC designed the content and wrote the manuscript. AM, HKM, MN, MM and SI contributed to the discussions and specific subtitles in the manuscript. All authors reviewed and corrected the manuscript.

## References

- [1] T.A. Waldmann, The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design, *Nature Rev. Immunol.* 6 (2006) 595–601.
- [2] J.X. Lin, W.J. Leonard, The common cytokine receptor gamma chain family of cytokines, *Cold Spring Harb Perspect Biol.* 10 (2018).
- [3] Y. Tagaya, R.N. Bamford, A.P. DeFilippis, T.A. Waldmann, IL-15: a pleiotropic cytokine with diverse receptor/signaling pathways whose expression is controlled at multiple levels, *Immunity* 4 (1996) 329–336.
- [4] S.H. Ross, D.A. Cantrell, Signaling and function of interleukin-2 in T lymphocytes, *Annu. Rev. Immunol.* 36 (2018) 411–433.
- [5] S.W. Stonier, K.S. Schluns, Trans-presentation: a novel mechanism regulating IL-15 delivery and responses, *Immunol. Lett.* 127 (2010) 85–92.
- [6] T.A. Waldmann, Y. Tagaya, The multifaceted regulation of interleukin-15 expression and the role of this cytokine in NK cell differentiation and host response to intracellular pathogens, *Annu. Rev. Immunol.* 17 (1999) 19–49.
- [7] A. Fuchs, W. Vermi, J.S. Lee, S. Lonardi, S. Gilfillan, R.D. Newberry, M. Celli, M. Colonna, Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN-gamma-producing cells, *Immunity* 38 (2013) 769–781.
- [8] M.L. Robinette, J.K. Bando, W. Song, T.K. Ulland, S. Gilfillan, M. Colonna, IL-15 sustains IL-7R-independent ILC2 and ILC3 development, *Nat. Commun.* 8 (2017) 14601.
- [9] Q. Yu, C. Tang, S. Xun, T. Yajima, K. Takeda, Y. Yoshikai, MyD88-dependent signaling for IL-15 production plays an important role in maintenance of CD8 alpha alpha TCR alpha beta and TCR gamma delta intestinal intraepithelial lymphocytes, *J. Immunol.* 176 (2006) 6180–6185.
- [10] S. Dubois, J. Mariner, T.A. Waldmann, Y. Tagaya, IL-15Ralpha recycles and presents IL-15 to neighboring cells, *Immunity* 17 (2002) 537–547.
- [11] M.K. Kennedy, M. Glaccum, S.N. Brown, E.A. Butz, J.L. Viney, M. Embers, N. Matsuki, K. Charrier, L. Sedger, C.R. Willis, K. Brasel, P.J. Morrissey, K. Stocking, J.C. Schuh, S. Joyce, J.J. Peschon, Reversible defects in natural killer and memory CD8 T cell lineages in interleukin 15-deficient mice, *J. Exp. Med.* 191 (2000) 771–780.
- [12] J.P. Lodolce, D.L. Boone, S. Chai, R.E. Swain, T. Dassopoulos, S. Trettin, A. Ma, IL-15 receptor maintains lymphoid homeostasis by supporting lymphocyte homing and proliferation, *Immunity* 9 (1998) 669–676.
- [13] K.S. Schluns, T. Stoklasek, L. Lefrancois, The roles of interleukin-15 receptor alpha: trans-presentation, receptor component, or both? *Int. J. Biochem. Cell Biol.* 37 (2005) 1567–1571.
- [14] E.F. Castillo, K.S. Schluns, Regulating the immune system via IL-15 transpresentation, *Cytokine* 59 (2012) 479–490.
- [15] Y. Guo, L. Luan, N.K. Patil, E.R. Sherwood, Immunobiology of the IL-15/IL-15Ralpha complex as an antitumor and antiviral agent, *Cytokine Growth Factor Rev.* 38 (2017) 10–21.
- [16] J.G. Giri, M. Ahdieh, J. Eisenman, K. Shanebeck, K. Grabstein, S. Kumaki, A. Namen, L.S. Park, D. Cosman, D. Anderson, Utilization of the beta and gamma chains of the IL-2 receptor by the novel cytokine IL-15, *EMBO J.* 13 (1994) 2822–2830.
- [17] T.A. Waldmann, The biology of IL-15: implications for cancer therapy and the treatment of autoimmune disorders, *J. Investigig. Dermatol. Symp. Proc.* 16 (2013) S28–S30.
- [18] P. Saikali, J.P. Antel, C.L. Pittet, J. Newcombe, N. Arbour, Contribution of astrocyte-derived IL-15 to CD8 T cell effector functions in multiple sclerosis, *J. Immunol.* 185 (2010) 5693–5703.
- [19] A. Vaknin-Dembinsky, S.D. Brass, R. Gandhi, H.L. Weiner, Membrane bound IL-15 is increased on CD14 monocytes in early stages of MS, *J. Neuroimmunol.* 195 (2008) 135–139.
- [20] B. Jabri, V. Abadie, IL-15 functions as a danger signal to regulate tissue-resident T cells and tissue destruction, *Nat. Rev. Immunol.* 15 (2015) 771–783.
- [21] J. Marks-Konczalik, S. Dubois, J.M. Losi, H. Sabzevari, N. Yamada, L. Feigenbaum, T.A. Waldmann, Y. Tagaya, IL-2-induced activation-induced cell death is inhibited in IL-15 transgenic mice, *Proc. Natl. Acad. Sci. U.S.A.* 97 (2000) 11445–11450.
- [22] D. Bobbala, X.L. Chen, C. Leblanc, M. Mayhue, J. Stankova, T. Tanaka, Y.G. Chen, S. Ilangumaran, S. Ramanathan, Interleukin-15 plays an essential role in the pathogenesis of autoimmune diabetes in the NOD mouse, *Diabetologia* 55 (2012) 3010–3020.
- [23] D. Pagliari, R. Cianci, S. Frosali, R. Landolfi, G. Cammarota, E.E. Newton, F. Pandolfi, The role of IL-15 in gastrointestinal diseases: a bridge between innate and adaptive immune response, *Cytokine Growth Factor Rev.* 24 (2013) 455–466.
- [24] S. Yokoyama, N. Watanabe, N. Sato, P.Y. Perera, L. Filkoski, T. Tanaka, M. Miyasaka, T.A. Waldmann, T. Hiroi, L.P. Perera, Antibody-mediated blockade of IL-15 reverses the autoimmune intestinal damage in transgenic mice that overexpress IL-15 in enterocytes, *Proc. Natl. Acad. Sci. U.S.A.* 106 (2009) 15849–15854.
- [25] I.B. McInnes, B.P. Leung, R.D. Sturrock, M. Field, F.Y. Liew, Interleukin-15 mediates T cell-dependent regulation of tumor necrosis factor-alpha production in rheumatoid arthritis, *Nat. Med.* 3 (1997) 189–195.
- [26] T.A. Waldmann, Targeting the interleukin-15/interleukin-15 receptor system in inflammatory autoimmune diseases, *Arthritis Res. Ther.* 6 (2004) 174–177.
- [27] A. Di Sabatino, R. Ciccioli, F. Cupelli, B. Cinque, D. Millimaggi, M.M. Clarkson, M. Paulli, M.G. Cifone, G.R. Corazza, Epithelium derived interleukin 15 regulates intraepithelial lymphocyte Th1 cytokine production, cytotoxicity, and survival in coeliac disease, *Gut* 55 (2006) 469–477.
- [28] B. Meresse, Z. Chen, C. Ciszewski, M. Tretiakova, G. Bhagat, T.N. Krausz,

- D.H. Raulet, L.L. Lanier, V. Groh, T. Spies, E.C. Ebert, P.H. Green, B. Jabri, Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease, *Immunity* 21 (2004) 357–366.
- [29] X.J. Zhang, K.L. Yan, Z.M. Wang, S. Yang, G.L. Zhang, X. Fan, F.L. Xiao, M. Gao, Y. Cui, P.G. Wang, L.D. Sun, K.Y. Zhang, B. Wang, D.Z. Wang, S.J. Xu, W. Huang, J.J. Liu, Polymorphisms in interleukin-15 gene on chromosome 4q31.2 are associated with psoriasis vulgaris in Chinese population, *J. Invest. Dermatol.* 127 (2007) 2544–2551.
- [30] P. Ylipaisto, B. Kutlu, S. Rasilainen, J. Rasschaert, K. Salmela, H. Teerijoki, O. Korsgren, R. Laheesmaa, T. Hovi, D.L. Eizirik, T. Otonkoski, M. Roivainen, Global profiling of coxsackievirus- and cytokine-induced gene expression in human pancreatic islets, *Diabetologia* 48 (2005) 1510–1522.
- [31] B.M. Schulz, K.H. Lanke, J.D. Piganelli, E.D. Kers-Rebel, R. Bottino, M. Trucco, R.J. Huijbens, T.R. Radstake, M.A. Engelse, E.J. de Koning, J.M. Galama, G.J. Adema, F.J. van Kuppeveld, Cytokine and chemokine production by human pancreatic islets upon enterovirus infection, *Diabetes* 61 (2012) 2030–2036.
- [32] V. Venetsanaki, A. Boutis, A. Chrisoulidou, P. Papakotoulas, Diabetes mellitus secondary to treatment with immune checkpoint inhibitors, *Curr. Oncol.* 26 (2019) e111–e114.
- [33] R. Barroso-Sousa, W.T. Barry, A.C. Garrido-Castro, F.S. Hodin, L. Min, I.E. Krop, S.M. Tolane, Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis, *JAMA Oncol.* 4 (2018) 173–182.
- [34] M. Pavkova Goldbergova, P. Nemec, J. Lipkova, J. Jarkovsky, J. Gatterova, D. Ambrozova, A. Vasku, M. Soucek, N. Pavek, Relation of IL-6, IL-13 and IL-15 gene polymorphisms to the rheumatoid factors, anti-CCP and other measures of rheumatoid arthritis activity, *Int. J. Immunogenet.* 41 (2014) 34–40.
- [35] C. Escudero-Hernandez, L. Plaza-Izureta, J.A. Garrote, J.R. Bilbao, Arranz E. Cegec, Association of the IL-15 and IL-15Ralpha genes with celiac disease, *Cytokine* 99 (2017) 73–79.
- [36] K.H. Grabstein, J. Eisenman, K. Shanebeck, C. Rauch, S. Srinivasan, V. Fung, C. Beers, J. Richardson, M.A. Schoenborn, M. Ahdieh, et al., Cloning of a T cell growth factor that interacts with the beta chain of the interleukin-2 receptor, *Science* 264 (1994) 965–968.
- [37] J.D. Burton, R.N. Bamford, C. Peters, A.J. Grant, G. Kurys, C.K. Goldman, J. Brennan, E. Roessler, T.A. Waldmann, A lymphokine, provisionally designated interleukin T and produced by a human adult T-cell leukemia line, stimulates T-cell proliferation and the induction of lymphokine-activated killer cells, *Proc. Natl. Acad. Sci. U.S.A.* 91 (1994) 4935–4939.
- [38] Y. Tagaya, G. Kurys, T.A. Thies, J.M. Losi, N. Azimi, J.A. Hanover, R.N. Bamford, T.A. Waldmann, Generation of secretable and nonsecretable interleukin 15 isoforms through alternate usage of signal peptides, *Proc. Natl. Acad. Sci. U.S.A.* 94 (1997) 14444–14449.
- [39] R.N. Bamford, A.P. DeFilippis, N. Azimi, G. Kurys, T.A. Waldmann, The 5' untranslated region, signal peptide, and the coding sequence of the carboxyl terminus of IL-15 participate in its multifaceted translational control, *J. Immunol.* 160 (1998) 4418–4426.
- [40] D.M. Anderson, L. Johnson, M.B. Glaccum, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, V. Valentine, M.N. Kirstein, D.N. Shapiro, S.W. Morris, et al., Chromosomal assignment and genomic structure of IL15, *Genomics* 25 (1995) 701–706.
- [41] C. Bergamaschi, M. Rosati, R. Jalal, A. Valentin, V. Kulkarni, C. Alicea, G.M. Zhang, V. Patel, B.K. Felber, G.N. Pavlakis, Intracellular interaction of interleukin-15 with its receptor alpha during production leads to mutual stabilization and increased bioactivity, *J. Biol. Chem.* 283 (2008) 4189–4199.
- [42] H. Nishimura, J. Washizu, N. Nakamura, A. Enomoto, Y. Yoshikai, Translational efficiency is up-regulated by alternative exon in murine IL-15 mRNA, *J. Immunol.* 160 (1998) 936–942.
- [43] R. Meazza, S. Verdiani, R. Biassoni, M. Coppolecchia, A. Gaggero, A.M. Orengo, M.P. Colombo, B. Azzarone, S. Ferrini, Identification of a novel interleukin-15 (IL-15) transcript isoform generated by alternative splicing in human small cell lung cancer cell lines, *Oncogene* 12 (1996) 2187–2192.
- [44] A. Onu, T. Pohl, H. Krause, S. Bulfone-Paus, Regulation of IL-15 secretion via the leader peptide of two IL-15 isoforms, *J. Immunol.* 158 (1997) 255–262.
- [45] R. Meazza, A. Gaggero, F. Neglia, S. Bassi, S. Sforzini, R. Pereno, B. Azzarone, S. Ferrini, Expression of two interleukin-15 mRNA isoforms in human tumors does not correlate with secretion: role of different signal peptides, *Eur. J. Immunol.* 27 (1997) 1049–1054.
- [46] R.N. Bamford, A.P. Battista, J.D. Burton, H. Sharma, T.A. Waldmann, Interleukin (IL) 15/IL-T production by the adult T-cell leukemia cell line HuT-102 is associated with a human T-cell lymphotropic virus type I region /IL-15 fusion message that lacks many upstream AUGs that normally attenuates IL-15 mRNA translation, *Proc. Natl. Acad. Sci. U.S.A.* 93 (1996) 2897–2902.
- [47] G. Kurys, Y. Tagaya, R. Bamford, J.A. Hanover, T.A. Waldmann, The long signal peptide isoform and its alternative processing direct the intracellular trafficking of interleukin-15, *J. Biol. Chem.* 275 (2000) 30653–30659.
- [48] S.L. Colpitts, T.A. Stoklasa, C.R. Plumlee, J.J. Obar, C. Guo, L. Lefrancois, Cutting edge: the role of IFN-alpha receptors and MyD88 signaling in induction of IL-15 expression in vivo, *J. Immunol.* 188 (2012) 2483–2487.
- [49] G. Cui, T. Hara, S. Simmons, K. Wagatsuma, A. Abe, H. Miyachi, S. Kitano, M. Ishii, S. Tani-Ichi, K. Ikuta, Characterization of the IL-15 niche in primary and secondary lymphoid organs in vivo, *Proc. Natl. Acad. Sci. U.S.A.* 111 (2014) 1915–1920.
- [50] T. Sosinowski, J.T. White, E.W. Cross, C. Haluszczak, P. Marrack, L. Gapin, R.M. Kedl, CD8alpha+ dendritic cell trans presentation of IL-15 to naive CD8+ T cells produces antigen-inexperienced T cells in the periphery with memory phenotype and function, *J. Immunol.* 190 (2013) 1936–1947.
- [51] S. Ilangumaran, S. Ramanathan, T. Ning, J. La Rose, B. Reinhardt, P. Poussier, R. Rottapel, Suppressor of cytokine signaling 1 attenuates IL-15 receptor signaling in CD8+ thymocytes, *Blood* 102 (2003) 4115–4122.
- [52] S. Ramanathan, J. Gagnon, C. Leblanc, R. Rottapel, S. Ilangumaran, Suppressor of cytokine signaling 1 stringently regulates distinct functions of IL-7 and IL-15 in vivo during T lymphocyte development and homeostasis, *J. Immunol.* 176 (2006) 4029–4041.
- [53] C.L. Chang, Y.G. Lai, M.S. Hou, P.L. Huang, N.S. Liao, IL-15Ralpha of radiation-resistant cells is necessary and sufficient for thymic invariant NKT cell survival and functional maturation, *J. Immunol.* 187 (2011) 1235–1242.
- [54] Y. Zhu, G. Cui, E. Miyachi, Y. Nakanishi, H. Mukohira, A. Shimba, S. Abe, S. Tani-Ichi, T. Hara, H. Nakase, T. Chiba, A. Sehara-Fujisawa, H. Seno, H. Ohno, K. Ikuta, Intestinal epithelial cell-derived IL-15 determines local maintenance and maturation of intraepithelial lymphocytes in the intestine, *Int. Immunopharmacol.* (2019).
- [55] K.S. Schluns, K.D. Klonowski, L. Lefrancois, Transregulation of memory CD8 T-cell proliferation by IL-15Ralpha+ bone marrow-derived cells, *Blood* 103 (2004) 988–994.
- [56] K.S. Schluns, E.C. Nowak, A. Cabrera-Hernandez, L. Puddington, L. Lefrancois, H.L. Aguila, Distinct cell types control lymphoid subset development by means of IL-15 and IL-15 receptor alpha expression, *Proc. Natl. Acad. Sci. U.S.A.* 101 (2004) 5616–5621.
- [57] E. Mortier, R. Advincula, L. Kim, S. Chmura, J. Barrera, B. Reizis, B.A. Malynn, A. Ma, Macrophage- and dendritic-cell-derived interleukin-15 receptor alpha supports homeostasis of distinct CD8+ T cell subsets, *Immunity* 31 (2009) 811–822.
- [58] Y. Cepero-Donates, V. Rakotoarivelio, M. Mayhue, A. Ma, Y.G. Chen, S. Ramanathan, Homeostasis of IL-15 dependent lymphocyte subsets in the liver, *Cytokine* 82 (2016) 95–101.
- [59] J.G. Giri, S. Kumaki, M. Ahdieh, D.J. Friend, A. Loomis, K. Shanebeck, R. DuBose, D. Cosman, L.S. Park, D.M. Anderson, Identification and cloning of a novel IL-15 binding protein that is structurally related to the alpha chain of the IL-2 receptor, *EMBO J.* 14 (1995) 3654–3663.
- [60] R.N. Bamford, A.J. Grant, J.D. Burton, C. Peters, G. Kurys, C.K. Goldman, J. Brennan, E. Roessler, T.A. Waldmann, The interleukin (IL) 2 receptor beta chain is shared by IL-2 and a cytokine, provisionally designated IL-T, that stimulates T-cell proliferation and the induction of lymphokine-activated killer cells, *Proc. Natl. Acad. Sci. U.S.A.* 91 (1994) 4940–4944.
- [61] N. Sato, H. Sabzevari, S. Fu, W. Ju, M.N. Petrus, R.N. Bamford, T.A. Waldmann, Y. Tagaya, Development of an IL-15-autocrine CD8 T-cell leukemia in IL-15-transgenic mice requires the cis expression of IL-15Ralpha, *Blood* 117 (2011) 4032–4040.
- [62] Y. Tagaya, J.D. Burton, Y. Miyamoto, T.A. Waldmann, Identification of a novel receptor/signal transduction pathway for IL-15/T in mast cells, *EMBO J.* 15 (1996) 4928–4939.
- [63] J.P. Lodolce, P.R. Burkett, D.L. Boone, M. Chien, A. Ma, T cell-independent interleukin 15Ralpha signals are required for bystander proliferation, *J. Exp. Med.* 194 (2001) 1187–1194.
- [64] R. Koka, P.R. Burkett, M. Chien, S. Chai, F. Chan, J.P. Lodolce, D.L. Boone, A. Ma, Interleukin (IL)-15[alpha]-deficient natural killer cells survive in normal but not IL-15R[alpha]-deficient mice, *J. Exp. Med.* 197 (2003) 977–984.
- [65] R.T. Sowell, J.W. Goldfusky, M. Rogozinska, Z. Quiles, Y. Cao, E.F. Castillo, A. Finnegan, A.L. Marzo, IL-15 complexes induce migration of resting memory CD8 T cells into mucosal tissues, *J. Immunol.* 199 (2017) 2536–2546.
- [66] E.H. Duitman, Z. Orinska, E. Bulanova, R. Paus, S. Bulfone-Paus, How a cytokine is chaperoned through the secretory pathway by complexing with its own receptor: lessons from interleukin-15 (IL-15)/IL-15 receptor alpha, *Mol. Cell. Biol.* 28 (2008) 4851–4861.
- [67] C. Bergamaschi, R. Jalal, V. Kulkarni, M. Rosati, G.M. Zhang, C. Alicea, A.S. Zolotukhin, B.K. Felber, G.N. Pavlakis, Secretion and biological activity of short signal peptide IL-15 is chaperoned by IL-15 receptor alpha in vivo, *J. Immunol.* 183 (2009) 3064–3072.
- [68] H. Nishimura, T. Yajima, Y. Naiki, H. Tsunobuchi, M. Umemura, K. Itano, T. Matsuguchi, M. Suzuki, P.S. Ohashi, Y. Yoshikai, Differential roles of interleukin 15 mRNA isoforms generated by alternative splicing in immune responses in vivo, *J. Exp. Med.* 191 (2000) 157–170.
- [69] H. Nishimura, A. Fujimoto, N. Tamura, T. Yajima, W. Wajjwalku, Y. Yoshikai, A novel autoregulatory mechanism for transcriptional activation of the IL-15 gene by a nonsecretable isoform of IL-15 generated by alternative splicing, *FASEB J.* 19 (2005) 19–28.
- [70] P.R. Burkett, R. Koka, M. Chien, S. Chai, D.L. Boone, A. Ma, Coordinate expression and trans presentation of interleukin (IL)-15Ralpha and IL-15 supports natural killer cell and memory CD8+ T cell homeostasis, *J. Exp. Med.* 200 (2004) 825–834.
- [71] M.M. Sandau, K.S. Schluns, L. Lefrancois, S.C. Jameson, Cutting edge: transpresentation of IL-15 by bone marrow-derived cells necessitates expression of IL-15 and IL-15R alpha by the same cells, *J. Immunol.* 173 (2004) 6537–6541.
- [72] M. Lucas, W. Schachterle, K. Oberle, P. Aichele, A. Dieffenbach, Dendritic cells prime natural killer cells by trans-presenting interleukin 15, *Immunity* 26 (2007) 503–517.
- [73] E. Mortier, T. Woo, R. Advincula, S. Gozalo, A. Ma, IL-15Ralpha chaperones IL-15 to stable dendritic cell membrane complexes that activate NK cells via trans presentation, *J. Exp. Med.* 205 (2008) 1213–1225.
- [74] T. Ohteki, K. Suzue, C. Maki, T. Ota, S. Koyasu, Critical role of IL-15-IL-15R for antigen-presenting cell functions in the innate immune response, *Nat. Immunol.* 2 (2001) 1138–1143.

- [75] H. Perdreau, E. Mortier, G. Bouchaud, V. Sole, Y. Boubluk, A. Plet, Y. Jacques, Different dynamics of IL-15R activation following IL-15 cis- or trans-presentation, *Eur. Cytokine Netw.* 21 (2010) 297–307.
- [76] M.P. Rubinstein, M. Kovar, J.F. Purton, J.H. Cho, O. Boyman, C.D. Surh, J. Sprent, Converting IL-15 to a superagonist by binding to soluble IL-15R $\alpha$ , *Proc. Natl. Acad. Sci. U.S.A.* 103 (2006) 9166–9171.
- [77] T.A. Stoklasiek, K.S. Schluns, L. Lefrancois, Combined IL-15/IL-15R $\alpha$  immunotherapy maximizes IL-15 activity in vivo, *J. Immunol.* 177 (2006) 6072–6080.
- [78] E. Mortier, A. Quemener, P. Vusio, I. Lorenzen, Y. Boubluk, J. Grotzinger, A. Plet, Y. Jacques, Soluble interleukin-15 receptor alpha (IL-15R $\alpha$ )-sushi as a selective and potent agonist of IL-15 action through IL-15R beta/gamma. Hyperagonist IL-15 x IL-15R $\alpha$  fusion proteins, *J. Biol. Chem.* 281 (2006) 1612–1619.
- [79] G. Bouchaud, L. Garrigue-Antar, V. Sole, A. Quemener, Y. Boubluk, E. Mortier, H. Perdreau, Y. Jacques, A. Plet, The exon-3-encoded domain of IL-15R $\alpha$  contributes to IL-15 high-affinity binding and is crucial for the IL-15 antagonistic effect of soluble IL-15R $\alpha$ , *J. Mol. Biol.* 382 (2008) 1–12.
- [80] W. Xu, M. Jones, B. Liu, X. Zhu, C.B. Johnson, A.C. Edwards, L. Kong, E.K. Jeng, K. Han, W.D. Marcus, M.P. Rubinstein, P.R. Rhode, H.C. Wong, Efficacy and mechanism-of-action of a novel superagonist interleukin-15: interleukin-15 receptor alphaSu/Fc fusion complex in syngeneic murine models of multiple myeloma, *Cancer Res.* 73 (2013) 3075–3086.
- [81] K. Margolin, C. Morishima, V. Velcheti, J.S. Miller, S.M. Lee, A.W. Silk, S.G. Holtan, A.M. Lacroix, S.P. Fling, J.C. Kaiser, J.O. Egan, M. Jones, P.R. Rhode, A.D. Rock, M.A. Cheever, H.C. Wong, M.S. Ernsthoff, Phase I trial of ALT-803, a novel recombinant IL15 complex, in patients with advanced solid tumors, *Clin. Cancer Res.* 24 (2018) 5552–5561.
- [82] D. Mathios, C.K. Park, W.D. Marcus, S. Alter, P.R. Rhode, E.K. Jeng, H.C. Wong, D.M. Pardoll, M. Lim, Therapeutic administration of IL-15 superagonist complex ALT-803 leads to long-term survival and durable antitumor immune response in a murine glioblastoma model, *Int. J. Cancer* 138 (2016) 187–194.
- [83] R. Romee, S. Cooley, M.M. Berrien-Elliott, P. Westervelt, M.R. Verneris, J.E. Wagner, D.J. Weisdorf, B.R. Blazier, C. Ustun, T.E. DeFor, S. Vivek, L. Peck, J.F. DiPersio, A.F. Cashen, R. Kyllo, A. Musiek, A. Schaffer, M.J. Anadkat, I. Rosman, D. Miller, J.O. Egan, E.K. Jeng, A. Rock, H.C. Wong, T.A. Fehniger, J.S. Miller, First-in-human phase 1 clinical study of the IL-15 superagonist complex ALT-803 to treat relapse after transplantation, *Blood* 131 (2018) 2515–2527.
- [84] J.M. Wrangle, V. Velcheti, M.R. Patel, E. Garrett-Mayer, E.G. Hill, J.G. Ravenel, J.S. Miller, M. Farhad, K. Anderton, K. Lindsey, M. Taffaro-Neskey, C. Sherman, S. Suriano, M. Swiderska-Syn, A. Sion, J. Harris, A.R. Edwards, J.A. Rytlewski, C.M. Sanders, E.C. Yusko, M.D. Robinson, C. Krieg, W.L. Redmond, J.O. Egan, P.R. Rhode, E.K. Jeng, A.D. Rock, H.C. Wong, M.P. Rubinstein, ALT-803, an IL-15 superagonist, in combination with nivolumab in patients with metastatic non-small cell lung cancer: a non-randomised, open-label, phase 1b trial, *Lancet Oncol.* 19 (2018) 694–704.
- [85] T.O. Robinson, K.S. Schluns, The potential and promise of IL-15 in immuno-oncogenic therapies, *Immunol. Lett.* 190 (2017) 159–168.
- [86] G. Bouchaud, S. Gehrke, C. Krieg, A. Kolios, J. Hafner, A.A. Navarini, L.E. French, O. Boyman, Epidermal IL-15R $\alpha$  acts as an endogenous antagonist of psoriasisiform inflammation in mouse and man, *J. Exp. Med.* 210 (2013) 2105–2117.
- [87] E. Mortier, J. Bernard, A. Plet, Y. Jacques, Natural, proteolytic release of a soluble form of human IL-15 receptor alpha-chain that behaves as a specific, high affinity IL-15 antagonist, *J. Immunol.* 173 (2004) 1681–1688.
- [88] C. Bergamaschi, J. Bear, M. Rosati, R.K. Beach, C. Alicea, R. Sowder, E. Chertova, S.A. Rosenberg, B.K. Felber, G.N. Pavlakis, Circulating IL-15 exists as heterodimeric complex with soluble IL-15R $\alpha$  in human and mouse serum, *Blood* 120 (2012) e1–e8.
- [89] S.M. Anthony, S.C. Rivas, S.L. Colpitts, M.E. Howard, S.W. Stonier, K.S. Schluns, Inflammatory Signals Regulate IL-15 in Response to Lymphodepletion, *J. Immunol.* 196 (2016) 4544–4552.
- [90] S.M. Anthony, M.E. Howard, Y. Hailemichael, W.W. Overwijk, K.S. Schluns, Soluble interleukin-15 complexes are generated in vivo by type I interferon dependent and independent pathways, *PLoS ONE* 10 (2015) e0120274.
- [91] K. Yamaji, S. Nabeshima, M. Murata, Y. Chong, N. Furusyo, H. Ikematsu, J. Hayashi, Interferon-alpha/beta upregulate IL-15 expression in vitro and in vivo: analysis in human hepatocellular carcinoma cell lines and in chronic hepatitis C patients during interferon-alpha/beta treatment, *Cancer Immunol. Immunother.* 55 (2006) 394–403.
- [92] H.K. Mishra, J. Ma, B. Walcheck, Ectodomain shedding by ADAM17: its role in neutrophil recruitment and the impairment of this process during sepsis, *Front. Cell. Infect. Microbiol.* 7 (2017) 138.
- [93] J. Giron-Michel, M. Giuliani, M. Fogli, D. Brouty-Boyie, S. Ferrini, F. Baychelier, P. Eid, C. Lebousse-Kerdiles, D. Durali, R. Biassoni, B. Charpentier, A. Vasquez, S. Chouai, A. Caignard, L. Moretta, B. Azzarone, Membrane-bound and soluble IL-15/IL-15R $\alpha$  complexes display differential signaling and functions on human hematopoietic progenitors, *Blood* 106 (2005) 2302–2310.
- [94] I. Zanoni, R. Spreafico, C. Bodio, M. Di Gioia, C. Cigni, A. Broggi, T. Gorletta, M. Caccia, G. Chirico, L. Sironi, M. Collini, M.P. Colombo, N. Garbi, F. Granucci, IL-15 cis presentation is required for optimal NK cell activation in lipopolysaccharide-mediated inflammatory conditions, *Cell Rep.* 4 (2013) 1235–1249.
- [95] F. Tamzalit, I. Barbeaux, A. Plet, J. Heim, S. Nedellec, S. Morisseau, Y. Jacques, E. Mortier, IL-15/IL-15R $\alpha$  complex shedding following trans-presentation is essential for the survival of IL-15 responding NK and T cells, *Proc. Natl. Acad. Sci. U.S.A.* 111 (2014) 8565–8570.
- [96] O.M. Anton, M.E. Peterson, M.J. Hollander, D.W. Dorward, G. Arora, J. Traba, S. Rajagopalan, E.L. Snapp, K.C. Garcia, T.A. Waldmann, E.O. Long, Trans-endocytosis of intact IL-15R $\alpha$ -IL-15 complex from presenting cells into NK cells favors signaling for proliferation, *Proc. Natl. Acad. Sci. U.S.A.* 117 (2020) 522–531.
- [97] K.C. Conlon, E. Lugli, H.C. Welles, S.A. Rosenberg, A.T. Fojo, J.C. Morris, T.A. Fleisher, S.P. Dubois, L.P. Perera, D.M. Stewart, C.K. Goldman, B.R. Bryant, J.M. Decker, J. Chen, T.A. Worthy, W.D. Figg Sr., C.J. Peer, M.C. Sneller, H.C. Lane, J.L. Yovandich, S.P. Creekmore, M. Roederer, T.A. Waldmann, Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer, *J. Clin. Oncol.* 33 (2015) 74–82.
- [98] E. Lugli, C.K. Goldman, L.P. Perera, J. Smedley, R. Pung, J.L. Yovandich, S.P. Creekmore, T.A. Waldmann, M. Roederer, Transient and persistent effects of IL-15 on lymphocyte homeostasis in nonhuman primates, *Blood* 116 (2010) 3238–3248.
- [99] M.C. Sneller, W.C. Kopp, K.J. Engelke, J.L. Yovandich, S.P. Creekmore, T.A. Waldmann, H.C. Lane, IL-15 administered by continuous infusion to rhesus macaques induces massive expansion of CD8+ T effector memory population in peripheral blood, *Blood* 118 (2011) 6845–6848.
- [100] T.A. Waldmann, E. Lugli, M. Roederer, L.P. Perera, J.V. Smedley, R.P. Macallister, C.K. Goldman, B.R. Bryant, J.M. Decker, T.A. Fleisher, H.C. Lane, M.C. Sneller, R.J. Kurlander, D.E. Kleiner, J.M. Fletcher, W.D. Figg, J.L. Yovandich, S.P. Creekmore, Safety (toxicity), pharmacokinetics, immunogenicity, and impact on elements of the normal immune system of recombinant human IL-15 in rhesus macaques, *Blood* 117 (2011) 4787–4795.
- [101] M. Felices, A.J. Lenvik, R. McElmurry, S. Chu, P. Hinderlie, L. Bendzik, M.A. Geller, J. Tolar, B.R. Blazier, J.S. Miller, Continuous treatment with IL-15 exhausts human NK cells via a metabolic defect, *JCI Insight* 3 (2018).
- [102] M. Zhang, B. Wen, O.M. Anton, Z. Yao, S. Dubois, W. Ju, N. Sato, D.J. DiLillo, R.N. Bamford, J.V. Ravetch, T.A. Waldmann, IL-15 enhanced antibody-dependent cellular cytotoxicity mediated by NK cells and macrophages, *Proc. Natl. Acad. Sci. U.S.A.* 115 (2018) E10915–E10924.
- [103] D. Meghnem, S. Morisseau, M. Frutoso, K. Trillet, M. Maillatson, I. Barbeaux, S. Khaddage, I. Leray, M. Hildinger, A. Quemener, Y. Jacques, E. Mortier, Cutting edge: differential fine-tuning of IL-2- and IL-15-dependent functions by targeting their common IL-2/15R $\beta$ /gammac receptor, *J. Immunol.* 198 (2017) 4563–4568.
- [104] M. Jinushi, T. Takehara, T. Tatsumi, T. Kanto, V. Groh, T. Spies, T. Suzuki, T. Miyagi, N. Hayashi, Autocrine/paracrine IL-15 is required for type I IFN-mediated dendritic cell expression of MHC class I-related chain A and B is impaired in hepatitis C virus infection, *J. Immunol.* 171 (2003) 5423–5429.
- [105] N. Azimi, K.M. Shiramizu, Y. Tagaya, J. Mariner, T.A. Waldmann, Viral activation of interleukin-15 (IL-15): characterization of a virus-inducible element in the IL-15 promoter region, *J. Virol.* 74 (2000) 7338–7348.
- [106] H. Gary-Gouy, P. Lebon, A.H. Dalloul, Type I interferon production by plasma-cytoid dendritic cells and monocytes is triggered by viruses, but the level of production is controlled by distinct cytokines, *J. Interferon Cytokine Res.* 22 (2002) 653–659.
- [107] F. Mattei, G. Schiavoni, F. Belardelli, D.F. Tough, IL-15 is expressed by dendritic cells in response to type I IFN, double-stranded RNA, or lipopolysaccharide and promotes dendritic cell activation, *J. Immunol.* 167 (2001) 1179–1187.
- [108] M.J. Chenoweth, M.F. Mian, N.G. Barra, T. Alain, N. Sonenberg, J. Bramson, B.D. Lichty, C.D. Richards, A. Ma, A.A. Ashkar, IL-15 can signal via IL-15R $\alpha$ , JNK, and NF-kappaB to drive RANTES production by myeloid cells, *J. Immunol.* 188 (2012) 4149–4157.
- [109] A.K. Singha, C. Sarkar, D. Majumder, R. Debnath, M. Saha, D. Maiti, IL-15 and GM-CSF stimulated macrophages enhances phagocytic activity in ENU induced leukemic mice, *Immunobiology* 151894 (2019).
- [110] S. Okada, S. Han, E.S. Patel, L.J. Yang, L.J. Chang, STAT3 signaling contributes to the high effector activities of interleukin-15-derived dendritic cells, *Immunol. Cell Biol.* 93 (2015) 461–471.
- [111] S. Anguille, E. Lion, J. Tel, I.J. de Vries, K. Coudere, P.D. Fromm, V.F. Van Tendeloo, E.L. Smits, Z.N. Berneman, Interleukin-15-induced CD56(+) myeloid dendritic cells combine potent tumor antigen presentation with direct tumoricidal potential, *PLoS ONE* 7 (2012) e51851.
- [112] S.K. Hira, I. Mondal, D. Bhattacharya, P.P. Manna, Downregulation of endogenous STAT3 augments tumoricidal activity of interleukin 15 activated dendritic cell against lymphoma and leukemia via TRAIL, *Exp. Cell Res.* 327 (2014) 192–208.
- [113] A.J. Silman, J.E. Pearson, Epidemiology and genetics of rheumatoid arthritis, *Arthritis Res. Ther.* 4 (Suppl 3) (2002) S265–S272.
- [114] N.J. Zvaifler, G.S. Firestein, Pannus and pannocytes. Alternative models of joint destruction in rheumatoid arthritis, *Arthritis Rheum.* 37 (1994) 783–789.
- [115] M.M. Ainola, J.A. Mandelin, M.P. Liljestrom, T.F. Li, M.V. Hukkanen, Y.T. Konttinen, Pannus invasion and cartilage degradation in rheumatoid arthritis: involvement of MMP-3 and interleukin-1 $\beta$ , *Clin. Exp. Rheumatol.* 23 (2005) 644–650.
- [116] J.A. Hamilton, Hypothesis: in vitro evidence for the invasive and tumor-like properties of the rheumatoid pannus, *J. Rheumatol.* 10 (1983) 845–851.
- [117] D. Aletaha, J. Funovits, J.S. Smolen, Physical disability in rheumatoid arthritis is associated with cartilage damage rather than bone destruction, *Ann. Rheum. Dis.* 70 (2011) 733–739.
- [118] K. Yoshihara, H. Yamada, A. Hori, T. Yajima, C. Kubo, Y. Yoshikai, IL-15 exacerbates collagen-induced arthritis with an enhanced CD4+ T cell response to produce IL-17, *Eur. J. Immunol.* 37 (2007) 2744–2752.
- [119] L. Petrovic-Rackov, N. Pejnovic, Clinical significance of IL-18, IL-15, IL-12 and TNF-alpha measurement in rheumatoid arthritis, *Clin. Rheumatol.* 25 (2006)

- 448–452.
- [120] I.B. McInnes, J. Al-Mughales, M. Field, B.P. Leung, F.P. Huang, R. Dixon, R.D. Sturrock, P.C. Wilkinson, F.Y. Liew, The role of interleukin-15 in T-cell migration and activation in rheumatoid arthritis, *Nat. Med.* 2 (1996) 175–182.
- [121] R. Knevel, A. Krabben, E. Brouwer, M.D. Posthumus, A.G. Wilson, E. Lindqvist, T. Saxne, D. de Rooy, N. Daha, M.P. van der Linden, G. Stoeken, L. van Toorn, B. Koeleman, R. Tsoukatos, A. Zhernakova, J.J. Houwing-Duistermaat, R. Toes, T.W. Huizinga, Mil A. van der Helm-van, Genetic variants in IL15 associate with progression of joint destruction in rheumatoid arthritis: a multicohort study, *Ann. Rheum. Dis.* 71 (2012) 1651–1657.
- [122] A.R. Stacey, P.J. Norris, L. Qin, E.A. Haygreen, E. Taylor, J. Heitman, M. Lebedeva, A. DeCamp, D. Li, D. Grove, S.G. Self, P. Borrow, Induction of a striking systemic cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1 infection, in contrast to more modest and delayed responses in acute hepatitis B and C virus infections, *J. Virol.* 83 (2009) 3719–3733.
- [123] S. Harada, M. Yamamura, H. Okamoto, Y. Morita, M. Kawashima, T. Aita, H. Makino, Production of interleukin-7 and interleukin-15 by fibroblast-like synoviocytes from patients with rheumatoid arthritis, *Arthritis Rheum.* 42 (1999) 1508–1516.
- [124] N. Oppenheimer-Marks, R.I. Brezinschek, M. Mohamadzadeh, R. Vita, P.E. Lipsky, Interleukin 15 is produced by endothelial cells and increases the transendothelial migration of T cells In vitro and in the SCID mouse-human rheumatoid arthritis model In vivo, *J. Clin. Invest.* 101 (1998) 1261–1272.
- [125] J.C. Nolz, J.T. Harty, IL-15 regulates memory CD8+ T cell O-glycan synthesis and affects trafficking, *J. Clin. Invest.* 124 (2014) 1013–1026.
- [126] A.K. Andersson, M. Feldmann, F.M. Brennan, Neutralizing IL-21 and IL-15 inhibits pro-inflammatory cytokine production in rheumatoid arthritis, *Scand. J. Immunol.* 68 (2008) 103–111.
- [127] M.E. Miranda-Carus, A. Balsa, M. Benito-Miguel, C. Perez de Ayala, E. Martin-Mola, IL-15 and the initiation of cell contact-dependent synovial fibroblast-T lymphocyte cross-talk in rheumatoid arthritis: effect of methotrexate, *J. Immunol.* 173 (2004) 1463–1476.
- [128] R. Ruckert, K. Brandt, M. Ernst, K. Marienfeld, E. Csernok, C. Metzler, V. Budagian, E. Bulanova, R. Paus, S. Bulfone-Paus, Interleukin-15 stimulates macrophages to activate CD4+ T cells: a role in the pathogenesis of rheumatoid arthritis? *Immunology* 126 (2009) 63–73.
- [129] P. Deshpande, M.M. Cavanagh, S. Le Saux, K. Singh, C.M. Weyand, J.J. Goronyi, IL-7 and IL-15-mediated TCR sensitization enables T cell responses to self-antigens, *J. Immunol.* 190 (2013) 1416–1423.
- [130] M.A. Atkinson, G.S. Eisenbarth, A.W. Michels, Type 1 diabetes, *Lancet* 383 (2014) 69–82.
- [131] R.D. Leslie, Predicting adult-onset autoimmune diabetes: clarity from complexity, *Diabetes* 59 (2010) 330–331.
- [132] P. Concannon, S.S. Rich, G.T. Nepom, Genetics of type 1A diabetes, *N. Engl. J. Med.* 360 (2009) 1646–1654.
- [133] C. Polychronakos, Q. Li, Understanding type 1 diabetes through genetics: advances and prospects, *Nat. Rev. Genet.* 12 (2011) 781–792.
- [134] S. Kuczynski, H. Winiarska, M. Abramczyk, K. Szczawinska, B. Wierusz-Wysocka, M. Dworacka, IL-15 is elevated in serum patients with type 1 diabetes mellitus, *Diabetes Res. Clin. Pract.* 69 (2005) 231–236.
- [135] C.R. van der Torren, A.A. Verrijn Stuart, D. Lee, J. Meerding, U. van de Velde, D. Pipeleers, P. Gillard, B. Keymeulen, W. de Jager, B.O. Roep, Serum cytokines as biomarkers in islet cell transplantation for type 1 diabetes, *PLoS ONE* 11 (2016) e0146649.
- [136] K. Araki, A.P. Turner, V.O. Shaffer, S. Gangappa, S.A. Keller, M.F. Bachmann, C.P. Larsen, R. Ahmed, mTOR regulates memory CD8 T-cell differentiation, *Nature* 460 (2009) 108–112.
- [137] M. Koulmanda, E. Budo, S. Bonner-Weir, A. Qipo, P. Puttheti, N. Degauque, H. Shi, Z. Fan, J.S. Flier, H. Auchincloss Jr., X.X. Zheng, T.B. Strom, Modification of adverse inflammation is required to cure new-onset type 1 diabetic hosts, *Proc. Natl. Acad. Sci. U.S.A.* 104 (2007) 13074–13079.
- [138] Y.S. Kim, W. Maslinski, X.X. Zheng, A.C. Stevens, X.C. Li, G.H. Tesch, V.R. Kelley, T.B. Strom, Targeting the IL-15 receptor with an antagonist IL-15 mutant/Fc gamma-2a protein blocks delayed-type hypersensitivity, *J. Immunol.* 160 (1998) 5742–5748.
- [139] J.D. Fontenot, J.P. Rasmussen, M.A. Gavin, A.Y. Rudensky, A function for interleukin 2 in Foxp3-expressing regulatory T cells, *Nat. Immunol.* 6 (2005) 1142–1151.
- [140] E.L. Brincks, D.L. Woodland, Novel roles for IL-15 in T cell survival, *F1000 Biol. Rep.* 2 (67) (2010).
- [141] G. Demirci, T.B. Strom, X.C. Li, Islet allograft rejection in nonobese diabetic mice involves the common gamma-chain and CD28/CD154-dependent and -independent mechanisms, *J. Immunol.* 171 (2003) 3878–3885.
- [142] V.A. Huurman, R. Hilbrands, G.G. Pinkse, P. Gillard, G. Duinkerken, P. van de Linde, P.M. van der Meer-Prins, M.F. Versteeg-van der Voort Maarschalk, K. Verbeeck, B.Z. Alizadeh, C. Mathieu, F.K. Goris, D.L. Roelen, F.H. Claas, B. Keymeulen, D.G. Pipeleers, B.O. Roep, Cellular islet autoimmunity associates with clinical outcome of islet cell transplantation, *PLoS One* 3 (2008) e2435.
- [143] W.W. Unger, J. Velthuis, J.R. Abreu, S. Laban, E. Quinten, M.G. Kester, S. Reker-Hadrup, A.H. Bakker, G. Duinkerken, A. Mulder, K.L. Franken, R. Hilbrands, B. Keymeulen, M. Peakman, F. Ossendorp, J.W. Drijfhout, T.N. Schumacher, B.O. Roep, Discovery of low-affinity preproinsulin epitopes and detection of autoreactive CD8 T-cells using combinatorial MHC multimers, *J. Autoimmun.* 37 (2011) 151–159.
- [144] P. Monti, M. Scirpoli, P. Maffi, N. Ghidoli, F. De Taddeo, F. Bertuzzi, L. Piemonti, M. Falcone, A. Secchi, E. Bonifacio, Islet transplantation in patients with autoimmune diabetes induces homeostatic cytokines that expand autoreactive memory T cells, *J. Clin. Invest.* 118 (2008) 1806–1814.
- [145] S. Ramanathan, S. Dubois, X.L. Chen, C. Leblanc, P.S. Ohashi, S. Ilangumaran, Exposure to IL-15 and IL-21 enables autoreactive CD8 T cells to respond to weak antigens and cause disease in a mouse model of autoimmune diabetes, *J. Immunol.* 186 (2011) 5131–5141.
- [146] H. Brauner, H.T. Hall, M. Flodstrom-Tullberg, K. Karre, P. Hoglund, S. Johansson, Depletion of IL-2 receptor beta-positive cells protects from diabetes in non-obese diabetic mice, *Immunol. Cell Biol.* 94 (2016) 177–184.
- [147] J. Chen, L. Feigenbaum, P. Awasthi, D.O. Butcher, M.R. Anver, Y.G. Golubeva, R. Bamford, X. Zhang, M.B. St Claire, C.J. Thomas, V. Discepolo, B. Jabri, T.A. Waldmann, Insulin-dependent diabetes induced by pancreatic beta cell expression of IL-15 and IL-15Ralpha, *Proc. Natl. Acad. Sci. U.S.A.* (2013).
- [148] X. Yuan, Y. Dong, N. Tsurushita, J.Y. Tso, W. Fu, CD122 blockade restores immunological tolerance in autoimmune type 1 diabetes via multiple mechanisms, *JCI Insight* 3 (2018).
- [149] J. Chen, L. Feigenbaum, P. Awasthi, D. Butcher, M. Anver, R. Bamford, C. Thomas, T. Waldmann, Co-expression of IL-15 and IL-15R $\alpha$  on pancreatic  $\beta$  islet cells induced insulin dependent diabetes mellitus in mice (161.2), *J. Immunol.* 188 (161) (2012) 162.
- [150] X. Yuan, Y. Dong, J.Y. Tso, W. Fu, Restoration of immune tolerance in type 1 diabetes by modulating interleukin-2 receptor signaling, *J. Immunol.* 198 (80) (2017) 16.
- [151] H. Rothe, A. Hausmann, H. Kolb, Immunoregulation during disease progression in prediabetic NOD mice: inverse expression of arginase and prostaglandin H synthase 2 vs. interleukin-15, *Horm. Metab. Res.* 34 (2002) 7–12.
- [152] A.K. Cardozo, P. Proost, C. Gysemans, M.C. Chen, C. Mathieu, D.L. Eizirik, IL-1beta and IFN-gamma induce the expression of diverse chemokines and IL-15 in human and rat pancreatic islet cells, and in islets from pre-diabetic NOD mice, *Diabetologia* 46 (2003) 255–266.
- [153] D. Bobbala, M. Mayhue, A. Menendez, S. Ilangumaran, S. Ramanathan, Trans-presentation of interleukin-15 by interleukin-15 receptor alpha is dispensable for the pathogenesis of autoimmune type 1 diabetes, *Cell. Mol. Immunol.* 14 (2017) 590–596.
- [154] H.S.P. de Souza, C. Fiocchi, D. Iliopoulos, The IBD interactome: an integrated view of aetiology, pathogenesis and therapy, *Nat. Rev. Gastroenterol. Hepatol.* 14 (2017) 739–749.
- [155] B.R. de Mattos, M.P. Garcia, J.B. Nogueira, L.N. Paiatto, C.G. Albuquerque, C.L. Souza, L.G. Fernandes, W.M. Tamashiro, P.U. Simioni, Inflammatory bowel disease: an overview of immune mechanisms and biological treatments, *Mediators Inflamm.* 2015 (2015) 493012.
- [156] M. Friedrich, M. Pohin, F. Powrie, Cytokine networks in the pathophysiology of inflammatory bowel disease, *Immunity* 50 (2019) 992–1006.
- [157] A. Kaser, S. Zeissig, R.S. Blumberg, Inflammatory bowel disease, *Annu. Rev. Immunol.* 28 (2010) 573–621.
- [158] S. Danese, J.F. Colombel, L. Peyrin-Biroulet, P. Rutgeerts, W. Reinisch, Review article: the role of anti-TNF in the management of ulcerative colitis – past, present and future, *Aliment. Pharmacol. Ther.* 37 (2013) 855–866.
- [159] W.K. van Deen, D.W. Hommes, IBD: Antibodies to anti-TNF therapy–consequences for IBD management, *Nat. Rev. Gastroenterol. Hepatol.* 10 (2013) 446–448.
- [160] S.C. Park, Y.T. Jeen, Current and emerging biologics for ulcerative colitis, *Gut Liver* 9 (2015) 18–27.
- [161] S.O. Adegbola, K. Sahnaj, J. Warusavitarne, A. Hart, P. Tozer, Anti-TNF therapy in Crohn's disease, *Int. J. Mol. Sci.* 19 (2018).
- [162] S.R. Targan, S.B. Hanauer, S.J. van Deventer, L. Mayer, D.H. Present, T. Braakman, K.L. DeWoody, T.F. Schaible, P. Rutgeerts, A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group, *N. Engl. J. Med.* 337 (1997) 1029–1035.
- [163] S.J. Van Deventer, Tumour necrosis factor and Crohn's disease, *Gut* 40 (1997) 443–448.
- [164] B.G. Feagan, W.J. Sandborn, C. Gasink, D. Jacobstein, Y. Lang, J.R. Friedman, M.A. Blank, J. Johanns, L.L. Gao, Y. Miao, O.J. Adedokun, B.E. Sands, S.B. Hanauer, S. Vermeire, S. Targan, S. Ghosh, W.J. de Villiers, J.F. Colombel, Z. Tulassay, U. Seidler, B.A. Salzberg, P. Desreux, S.D. Lee, E.V. Loftus Jr., L.A. Dieleman, S. Katz, P. Rutgeerts, Group U-I-US, Ustekinumab as induction and maintenance therapy for Crohn's disease, *N. Engl. J. Med.* 375 (2016) 1946–1960.
- [165] K.N. Weaver, M. Gregory, G. Syal, P. Hoversten, S.B. Hicks, D. Patel, G. Christophi, P. Beniwal-Patel, K.L. Isaacs, L. Raffals, P. Deepak, H.H. Herfarth, E.L. Barnes, Ustekinumab is effective for the treatment of Crohn's disease of the pouch in a multicenter cohort, *Inflamm. Bowel Dis.* 25 (2019) 767–774.
- [166] B.E. Sands, W.J. Sandborn, R. Panaccione, C.D. O'Brien, H. Zhang, J. Johanns, O.J. Adedokun, K. Li, L. Peyrin-Biroulet, G. Van Assche, S. Danese, S. Targan, M.T. Abreu, T. Hisamatsu, P. Szapary, C. Marano, Group US, Ustekinumab as induction and maintenance therapy for ulcerative colitis, *N Engl. J. Med.* 381 (2019) 1201–1214.
- [167] R.J. Farrell, Biologics beyond Anti-TNF agents for ulcerative colitis – efficacy, safety, and cost? *N. Engl. J. Med.* 381 (2019) 1279–1281.
- [168] A.R. Moschen, H. Tilg, T. Raine, IL-12, IL-23 and IL-17 in IBD: immunobiology and therapeutic targeting, *Nat. Rev. Gastroenterol. Hepatol.* 16 (2019) 185–196.
- [169] S.L. Gaffen, R. Jain, A.V. Garg, D.J. Cua, The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing, *Nat. Rev. Immunol.* 14 (2014) 585–600.
- [170] L. Jostins, S. Ripke, R.K. Weersma, R.H. Duerr, D.P. McGovern, K.Y. Hui, J.C. Lee, L.P. Schumm, Y. Sharma, C.A. Anderson, J. Essers, M. Mitrovic, K. Ning, I. Cleynen, E. Theatre, S.L. Spain, S. Raychaudhuri, P. Goyette, Z. Wei, C. Abraham, J.P. Achkar, T. Ahmad, L. Amininejad, A.N. Ananthakrishnan, V. Andersen, J.M. Andrews, L. Baidoo, T. Balschun, P.A. Bampton, A. Bitton,

- G. Boucher, S. Brand, C. Buning, A. Cohain, S. Cichon, M. D'Amato, D. De Jong, K.L. Devaney, M. Dubinsky, C. Edwards, D. Ellinghaus, L.R. Ferguson, D. Franchimont, K. Fransen, R. Gearry, M. Georges, C. Gieger, J. Glas, T. Haritunians, A. Hart, C. Hawkey, M. Hedl, X. Hu, T.H. Karlsen, L. Kupcinskas, S. Kugathasan, A. Latiano, D. Laukens, I.C. Lawrence, C.W. Lees, E. Louis, G. Mahy, J. Mansfield, A.R. Morgan, C. Mowat, W. Newman, O. Palmieri, C.Y. Ponsioen, U. Potocnik, N.J. Prescott, M. Regueiro, J.I. Rotter, R.K. Russell, J.D. Sanderson, M. Sans, J. Satsangi, S. Schreiber, L.A. Simms, J. Sventoratyte, S.R. Targan, K.D. Taylor, M. Tremelling, H.W. Verspaget, M. De Vos, C. Wijmenga, D.C. Wilson, J. Winkelmann, R.J. Xavier, S. Zeissig, B. Zhang, C.K. Zhang, H. Zhao, International IBDG, M.S. Silverberg, V. Annese, H. Hakanson, S.R. Brant, G. Radford-Smith, C.G. Mathew, J.D. Rioux, E.E. Schadt, M.J. Daly, A. Franke, M. Parkes, S. Vermeire, J.C. Barrett, J.H. Cho, Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease, *Nature* 491 (2012) 119–124.
- [171] J. Wang, A. Bhatia, N. Krugliak Cleveland, N. Gupta, S. Dalal, D.T. Rubin, A. Sakuraba, Rapid Onset of Inflammatory Bowel Disease after Receiving Secukinumab Infusion, *ACG Case Rep J* 5 (2018) e56.
- [172] V. Abadie, B. Jabri, IL-15: a central regulator of celiac disease immunopathology, *Immunol. Rev.* 260 (2014) 221–234.
- [173] K. Yoshihara, T. Yajima, C. Kubo, Y. Yoshikai, Role of interleukin 15 in colitis induced by dextran sulphate sodium in mice, *Gut* 55 (2006) 334–341.
- [174] J. Schulthess, B. Meresse, E. Ramiro-Puig, N. Montcuquet, S. Darche, B. Begue, F. Ruemmele, C. Combadiere, J.P. Di Santo, D. Buzoni-Gatel, N. Cerf-Bensussan, Interleukin-15-dependent NKP46+ innate lymphoid cells control intestinal inflammation by recruiting inflammatory monocytes, *Immunity* 37 (2012) 108–121.
- [175] J.H. Bernink, C.P. Peters, M. Munneke, A.A. te Velde, S.L. Meijer, K. Weijer, H.S. Hreggvidsdottir, S.E. Heinsbroek, N. Legrand, C.J. Buskens, W.A. Bemelman, J.M. Mjosberg, H. Spits, Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues, *Nat. Immunol.* 14 (2013) 221–229.
- [176] Z. Liu, K. Geboes, S. Colpaert, G.R. D'Haens, P. Rutgeerts, J.L. Ceuppens, IL-15 is highly expressed in inflammatory bowel disease and regulates local T cell-dependent cytokine production, *J. Immunol.* 164 (2000) 3608–3615.
- [177] T. Sakai, K. Kusugami, H. Nishimura, T. Ando, T. Yamaguchi, M. Ohsuga, K. Ina, A. Enomoto, Y. Kimura, Y. Yoshikai, Interleukin 15 activity in the rectal mucosa of inflammatory bowel disease, *Gastroenterology* 114 (1998) 1237–1243.
- [178] T. Nishiwaki, K. Ina, H. Goto, O. Watanabe, T. Tsuzuki, R. Furuta, T. Ando, K. Hibi, K. Kusugami, Possible involvement of the interleukin-15 and interleukin-15 receptor system in a heightened state of lamina propria B cell activation and differentiation in patients with inflammatory bowel disease, *J. Gastroenterol.* 40 (2005) 128–136.
- [179] A.J. Leon, E. Gomez, J.A. Garrote, D. Bernardo, A. Barrera, J.L. Marcos, L. Fernandez-Salazar, B. Velayos, A. Blanco-Quiros, E. Arranz, High levels of proinflammatory cytokines, but not markers of tissue injury, in unaffected intestinal areas from patients with IBD, *Mediators Inflamm.* 2009 (2009) 580450.
- [180] G. Bouchaud, E. Mortier, M. Flamant, I. Barbeaux, A. Plet, J.P. Galimiche, Y. Jacques, A. Bourreille, Interleukin-15 and its soluble receptor mediate the response to infliximab in patients with Crohn's disease, *Gastroenterology* 138 (2010) 2378–2387.
- [181] S. Vitale, C. Striscuglio, L. Pisapia, E. Miele, P. Barba, A. Vitale, S. Cenni, V. Bassi, M. Maglio, G. Del Pozzo, R. Troncone, A. Staiano, C. Gianfrani, Cytokine production profile in intestinal mucosa of paediatric inflammatory bowel disease, *PLoS ONE* 12 (2017) e0182313.
- [182] M. Meisel, T. Mayassi, H. Fehlner-Peach, J.C. Koval, S.L. O'Brien, R. Hinterleitner, K. Lesko, S. Kim, R. Bouziat, L. Chen, C.R. Weber, S.K. Mazmanian, B. Jabri, D.A. Antonopoulos, Interleukin-15 promotes intestinal dysbiosis with butyrate deficiency associated with increased susceptibility to colitis, *ISME J.* 11 (2017) 15–30.
- [183] W.D. Rees, M. Stahl, K. Jacobson, B. Bressler, L.M. Sly, B.A. Vallance, T.S. Steiner, Enteroids derived from inflammatory bowel disease patients display dysregulated endoplasmic reticulum stress pathways, leading to differential inflammatory responses and dendritic cell maturation, *J. Crohns Colitis* (2019).
- [184] M.E. Raeber, Y. Zurbuchen, D. Impellizzieri, O. Boyman, The role of cytokines in T-cell memory in health and disease, *Immunol. Rev.* 283 (2018) 176–193.
- [185] K.C. Duffin, G.G. Krueger, Genetic variations in cytokines and cytokine receptors associated with psoriasis found by genome-wide association, *J. Invest. Dermatol.* 129 (2009) 827–833.
- [186] R.L. Smith, S. Eyre, R.B. Warren, H.S. Young, C.E. Griffiths, J. Worthington, No association between polymorphisms in the interleukin-15 gene and early-onset psoriasis in a UK cohort suggests heterogeneity for this susceptibility locus identified in Chinese psoriasis patients, *J. Invest. Dermatol.* 128 (2008) 2904–2905.
- [187] W. Weger, A. Hofer, P. Wolf, Y. El-Shabrawi, W. Renner, H. Kerl, W. Salmhofer, Role of the interleukin 15 96516A > T and IL15 96330C > A gene polymorphisms in Caucasian patients with chronic plaque psoriasis, *J. Dermatol. Sci.* 51 (2008) 147–149.
- [188] O. Boyman, H.P. Hefti, C. Conrad, B.J. Nickoloff, M. Suter, F.O. Nestle, Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumor necrosis factor-alpha, *J. Exp. Med.* 199 (2004) 731–736.
- [189] L.S. Villadsen, J. Schuurman, F. Beurskens, T.N. Dam, F. Dagnaes-Hansen, L. Skov, J. Rygaard, M.M. Voorhorst-Ogink, A.F. Gerritsen, M.A. van Dijk, P.W. Parren, O. Baadsgaard, J.G. van de Winkel, Resolution of psoriasis upon blockade of IL-15 biological activity in a xenograft mouse model, *J. Clin. Invest.* 112 (2003) 1571–1580.
- [190] J.T. Elder, IL-15 and psoriasis: another genetic link to Th17? *J. Invest. Dermatol.* 127 (2007) 2495–2497.
- [191] S. Cheuk, H. Schlums, I. Gallais Serezal, E. Martini, S.C. Chiang, N. Marquardt, A. Gibbs, E. Detloffsson, A. Introini, M. Forkel, C. Hoog, A. Tjernlund, J. Michaelsson, L. Folkersen, J. Mjosberg, L. Blomqvist, M. Ehrstrom, M. Stahle, Y.T. Bryceson, L. Eidsmo, CD49a expression defines tissue-resident CD8(+)-T cells poised for cytotoxic function in human skin, *Immunity* 46 (2017) 287–300.
- [192] J. Frieder, D. Kivelevitch, A. Menter, Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis, *Ther. Adv. Chronic Dis.* 9 (2018) 5–21.
- [193] E.A. Wang, E. Suzuki, E. Maverakis, I.E. Adamopoulos, Targeting IL-17 in psoriatic arthritis, *Eur. J. Rheumatol.* 4 (2017) 272–277.
- [194] S. Maeda, Y. Hayami, T. Naniwa, R. Ueda, The Th17/IL-23 axis and natural immunity in psoriatic arthritis, *Int. J. Rheumatol.* 2012 (2012) 539683.
- [195] S. Ferrari-Lacraz, E. Zanelli, M. Neuberg, E. Donskoy, Y.S. Kim, X.X. Zheng, W.W. Hancock, W. Maslinski, X.C. Li, T.B. Strom, T. Moll, Targeting IL-15 receptor-bearing cells with an antagonist mutant IL-15/Fc protein prevents disease development and progression in murine collagen-induced arthritis, *J. Immunol.* 173 (2004) 5818–5826.
- [196] H. Ruchatz, B.P. Leung, X.Q. Wei, I.B. McInnes, F.Y. Liew, Soluble IL-15 receptor alpha-chain administration prevents murine collagen-induced arthritis: a role for IL-15 in development of antigen-induced immunopathology, *J. Immunol.* 160 (1998) 5654–5660.
- [197] T. Zhang, X. Bai, X. Mao, Systemic delivery of small interfering RNA targeting the interleukin-2/15 receptor beta chain prevents disease progression in experimental arthritis, *PLoS ONE* 8 (2013) e78619.
- [198] D. Wang, X. Deng, X. Leng, X. Mao, Interleukin-15 receptor-directed immunotoxins attenuate disease severity in rat adjuvant arthritis, *Mol. Immunol.* 47 (2010) 1535–1543.
- [199] Z. Rosman, Y. Shoenfeld, G. Zandman-Goddard, Biologic therapy for autoimmune diseases: an update, *BMC Med.* 11 (2013) 88.
- [200] M. Campa, B. Mansouri, R. Warren, A. Menter, A review of biologic therapies targeting IL-23 and IL-17 for use in moderate-to-severe plaque psoriasis, *Dermatol. Ther. (Heidelberg)* 6 (2016) 1–12.
- [201] S. Ernestam, E. af Klint, A.I. Catrina, E. Sundberg, M. Engstrom, L. Klareskog, A.K. Ulfgren, Synovial expression of IL-15 in rheumatoid arthritis is not influenced by blockade of tumour necrosis factor, *Arthritis Res. Ther.* 8 (2006) 18.
- [202] B. Baslund, N. Tvede, B. Dannekiold-Samsøe, P. Larsson, G. Panayi, J. Petersen, L.J. Petersen, F.J. Beurskens, J. Schuurman, J.G. van de Winkel, P.W. Parren, J.A. Gracie, S. Jongbloed, F.Y. Liew, I.B. McInnes, Targeting interleukin-15 in patients with rheumatoid arthritis: a proof-of-concept study, *Arthritis Rheum.* 52 (2005) 2686–2692.
- [203] R.M. Fleischmann, M.C. Genovese, J.V. Enejosa, E. Mysler, L. Bessette, C. Peterfy, P. Durez, A. Ostro, Y. Li, I.H. Song, Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response, *Ann. Rheum. Dis.* 78 (2019) 1454–1462.
- [204] P.C. Taylor, Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis, *Rheumatology (Oxford)* 58 (2019) i17–i26.
- [205] L. Senolt, Emerging therapies in rheumatoid arthritis: focus on monoclonal antibodies, *F1000Res* 8 (2019).
- [206] M.L. Lahdeaho, M. Scheinin, P. Vuotikka, J. Taavela, A. Popp, J. Laukkarinen, J. Koffert, O.P. Koivurova, M. Pesu, L. Kivelä, Z. Lovro, J. Keisala, J. Isola, J.R. Parnes, F. Leon, M. Maki, Safety and efficacy of AMG 714 in adults with coeliac disease exposed to gluten challenge: a phase 2a, randomised, double-blind, placebo-controlled study, *Lancet Gastroenterol. Hepatol.* 4 (2019) 948–959.
- [207] C. Cellier, G. Bouma, T. van Gils, S. Khater, G. Malamut, L. Crespo, P. Collin, P.H.R. Green, S.E. Crowe, W. Tsuji, E. Butz, N. Cerf-Bensussan, E. Macintyre, J.R. Parnes, F. Leon, O. Hermine, C.J. Mulder, R.-I.S.G. Investigators, Safety and efficacy of AMG 714 in patients with type 2 refractory coeliac disease: a phase 2a, randomised, double-blind, placebo-controlled, parallel-group study, *Lancet Gastroenterol. Hepatol.* 4 (2019) 960–970.
- [208] H. Lebrec, M.J. Horner, K.S. Gorski, W. Tsuji, D. Xia, W.J. Pan, G. Means, G. Pietz, N. Li, M. Retter, K. Shaffer, N. Patel, P.K. Narayanan, E.A. Butz, Homeostasis of human NK cells is not IL-15 dependent, *J. Immunol.* 191 (2013) 5551–5558.
- [209] A.P. Vicari, A.M. Schoepfer, B. Meresse, L. Goffin, O. Leger, S. Josserand, N. Guegan, S. Yousefi, A. Straumann, N. Cerf-Bensussan, H.U. Simon, Y. Chvatchko, Discovery and characterization of a novel humanized anti-IL-15 antibody and its relevance for the treatment of refractory coeliac disease and eosinophilic esophagitis, *MAbs* 9 (2017) 927–944.
- [210] K. Sestak, J.P. Dufour, D.X. Liu, N. Rout, X. Alvarez, J. Blanchard, A. Falda, D.J. Laine, A.W. Clarke, A.G. Doyle, Beneficial effects of human anti-interleukin-15 antibody in gluten-sensitive rhesus macaques with celiac disease, *Front. Immunol.* 9 (2018) 1603.
- [211] S. Yokoyama, K. Takada, M. Hirasawa, L.P. Perera, T. Hiroi, Transgenic mice that overexpress human IL-15 in enterocytes recapitulate both B and T cell-mediated pathologic manifestations of celiac disease, *J. Clin. Immunol.* 31 (2011) 1038–1044.
- [212] J.M. Richmond, J.P. Strassner, L. Zapata Jr., M. Garg, R.L. Riding, M.A. Refat, X. Fan, V. Azzolini, A. Tovar-Garza, N. Tsurushita, A.G. Pandya, J.Y. Tso, J.E. Harris, Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo, *Sci. Transl. Med.* 10 (2018).
- [213] T.A. Waldmann, K.C. Conlon, D.M. Stewart, T.A. Worthy, J.E. Janik, T.A. Fleisher, P.S. Albert, W.D. Figg, S.D. Spencer, M. Raffeld, J.R. Decker, C.K. Goldman, B.R. Bryant, M.N. Petrus, S.P. Creekmore, J.C. Morris, Phase 1 trial of IL-15 trans presentation blockade using humanized Milktbeta1 mAb in patients with T-cell large granular lymphocytic leukemia, *Blood* 121 (2013) 476–484.
- [214] Y. Enose-Akahata, U. Oh, J. Ohayon, B.J. Billiou, R. Massoud, B.R. Bryant, A. Vellucci, N. Ngouth, I. Cortese, T.A. Waldmann, S. Jacobson, Clinical trial of a

- humanized anti-IL-2/IL-15 receptor beta chain in HAM/TSP, *Ann. Clin. Transl. Neurol.* 6 (2019) 1383–1394.
- [215] T.T. Wang, J. Yang, Y. Zhang, M. Zhang, S. Dubois, K.C. Conlon, Y. Tagaya, C.E. Hamielec, S. Dighe, T.L. Olson, D.J. Feith, N. Azimi, T.A. Waldmann, T.P. Loughran Jr., IL-2 and IL-15 blockade by BNZ-1, an inhibitor of selective gamma-chain cytokines, decreases leukemic T-cell viability, *Leukemia* 33 (2019) 1243–1255.
- [216] Y. Rodriguez-Alvarez, Y. Morera-Diaz, H. Geronimo-Perez, J. Castro-Velazco, R. Martinez-Castillo, P. Puente-Perez, V. Besada-Perez, E. Hardy-Rando, A. Chico-Capote, K. Martinez-Cordovez, A. Santos-Savio, Active immunization with human interleukin-15 induces neutralizing antibodies in non-human primates, *BMC Immunol.* 17 (2016) 30.
- [217] S. Yokoyama, P.Y. Perera, T.A. Waldmann, T. Hiroi, L.P. Perera, Tofacitinib, a janus kinase inhibitor demonstrates efficacy in an IL-15 transgenic mouse model that recapitulates pathologic manifestations of celiac disease, *J. Clin. Immunol.* 33 (2013) 586–594.