

Survey

IL-15/IL-15 receptor biology: A guided tour through an expanding universe

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Abstract

The cytokine interleukin-15 (IL-15) has a key role in promoting survival, proliferation and activation of natural killer (NK) and CD8+ T cells. Despite its functional similarities to IL-2, IL-15 affects a wider range of target cell populations and utilizes different mechanisms of signaling. Here, we review recent advances in the IL-15-mediated signaling, and in the functional properties on cells besides T lymphocytes and NK cells. These are discussed in the context of their potential clinical and therapeutic relevance.

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Keywords: IL-15; IL-15 receptor α ; Apoptosis; Signal transduction; *trans*-Presentation

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1. Introduction

Interleukin-15 (IL-15) is a pleiotropic cytokine of the 4- α -helix bundle cytokine family that includes not only cytokines such as IL-2, IL-3, IL-4, IL-6 and IL-21, but also growth factors like granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), erythropoietin and classical hormones, including human growth hormone and prolactin [1]. As a member of this large and very diverse family, IL-15 exerts profound effects on the proliferation, survival and differentiation of many more distinct cell types than was originally appreciated at the time of its discovery.

IL-15 was independently discovered in 1994 by two groups, due to its ability to mimic IL-2-dependent T cell proliferation [2,3]. Burton *et al.* demonstrated that the human T-cell leukemia virus-1 (HTLV-1) cell line HuT-102 secreted a 14 kDa lymphokine capable of stimulating T cell proliferation and large granular lymphocytes activation, which was provisionally designated as IL-T [2]. Simultaneously, Grabstein *et al.* reported the isolation of a 14–15 kDa cytokine termed IL-15, which shared many biological properties with IL-2, from the supernatants of the simian kidney epithelial cell line CV-1/EBNA [3]. Human IL-15 has been cloned from the human bone marrow (BM) stromal cell line IMTLH, using simian IL-15 cDNA as a probe [3]. The predominant IL-15 message in HuT-102 cells corresponded to a chimeric mRNA where a segment of the long terminal repeat of HTLV-1 was fused in frame upstream of the 5'-untranslated region (UTR) of IL-15, thereby eliminating about 200 nucleotides of the IL-15 5'-UTR, including 8 of 10 AUGs, which are present in normal IL-15 messages and impede IL-15 translation [4]. Later, it was confirmed using anti-cytokine antibodies that both groups had identified the same interleukin [4]. This was designated IL-15.

A special feature of IL-15 is that it shares with IL-2, another member of the 4- α -helix bundle cytokine family, the

IL-2 receptor beta (IL-2R β) and IL-2 receptor gamma/gamma common (IL-2R γ / γ c) chains [5]. The γ c receptor chain is also shared by several other cytokines, such as IL-4, IL-7, IL-9 and IL-21, all of which use additional private receptor subunit(s) responsible for the specificity of binding and/or downstream signaling [6]. Given that cytokines often share receptor subunits and can therefore display a high degree of redundancy, the existing similarities in the action between IL-2 and IL-15 on cells of the same type are not surprising [2,3,7]. Together with the observed proliferation-stimulatory effects of both cytokines on various T-cell populations *in vitro*, this had initially encouraged the speculation that IL-2 and IL-15 exert very similar, if not identical functions [2,3]. However, a series of later studies have shown that, despite their many overlapping functional properties, IL-2 and IL-15 are, in fact, quite distinct players in the immune system (see below).

In essence, the concept has emerged that while IL-2 operates as a key modulator of T-cell-dependent adaptive immune responses, IL-15 serves a much broader spectrum of bioregulatory purposes. These range from those of a prototypic cytokine of innate immunity [8] via the modulation of selected adaptive immune responses [9,10] and a key role in the development of distinct immunocyte populations (namely natural killer (NK) cells) [11] to those of a potent, general inhibitor of apoptosis in multiple systems [12]. In addition, while IL-2 expression appears to be restricted to T cells [13], and possibly dendritic cells (DCs) stimulated with LPS [14], numerous different cell types engage in IL-15 transcription (even though much fewer seem to actually translate and secrete it (see below)). As the literature witnesses a steady flow of documented or proposed new functions of IL-15, initial proposals that IL-15 is a rather special member of the 4- α -helix bundle family with distinct functions have turned into an irreversible torrent of evidence [11,12,15–17].

This review argues that IL-15, indeed, is not only an unusually pleiotropic, but also a unique cytokine in several

respects (including mechanisms of cytokine synthesis, presentation, secretion and cytokine-induced signaling events), which we shall explore. Undoubtedly, one reason for the distinctness of IL-2 and IL-15 functions is that each cytokine has its own unique high affinity α chain, which recognizes only its cognate cytokine, thereby conferring ligand specificity [18,19]. However, as we shall emphasize, the differences between IL-2 and IL-15 (and, for that matter, any other member of this cytokine family!) do not stop here, but extend to almost every level of cytokine biology—from the regulation of cytokine gene transcription, translation, cytokine membrane expression and secretion, and the signaling induced by it. This ever-expanding universe of IL-15/IL-15R biology makes it one of the currently most fascinating in the cytokine world. Since the functional importance of IL-15/IL-15R biology in T cells and NK cells has been exceptionally well-covered before [8,9,10,11,17], the current review will purposely explore the physiological role of IL-15/IL-15R signaling in systems other than T and NK cells.

2. IL-15

2.1. Genetic and structural features of IL-15

IL-15 is conserved among different species, exhibiting 97% sequence identity in the coding region between human and simian IL-15 [3], 82% identity between human and porcine IL-15 [20] and 73% of identity comparing human and mouse forms of this cytokine [21]. Recently, rabbit [22], feline [23], woodchuck [24] and chicken [25] IL-15 have been cloned, as well. The *IL-15* gene spans more than 34 kb, and was mapped to the human chromosome 4q31 and the central region of the mouse chromosome 8 [21,26]. In contrast to the genomic architecture of *IL-2*, whose structural pattern is characterized by four exons and three introns [27], the *IL-15* gene consists of nine exons and eight introns [21,28–32]. These include previously reported exons 1–8 [21,26] and an additional alternative exon 4a that was subsequently identified in humans [28–32] (Fig. 1). Yet, the mature 114-aa IL-15 protein is coded by only four exons (*i.e.* exons 5–8) and three introns [21]. This resembles the exon/intron structure of other α -helix bundle family cytokines, including IL-2 [1].

IL-15 contains two disulfide bonds at positions ⁴²Cys–⁸⁸Cys (which is analogous to the only disulfide bond in IL-2) and ³⁵Cys–⁸⁵Cys [3]. The secondary structure prediction for IL-15 indicates strong helical sections for regions 1–17, 18–57, 65–78 and 94–112, supporting a 4- α -helix bundle-like structure of this cytokine [3,33]. The C-terminus of IL-15 also contains two sites for N-linked glycosylation [34]. Although structural similarities between IL-15 and IL-2 are clearly conserved, IL-15 has no primary sequence homology at the nucleotide or protein level with IL-2 or other members of the cytokine superfamily [3].

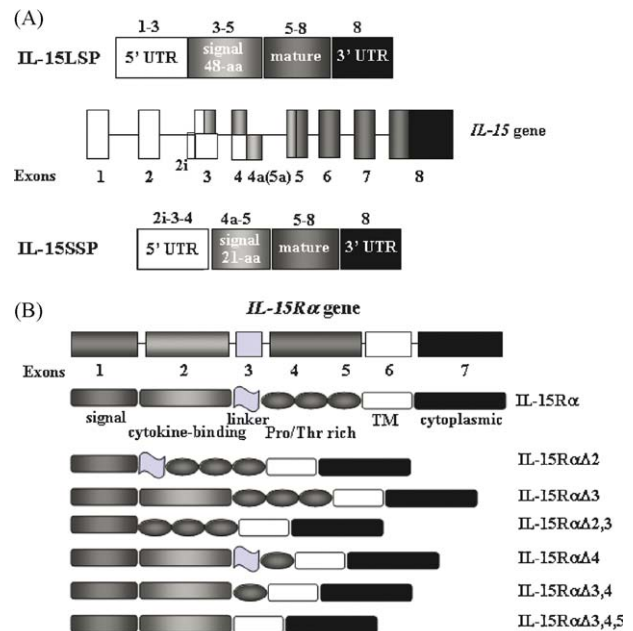


Fig. 1. Schematic diagram of IL-15 and IL-15R α genes. (A) *IL-15* gene consists of nine exons and eight introns located on human chromosome 4q31 and mouse chromosome 8. Two isoforms of IL-15 containing short (21-aa) or long (48-aa) signal peptide (IL-15SSP and IL-15LSP, respectively) exist. Alternative exon 4a in human corresponds to exon 5A in the mouse *IL-15* gene. (B) *IL-15R α* gene consists of seven exons, and a number of various protein isoforms were described as a result of an alternative splicing mechanism in both human and mice.

2.2. Expression of IL-15

Two alternatively spliced mRNA products account for the existence of two distinct IL-15 isoforms, which differ only in the length of their signal peptide [28–32]. The originally identified form of human IL-15 cDNA contains a rather long 5'-untranslated region of at least 316 base pairs (bp), a coding sequence of 486 bp, 3'-UTR of at least 400 bp; this translates into an IL-15 precursor protein with a 48-aa long signal peptide (IL-15LSP) [3]. This classical signal peptide is encoded by exons 3–5 of the human *IL-15* gene, and is present in a 1.6 kb mRNA. Later, another transcript was described that contains three premature termination codons, and an alternative downstream translation initiation site with a poor Kozak context, resulting in a precursor IL-15 protein with a 21-aa short signal peptide (IL-15SSP) [28–32]. This signal peptide shares with the long variant 11-aa encoded by exon 5, but has an additional 119 bp sequence inserted between exons 4 and 5. This is encoded by a new alternative exon 4a, and is present in a transcript that lacks exon 1 of the original message [28,30]. A similar alternative transcript was also described in the mouse, where insertion of exon 5A (136 bp in length) would lead to IL-15 isoform, with a shortened 26-aa signal peptide compared to the 48-aa leader sequence encoded by the transcript lacking exon 5A [29]. Thus, in human and mouse, both alternative transcripts produce a mature IL-15 protein

that contains differences only in the sequence of the signal peptide (Fig. 1).

Two distinct isoforms of IL-15 exhibit differential patterns of intracellular distribution, trafficking, secretion and endosomal localization; this points to an important role of the signal peptide in multiple mechanisms controlling IL-15 production [28–32,34–36]. Importantly, IL-15SSP is not secreted, but rather stored intracellularly in the cytoplasm, where it does not co-localize either with the Golgi apparatus, early endosomes or the endoplasmic reticulum (ER) [34,35]. Conversely, IL-15LSP is found in the Golgi, early endosomes and the ER, a pathway possibly leading to cytokine secretion [34–36]. Two IL-15 isoforms may also exhibit nuclear localization [36]. The localization of both IL-15 and IL-15R α in the nuclear membrane or nucleus raises the question whether IL-15 and/or IL-15R α may act as direct or indirect regulators of distinct transcriptional events [36,37]. Indeed, Nishimura *et al.* recently showed that the non-secreted IL-15 isoform co-localizes with IL-15R α in the nucleus, where it downregulates *IL-15* gene transcription through a novel autocrine regulatory mechanism [38]. However, additional studies are necessary to gain a comprehensive understanding of how intracellular IL-15 and/or IL-15R α may be involved in diverse intracellular functions, including the control of transcription.

2.3. Transcriptional and translational regulation

Contrary to IL-2, which is produced mainly by activated T cells, IL-15 mRNA is constitutively expressed by a large variety of cell types and tissues, including monocytes/macrophages, DCs, keratinocytes and epidermal skin cells, fibroblasts and epithelial cells of various origin, nerve cells, kidney, placenta, lung, heart and skeletal muscle [3,39–46]. Freshly isolated peripheral blood mononuclear cells (PBMCs), normal T cells and T-cell lines express IL-15 mRNA at very low levels [3,30], whereas detection of IL-15 protein appears to be mostly restricted to monocytes, epithelial cells, DCs and fibroblasts [39,41,43,47]. Despite such widespread distribution, however, it is extremely difficult to detect IL-15 in cell culture supernatants. Indeed, most primary cells and cell lines which express IL-15 mRNA do not release detectable amounts of this cytokine into the culture medium [28,34,35].

This striking discrepancy between IL-15 transcription and protein secretion is explained by the fact that IL-15 has a complex, multifaceted control of expression with regulation at the levels of transcription, translation and intracellular trafficking and translocation [32,34–36,38,48], while control of IL-2 expression predominantly occurs at the levels of transcription and message stabilization [49]. Since the diverse mechanisms controlling IL-15 production have been extensively discussed elsewhere [50], only the major checkpoints that regulate IL-15 transcription as well as

mRNA translation into the IL-15 precursor protein are summarized below.

Human and mouse IL-15 have a number of conserved regulatory transcription factor binding motifs that control IL-15 transcription. These include consensus sites within the human and mouse promoter regions for NF- κ B, IRF-E, γ IRE, NF-IL-6, myb, α IFN-2 and GCF [48]. The NF- κ B consensus sequence is located at the –75 and –65 regions upstream of the transcription initiation site of the human IL-15 promoter, and is important for transactivation of the IL-15 gene by HTLV-1-encoded Tax protein [48]. This suggests a potential role of IL-15 in HTLV-1-associated diseases, such as adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [48]. Interferon regulatory factor 1 (IRF-1)-induced IL-15 expression controls the development of NK, NK/T cells and intraepithelial lymphocytes (IELs) [51]. Remarkably, an upregulated IL-15 expression was observed upon infection with various pathogens, including *Candida albicans*, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, *Bacillus Calmette-Guerin* (BCG) as well as with *herpesvirus 6* and 7 [40,50,52,53].

IL-15 translation is handicapped, first, by multiple translation initiation sites (AUGs) located in the 5'-UTR (12 in humans, 5 in mice), and the removal of such upstream start codons enhances IL-15 production approximately 10–15-fold [4]. Nevertheless, the overall IL-15 concentration was still three-fold lower than that of IL-2 after transfection with a comparable IL-2 construct, despite equal mRNA levels for these two cytokines [54]. Second, the IL-15 signal peptide drives cytokine production rather inefficiently (e.g. the replacement of the long signal peptide of IL-15 by that of IL-2 increases IL-15 production 17–20-fold, and translation and secretion of IL-15 also increases when the IL-15 signal peptide is replaced by the CD33 signal peptide [30,54]). A third molecular brake on IL-15 production seems to be present in the C-terminus of the IL-15 mature protein coding sequence or protein [54]. The relevance of these constraints on IL-15 production is illustrated by the finding that deletion of all three major checkpoints leads to a more than 250-fold increase in IL-15 production [54].

Based on this experimental evidence, Bamford *et al.* have suggested that mRNA for IL-15, unlike that for IL-2, may exist in translationally inactive pools [54]. This already hints at the possibility that an excessive IL-15 activity could exert potentially harmful effects upon an individual cell or the entire organism.

3. IL-15 receptor complex

3.1. High affinity IL-15 receptor α

IL-15 receptor α (IL-15R α) is a type I transmembrane protein structurally related to the IL-2R α chain [18,19]

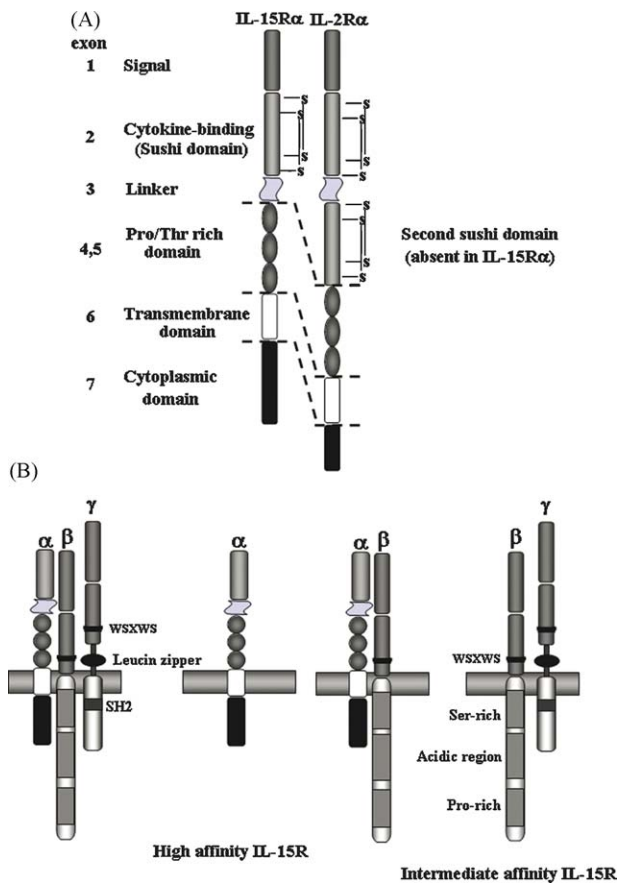


Fig. 2. Schematic structure of IL-15Rα and IL-15R complex. (A) Structural comparison between IL-15Rα and IL-2Rα. Disulfide bridges characteristic of the sushi domain are shown. IL-15Rα contains one sushi domain, whereas IL-2Rα contains two. (B) High affinity IL-15Rα complex consists of IL-15Rαβγ, IL-15Rα or IL-15Rαβ chains. Intermediate affinity IL-15Rα complex consists of IL-15Rβγ chains. The typical characteristics of β and γ chain domains are shown.

(Fig. 2). In both the human and the mouse genome, the *IL-15Rα* and *IL-2Rα* genes are very closely linked, mapped to chromosome 10 in human and to chromosome 2 in mouse, and have similarities in the intron–exon structure [19]. This suggests that these genes have a common ancestral origin, and positions these two receptors as founding members of a new receptor family [18,19]. However, IL-15 binds to its private α receptor chain with high affinity—even in the absence of the IL-2β and IL-2γ/γc receptor subunits (with a K_a greater or equal to 10^{11} M^{-1}) [18]. This is in striking contrast to IL-2Rα, which shows only low affinity for IL-2 ($K_a \sim 10^8 \text{ M}^{-1}$) in the absence of IL-2Rβγ [55].

Both IL-15Rα and IL-2Rα have common structural features that include rather short cytoplasmic domains and Pro/Thr-rich extracellular regions containing a conserved protein-binding motif (sushi domain, also known as the glycoprotein-I motif or short consensus repeat) [18] (Fig. 2). Sushi domains are common motifs, which contain four cysteines forming two disulfide bonds in a 1–3 and 2–4 pattern and found in a number of proteins involved in the complement and coagulation cascades [56]. The Sushi

domain is essential for the ligand binding [57]. However, IL-15Rα contains only one sushi domain, while IL-2Rα has two [18]. Remarkably, human IL-15 has at least two binding sites for recombinant soluble IL-15Rα (sIL-15Rα) [58], and the interaction between IL-15 and IL-15Rα involves a large network of ionic interactions [59], which explains the exceptionally high affinity of the IL-15/IL-15Rα complex essential for the biological effects of this cytokine. This is in contrast to the familiar hydrophobic forces dominating the interaction interface between cytokines and their cognate receptors [55].

Human IL-15Rα protein has a signal peptide of 32-aa, a 173-aa extracellular domain, a 21-aa single membrane-spanning transmembrane stretch, a rather short 37-aa cytoplasmic part, and contains *N*- and *O*-linked glycosylation sites [19]. Remarkably, the cytoplasmic portion of human IL-15Rα is considerably longer than that of IL-2Rα (37-aa versus 11-aa, respectively), whereas in mouse this difference is even more obvious (41-aa versus 11-aa, respectively) [18,19] qualifying the IL-15Rα chain as a signaling receptor.

Like mRNA for IL-15, the IL-15Rα message is expressed in a variety of immune and non-immune cell types and tissues, including T cells, B cells, NK cells, macrophages, thymic and bone-marrow cells, brain, intestine, liver, skeletal muscle, lung, heart and kidney [18,19,50,60–62]. This suggests that the IL-15/IL-15Rα signaling system operates at multiple levels of bioregulation throughout the organism, which is not only recruited to modulate cellular functions in many different systems, but which, in principle, is also capable of functionally linking these systems with each other.

A number of different isoforms of human and murine IL-15Rα were recently described that result from alternative splicing within the *IL-15Rα* gene [19,37,63]. These isoforms include deletions of exon 2, exon 3, an alternative usage of exon 7 or 7' [19,37] as well as deletions of exon 4, exons 3 and 4, and exons 3–5 [63]. These isoforms exhibit a diffuse cellular distribution and have been detected within the plasma membrane, the ER and the Golgi apparatus; the isoform that contains exon 2 has also been co-localized with the nuclear membrane [37,63]. Interestingly, IL-15Rα lacking exon 2 was unable to bind IL-15, suggesting that this isoform may associate with IL-2/IL-15Rβγ subunits, thereby limiting their availability for the functional high affinity IL-15R complex [37]. Exon 2 reportedly contains a putative nuclear localization signal, and the isoform lacking this exon was found only in the non-nuclear membrane compartments, indicating an important role for exon 2 in post-translational routing of IL-15Rα [37].

3.2. Intermediate affinity IL-15R complex (IL-2/IL-15Rβγ/γc)

Similar to IL-2, IL-15 can bind and signal through the heterodimeric, intermediate affinity IL-2/IL-15Rβγ com-

plex ($K_a \sim 10^9 \text{ M}^{-1}$) – even in the absence of its high affinity α chain (Fig. 2) [5,64]. The IL-2/IL-15R β and γ c receptors participate in both ligand binding and signal transduction. Mature human IL-2R β (CD122, p75) protein is preceded by a 26-aa signal peptide and consists of 525-aa. These include a 214-aa extracellular part, a 25-aa hydrophobic transmembrane domain and a 286-aa cytoplasmic tail [65]. The human γ c (CD132, p64) chain is 369-aa in length, consisting of a 22-aa signal peptide, a 233-aa extracellular part, a 28-aa hydrophobic transmembrane sequence and an 86-aa cytoplasmic tail [66]. Both proteins are members of the hematopoietin family of cell surface receptors, which is characterized by extracellular domains that include the canonical Trp-Ser-Xaa-Trp-Ser (WSXWS) pentapeptide motif (where Xaa is any amino acid), and four conserved cysteines [67] (Fig. 2). Because these proteins do not possess intrinsic enzymatic activity, cytokine binding induces their oligomerization, and signaling by the IL-2R β and γ c subunits requires the association or recruitment of kinases to the cytoplasmic domains of these molecules (see below).

3.3. Soluble IL-15R α

We [68] and others [69] have recently demonstrated that murine and human IL-15R α not only exist in membrane-bound, but also in a soluble form. In both species, natural sIL-15R α is constitutively generated from the transmembrane receptor through a defined proteolytic cleavage, and this process is further enhanced by certain chemical agents, such as PMA [68,69]. The constitutive and inducible shedding of murine IL-15R α involves the activity of tumor necrosis factor- α -converting enzyme (TACE/ADAM17), and is inhibited by appropriate metalloproteinase inhibitors [68,69].

Murine sIL-15R α has a molecular mass of about 30 kDa due to the *N*-linked glycosylation, which is reduced to 26 kDa after *N*-glycosidase treatment [68], whereas the human soluble form was reported to be about 42 kDa in size [69], and, supposedly, is also glycosylated. Murine or human sIL-15R α could be detected in mouse serum and cell-conditioned medium, or cell supernatants, respectively [68,69].

In distinct physiological and/or pathological situations, the proteolytic release of *N*-glycosylated IL-15R α could be of substantial functional importance, and could affect the signaling properties of IL-15 in several respects. The presence of sIL-15R α in biological fluids may negatively affect the availability of free IL-15, in the first place by competing for the cytokine with cognate membrane-bound receptors, thereby counteracting the IL-15-induced signaling. Thus, sIL-15R α could represent an important protective mechanism against excessive IL-15 activity [15,68,69]. Given that this pleiotropic cytokine plays important roles in both innate and adaptive immunity, and is associated with a wide range of immunopathological reactions, the bioavail-

ability of sIL-15R α could represent yet another checkpoint in the complex mechanisms regulating IL-15 release, which is tightly controlled at multiple levels. Conversely, sIL-15R α could also prolong the half-life of IL-15 and slow the release of the ligand from a complex between the soluble receptor and IL-15 so as to control the actual cytokine concentration in a given tissue environment. Distinct sIL-15R α isoforms could also potentiate IL-15 signaling, as was already shown for the soluble IL-6 receptor [70]. In fact, a recent report of Mortier *et al.* shows that a recombinant soluble sushi domain of IL-15R α serves as a potent and selective agonist of IL-15 action through intermediate affinity IL-2/IL-15R β γ heterodimer, although it does not affect IL-15 binding and function of the trimeric IL-15R α β γ [71]. Conversely, such sushi domains were also reported to antagonize IL-15 function [57]. In this manner, sIL-15R α may not only influence the nature and/or duration of IL-15-dependent signaling, but may also expand IL-15 actions from autocrine or juxtacrine signaling to paracrine or endocrine modes of signaling, including systemic cytokine effects [15]. This demonstrates a new level of complexity in the biology of the IL-15/IL-15R α system. In addition, the ability of sIL-15R α to form receptor–ligand complexes with IL-15 may cause difficulties in the detection of free IL-15, and may confound corresponding measurements in serum or culture supernatants [15].

4. IL-15-mediated signal transduction

4.1. Signaling mediated by the IL-15 receptor

Sharing of receptor subunits (IL-2R/IL-15R β γ / γ c chains) can explain in part the existing functional similarities between IL-2 and IL-15 [5,64]. IL-15-mediated signaling in T lymphocytes results in the activation of Janus kinase (JAK) [72]. JAKs play critical signaling roles for a number of members of the cytokine receptor superfamily by activating signal transducer and activator of transcription (STAT) proteins [73]. After receptor–ligand interaction, associated JAKs are brought into close apposition, which allows their cross-phosphorylation and activation. The IL-2R β chain recruits JAK1, whereas IL-2R γ / γ c activates JAK3, which in turn results in the phosphorylation and activation of STAT3 and STAT5, respectively [72]. Specific tyrosine residues in the cytoplasmic domains of the IL-2R β and γ c subunits also become phosphorylated, and serve as docking site(s) for STATs via the STAT Src homology 2 (SH2) domain [74] (Fig. 3). Subsequently, recruited STATs are phosphorylated by activated JAKs [73]. The tyrosine-phosphorylated STAT transcription factors form either homo- and/or heterodimers and translocate to the nucleus to bind to their target DNA regulatory elements and participate in the activation of gene expression [73].

JAK-STAT signaling by IL-2, IL-4, IL-7, IL-9 and IL-15 is critically important in the generation of immune and

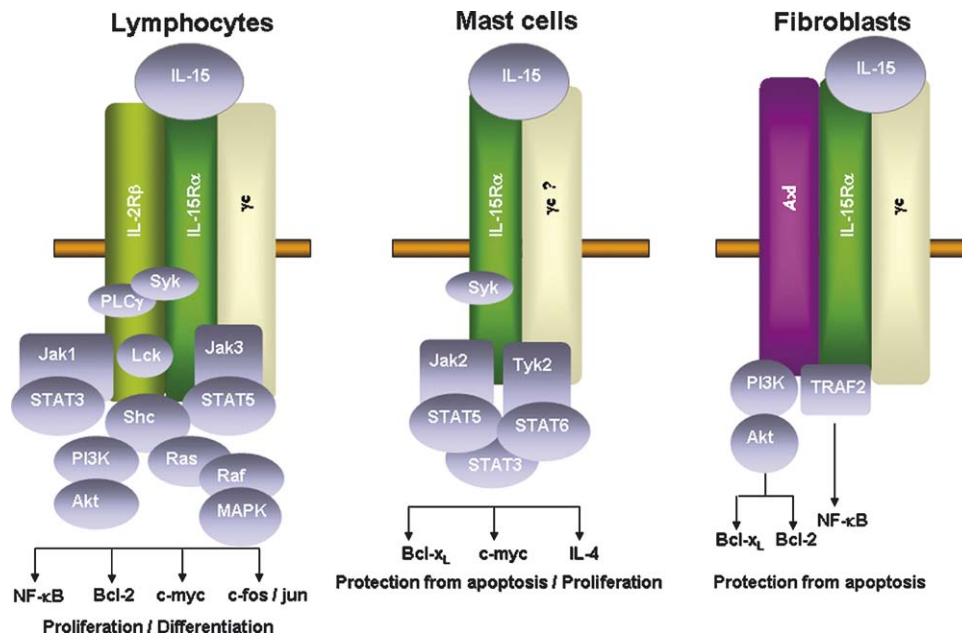


Fig. 3. Summary of the IL-15R-mediated signal transduction events in different cells. In lymphocytes that express the IL-15R complex consisting of three subunits (IL-15R α /IL-2R β / γ chains), IL-15 activates Jak1/Jak3 and STAT3/STAT5 pathways, Syk kinase and PLC γ , Lck kinase, Shc, resulting in the activation of PI3K/Akt and Ras/Raf/MAPK cascades. These pathways lead to the subsequent expression of *bcl-2*, *c-myc* and *c-fos/jun* genes and NF- κ B activation. IL-15R α activation in mast cells that express IL-15R α and γ c chains involves Jak2, Tyk2 and Syk kinases, STAT3, STAT5 and STAT6, leading to the expression of Bcl-x_L and *c-myc*, and secretion of IL-4. In fibroblasts that express IL-15R α and γ c chains, IL-15 stimulation leads to transactivation of Axl receptor tyrosine kinase pathway, including the phosphorylation of PI3K/Akt and upregulation of Bcl-x_L and Bcl-2, as well as the recruitment of TRAF2 to IL-15R α and activation of NF- κ B.

inflammatory responses and in T-cell expansion and differentiation. Lack of signaling by these cytokines, as occurs in genetic deficiency of either IL-2R γ or JAK1/JAK3, results in severe combined immunodeficiency (SCID) in humans and mice, demonstrating the importance of the JAKs in signaling by γ c chain-utilizing cytokines [75]. Knock-out mice lacking STAT5a/b, STAT5b and JAK3 are NK cell deficient [60,76–78].

Additional signaling pathways activated by IL-2 and IL-15 involve the phosphorylation of the Src family cytoplasmic tyrosine kinases Lck, Fyn, and Lyn, Syk kinase, phosphatidylinositol 3 kinase (PI3-kinase) and Akt, induction of Bcl-2 anti-apoptotic protein as well as the Ras/Raf/MEK/mitogen-activated protein kinase (MAPK) pathway [79–82]. IL-15 has also been shown to activate NF- κ B and AP-1 transcription factors [79,83], and control c-myc [84].

It has been shown that IL-2R α , IL-15R α , IL-2/IL-15R β and γ c chains, as well as MHC class I and II glycoproteins, form supramolecular receptor clusters in lipid rafts, and both α chains are at least partially homodimerized/oligomerized [85,86]. The binding of the respective cytokine results in the formation of high-affinity heterotrimeric receptors, suggesting a direct role for the α -subunits in tuning cellular responses to IL-15 or IL-2 [86].

Given that the cytoplasmic portion of IL-15R α is rather short and seemingly does not contain obvious signaling motifs and docking sites, it has been suggested that the IL-15R α chain, like IL-2R α , is not capable of signaling when it

is expressed in the absence of IL-2R β or γ c [5]. Contrary to this idea, IL-15 was shown to induce signaling in a colonic epithelial cell line expressing IL-15R α , but not IL-15R β [87]. Furthermore, our data demonstrated that IL-15 is capable of rescuing murine L929 fibroblasts from the TNF α -induced apoptosis through recruitment of TNFR-associated factor 2 (TRAF2) to the IL-15R α chain, and NF- κ B activation [88]. The ability of IL-15R α to recruit TRAF2 was also supported by studies in other cell systems [36]. We have since shown that IL-15R α mediates signaling in the human B cell line Raji via the association of IL-15R α chain with Syk kinase, significantly reducing the numbers of C2-ceramide-induced apoptotic cells [82]. These findings were further confirmed by study of Rathé and Girard, which showed the importance of the IL-15R α chain for the ability of IL-15 to enhance neutrophil phagocytosis via Syk-dependent mechanism [89]. Experimental evidence argues in favor of a direct physical association between IL-15R α and Syk [82,89]. Therefore, IL-15R α may function and signal independently of the other two chains of the heterotrimeric complex (Fig. 3).

Signaling pathways mediated by IL-15 in mast cells reportedly occur through an alternative receptor, provisionally designated as IL-15RX, and do not require IL-2 β and γ c chains, leading to the activation of JAK2/STAT5 or Tyk2/STAT6 [90–92]. We recently reported that murine mast cells also express several functional alternatively spliced isoforms of conventional IL-15R α [63]. The IL-15-mediated signaling through the newly identified IL-15R α isoforms in

murine mast cells involves the phosphorylation of STAT3, STAT5, STAT6, JAK2 and Syk kinase, which is dependent, at least partially, on the particular IL-15R α subtype [63] (Fig. 3).

Cross-communication between diverse signaling networks represents a growing field in our understanding of how complex and diverse environmental stimuli are translated into appropriate cellular reactions and adaptive responses. Recently, we found that the IL-15R α chain constitutively associates in murine fibroblasts with a receptor tyrosine kinase, Axl, whereby stimulation of IL-15R α by IL-15 transactivates Axl [93]. The subsequent activation of the Axl signaling pathway induces activation of PI3K/Akt and upregulation of Bcl-2 and Bcl-x_L, which is essential for the anti-apoptotic action of IL-15 [93] (Fig. 3). These facts lend further credence to the emerging concept that unrelated receptors systems are engaged in cross-communication, a biological phenomenon which might underlie the ability of cell to integrate a variety of stimuli under physiological or pathological conditions through diversification of downstream signaling. Transactivation of epidermal growth factor receptors is considered as a classical example of interreceptor signal transmission [94]. Our findings identify Axl as yet another member of the RTK family that can integrate signaling from heterologous receptor systems and may serve as a key signaling element for the integration of multiple, changing environmental influences.

4.2. Juxtacrine signaling

Although IL-15 was initially identified as a soluble factor and belongs to the cytokine superfamily, there is increasing evidence that IL-15 mediates many specific biological responses also in a cell membrane-associated form [16,39,43,62,95–98]. In fact, the difficulties in the detection of free IL-15 in biological fluids, taken together with a rather widespread existence of cell-associated IL-15, suggest that this protein may perform a number of its primary biological functions in a membrane-bound form.

Substantial experimental evidence clearly indicates an important role for the membrane-associated IL-15 in supporting growth of nearby cells, which express only IL-2 β and IL-2 γ /IL-15 γ (γ c) subunits or the trimeric IL-15R complex [95–98]. In this model, IL-15 is not directly anchored onto the plasma membrane and the presence of IL-15 associated to the cell membrane is explained by the ability of IL-15R α and IL-15 to form stable complexes on the cell surface of activated monocytes [95]. The formation of specific high affinity IL-15/IL-15R α complexes on the cell membrane induces a *trans*-endosomal recycling of both molecules, thereby resulting in the persistence of surface-bound IL-15. An essential role of the IL-15R α cytoplasmic domain for the recycling process has been demonstrated [95]. While the expression of the high affinity IL-15R α on T cells is dispensable for the generation and maintenance of

memory CD8 $^{+}$ T cells [99], it is important to recognize that the expression of the high affinity IL-15R α on cells other than T cells (*e.g.* stromal or DCs) is absolutely crucial for the generation and maintenance of memory CD8 $^{+}$ T cells via IL-15R α -mediated presentation of IL-15 in *trans* to memory CD8 $^{+}$ T cells expressing intermediate affinity IL-2/IL-15R β γ /c subunits [62,97,100].

This concept is exemplarily underlined by the finding that, *e.g.* wild-type memory CD8 $^{+}$ T cells did not divide after transfer into IL-15R α –/– mice and that virus-specific memory CD8 $^{+}$ T-cell proliferation was driven by IL-15 produced either by BM-derived or parenchymal cells [62]. BM-derived cells were critical in driving memory CD8 $^{+}$ T-cell division in the spleen, while both parenchymal and BM-derived cells promoted cell division in the lung. The basal proliferation of memory CD8 $^{+}$ T cells was shown to be mediated by *trans*-presentation of IL-15 on BM-derived cells [62].

Experiments using mixed BM chimera from IL-15R α - and IL-2/IL-15R β -deficient mice showed that IL-15R α -competent, IL-2/IL-15R β -deficient cells are able to support IL-15R α -deficient NK and memory CD8 $^{+}$ T cells, thereby demonstrating that IL-15R α -mediated presentation of IL-15 in *trans* may represent a primary mechanism by which IL-15R α functions *in vivo* [62,97]. Surprisingly, these studies also revealed that both IL-15 and IL-15R α must be co-expressed by the same cells to *trans*-present IL-15, indicating the existence of some cellular mechanism(s) responsible for the elaboration of IL-15 [97]. Thus, IL-15R α appears to control both the production and the presentation of IL-15 in *trans* to neighboring NK and CD8 $^{+}$ T cells [62,96,97].

It is still not clear how long IL-15 is retained on the cell surface bound to its high affinity chain, and why it does not induce detectable levels of activation of signaling molecules on the cells, which express it in *trans*. Remarkably, human IL-15 reportedly has at least two binding sites for recombinant sIL-15R α [58], thereby inviting a speculation that binding of *trans*-presented IL-15 to IL-15R α on cells, which also express this high affinity chain, may result in the formation of a receptor–ligand–receptor structure, where IL-15 is supposedly captured by two IL-15R α molecules expressed on the surface of different cell types. This complex structure could theoretically be able to induce signaling in both directions, triggering activation of IL-15R α -mediated signaling events in both cell types. Future experiments are necessary to address whether such bidirectional signaling is possible.

Given the fact that virtually no free IL-15 could be detected in biological fluids or the supernatants of activated cells expressing IL-15 mRNA at considerable levels, the *trans*-presentation of IL-15 in complex with its high affinity chain on the plasma membrane, thereby enabling IL-15 to activate nearby cells, provides an attractive explanation as to how IL-15 elicits its diverse effects on NK cells and CD8 $^{+}$ T cells, although mechanism(s) by which IL-15 reaches its

high affinity receptor chain on the cell membrane remain obscure.

4.3. Reverse signaling

Another important aspect of membrane-associated IL-15 is its ability to mediate reverse signaling events. We have recently demonstrated that membrane-associated IL-15 is implicated in reverse signaling in human monocytes and PC-3 prostate carcinoma cells [15,101,102]. In monocytes, the amount of membrane-associated IL-15 was reduced after acidic treatment, indicating that at least some proportion of endogenous IL-15 is bound to its high affinity α chain [101]. Conversely, PC-3 human prostate cancer cells were devoid of components of the IL-15R complex, and did not exhibit any reduction in the number of membrane-bound IL-15LSP molecules after the acidic treatment or trypsinization, thereby indicating that, at least in these cells, IL-15LSP is presumably directly anchored to the cell surface [101]. Notwithstanding, the mechanism(s) that account for IL-15 anchoring remain to be elucidated. These may include the usage of the unusually long signal peptide or a predicted GPI-anchor [101,102].

The existence of reverse signaling is well established by now, and a broad array of experimental data from diverse sources and systems convincingly demonstrate its biological significance. This biological phenomenon is well exemplified by members of the TNF ligand (L) family, which exist in both soluble forms and as transmembrane proteins with relatively long intracellular domains, many of which are involved in reverse signaling. Reverse signaling has been shown for such members of the TNFL family as TNF α , CD30L, CD40L, OX40L, CD137L and FasL [103].

Upon stimulation with recombinant sIL-15R α or anti-IL-15 Abs, membrane-bound IL-15 mediated the phosphorylation of members of the MAP kinase family ERK1/2 and p38, and focal adhesion kinase (FAK) [101]. Importantly, although no physical association between IL-15 and MAP kinases or FAK was detected, transmembrane IL-15 was phosphorylated at serine residues upon agonistic stimulation [101]. Furthermore, the reverse signaling through membrane IL-15 considerably increased the production of several pro-inflammatory cytokines by monocytes including IL-6, IL-8 and TNF α , thereby indicating the relevance of this process to the complex immunomodulatory function of these cells [101,102]. The stimulation of transmembrane IL-15 also enhanced the transcription of IL-6 and IL-8 in PC-3 cell line, and promoted migration of PC-3 cells as well as LnCap human prostate carcinoma cells stably expressing IL-15 upon the cell surface [101]. These data are in agreement with a recent report of Neely *et al.*, showing the ability of monocyte surface-bound IL-15 to function as an activating receptor and participate in reverse signaling events [102]. The ligation of surface IL-15 by cross-linked anti-IL-15 Abs was found to activate a number of signaling pathways, including ERK1/2 and p38, as well as the small Rho-family

GTPase Rac3. In addition, it resulted in the MAPK-dependent IL-8 secretion, and induced monocyte adhesion [101,102].

Interestingly, IL-15LSP and TNF α showed remarkable similarities in the protein structure organization [15]. It is thus plausible that IL-15LSP may naturally function as a membrane-bound type II protein and mediate biologically relevant reverse signaling events in a manner similar to the members of the TNFL family. The fact that IL-15 can exist as a biologically active transmembrane molecule that possesses dual ligand/receptor qualities with a potential to induce bi-directional signaling provides another striking example of a unique role of this pleiotropic cytokine in immune homeostasis.

5. Physiological functions of IL-15/IL-15R α signaling

5.1. IL-15 and immune cells (except T and NK cells)

It is now recognized that signaling via the IL-15/IL-15R system modulates not only T-cell functions, but numerous different other cell populations, as well. Given that a number of recent reviews have discussed in depth the functional importance of IL-15/IL-15R biology for T lymphocyte development and homeostasis, and memory CD8 $^{+}$ T-cell and NK cell development, maintenance, expansion and activities (see [8,9,10,11,17]), in the following we shall only explore the functional role of IL-15/IL-15R signaling in systems other than T and NK cells. Effects and signaling pathways induced by IL-15 in other immune cells are summarized in Table 1.

5.1.1. Neutrophils and eosinophils

IL-15 controls secretory activities and survival of neutrophils and eosinophils, and modulates phagocytosis [104–109]. In human neutrophils, IL-15 stimulates IL-8 but not superoxide anion production, enhances antifungal activity and phagocytosis of *C. albicans* and opsonized sheep red blood cells [83,105,106] and induces synthesis and secretion of IL-1R antagonist [108]. IL-15 can inhibit neutrophil apoptosis by at least three mechanisms: (1) induction of *de novo* synthesis and secretion of IL-1R antagonist [108] (although the blocking of IL-1 β activity by preincubation with IL-1R antagonist reversed the suppression of inflammatory neutrophil apoptosis [110]); (2) prevention of the loss of the anti-apoptotic myeloid cell differentiation factor-1 (Mcl-1) expression [107,108]; (3) decrease in the activity of caspases-3 and -8 that results in an inhibition of vimentin cleavage, and downregulation of pro-apoptotic Bax protein expression [108,111]. Signaling pathways induced by IL-15 in neutrophils include the activation of Jak2, p38 and ERK1/2 MAP kinases, Syk kinase and NF- κ B transcription factor [83,89,107]. Remarkably, IL-15 can enhance human neutrophil phagocytosis by a

Table 1

Functional effects and signal transduction mechanisms of IL-15 on immune cells (besides T and NK cells)

Cell type	Signaling mechanisms	Functional effects	References
B lymphocytes	Activation of Syk kinase and PLC γ	Protection from apoptosis, induction of proliferation and differentiation, and Ig production	[12,63,82,129–133]
Mast cells	Activation of STAT3, Jak2/STAT5, Tyk2/STAT6 and Syk, induction of Bcl-x _L and c-Myc expression	Inhibition of apoptosis, support of proliferation, IL-4 secretion	[63,90–92]
Neutrophils	Activation of Jak2, Syk, p38, ERK1/2, NF- κ B. Downregulation of Bax, increase in Mcl-1 stability, decrease in caspases-3 and -8 activity	Protection from apoptosis, activation of phagocytosis, production of IL-8 and IL-1R antagonist, activation of anti-microbial functions	[83,89,104–108,111]
Eosinophils	Induction of NF- κ B expression	Protection from apoptosis, stimulation of GM-SCF production	[109,112]
Monocytes/macrophages	Activation of Lck, ERK1/2 in U937 cells Reverse signaling: activation of FAK, Rac3, p38, ERK1/2	Increases phagocytosis and bacteria clearance, induction of IL-8, IL-12, MCP-1, and superoxide production. Stimulation of IL-6, IL-8, TNF α secretion and migration via reverse signaling	[39,40,52,101,102,114–118]
Dendritic cells	?	Protection from apoptosis. Increases expression of CD86, CD40 and MHC II, IFN γ release and enhances the ability to stimulate T cells	[41,100,119,120]

Syk-dependent mechanism, whereby IL-15R α plays a key role in mediating this process by interacting with Syk [89].

In human eosinophils, IL-15 regulates survival by reducing spontaneous eosinophil apoptosis *in vitro* via upregulating the autocrine production of GM-CSF and NF- κ B activation [109]. This is in accordance with a clinical case report of a patient with hypereosinophilic syndrome that had elevated serum levels of IL-15 [112], and underscores the concept that IL-15 is capable of upregulating the expression and secretion of other apoptosis-inhibitory factors.

5.1.2. Mast cells

The development and proliferation of mast cells require proper signaling from multiple growth factors and cytokines, among which the stem cell factor (SCF) and IL-3 are the best studied [113]. However, IL-15 can also serve as a growth factor for mast cells: in rather high concentrations *in vitro*, it supports the proliferation of bone marrow-derived mast cells (BMMCs) [90] and prevents apoptosis of BMMCs and MC/9 cells upon withdrawal of IL-3 or treatment with anti-Fas antibodies through STAT6-mediated Bcl-x_L expression [91]. In addition, IL-15 induces STAT6-dependent production of IL-4 [92].

As already mentioned above, despite the widespread expression of conventional IL-15R α , IL-15 reportedly uses a novel distinct high affinity-binding receptor and a different signal transduction pathway in mast cells, whereas the classical IL-15R α chain has been suggested to play a negligible role [90]. This receptor, provisionally designated as IL-15RX, has a molecular mass of about 60–65 kDa [90]. In contrast to T lymphocytes, where IL-15 activates JAK1/JAK3 and STAT3/STAT5 [72], signaling pathways mediated by IL-15 in mast cells lead to the activation of JAK2/STAT5 or Tyk2/STAT6, and do not require IL-2 β and γ c chains [90–92]. On the other hand, we showed that murine mast cells

also express several functional isoforms of conventional IL-15R α which derive from an alternative splicing mechanism within the *IL-15R α* gene: IL-15R α Δ 4 (missing exon 4), IL-15R α Δ 3,4 (missing exons 3 and 4) and IL-15R α Δ 3,4,5 (missing three exons 3–5) [63]. These isoforms are fully functional and bind IL-15 with the affinity similar to that of the full-length receptor, whereby IL-15 induces the phosphorylation of STAT3, STAT5, STAT6, JAK2 and Syk. Given that three different, fully functional conventional IL-15R α isoforms are expressed and utilized by mast cells, the physiological significance of the alternative high affinity IL-15RX [90] remains to be demonstrated conclusively.

5.1.3. Monocytes/macrophages and dendritic cells

Monocyte and macrophage cell lineages effectively transcribe and translate IL-15 mRNA, which is further upregulated by infection-associated key stimuli like IFN γ and LPS as well as by bacterial, protozoan, and viral infection [39,40,52,53,114]. They also answer to stimulation with IL-15 by augmented anti-infection immune responses: for example, IL-15 increases *Leishmania infantum* clearance by PMA-activated macrophages via upregulation of IL-12 production [115], and clearance of *M. tuberculosis* in mice [116]. IL-15 also induces the production of IL-8 and monocyte chemotactic protein 1 (MCP-1) by monocytes [117], and TLR-dependent IL-15/IL-15R α upregulation is essential for differentiation and expansion of DC-SIGN⁺ phagocytic monocytes in leprosy [118]. Membrane-bound IL-15 on monocytes stimulates via juxtacrine signalling, e.g. the proliferation of ConA-stimulated T cells and CTLL cell line [39,114], whereas its stimulation with specific agonists (sIL-15R α or anti-IL-15 antibodies) induces reverse signaling events in host cells, resulting in activation of FAK, Rho, p38, ERK1/2, and expression of pro-inflammatory cytokines, such as TNF α , IL-6 and IL-8 [101,102]. This underscores the

features of IL-15 as a protagonistic innate immune defense cytokine.

However, since IL-15 also affects key aspects of acquired immunity, it provides the perfect example of a cytokine which demonstrates that the long-cherished innate/acquired immunity dichotomy is far too simplistic and, in fact, misleading: IL-15 clearly modulates immune responses beyond the innate/acquired divide, and effectively links these two immune response theatres. For example, DCs express mRNA for both IL-15 and IL-15R α , which is further upregulated by IFN $\alpha\beta$, double-stranded RNA, LPS or *Listeria monocytogenes* infection [41,100,119]. Moreover, stimulation of DCs with IL-15 leads to upregulation of the co-stimulatory molecules CD86, CD40, MHC class II and MHC class I-related chains A and B on the cell surface, increases IFN γ release and enhances the ability of DCs to stimulate Ag-specific CD8 $^{+}$ T cell proliferation and to activate NK cells [41,120].

The IL-15/IL-15R system is critical for the functional maturation of DCs and macrophages in response to microbial infection, controlling both IL-12 production and IL-12 responsiveness of APCs [8]. Also, the production of IL-2 by myeloid DCs depends on the IL-15 expression in humans and mice [121]. Furthermore, IL-15 is a survival signal for murine DCs: these show signs of increased apoptosis in IL-15 $^{-/-}$ mice, and both IL-15 $^{-/-}$ and IL-15R $\alpha^{-/-}$ mice have reduced amounts of DCs in peripheral blood and spleen, which can partially be compensated by transgenic expression of IL-15 or by IL-15 injection [100].

Moreover, in combination with GM-CSF, IL-15 is able to skew the differentiation of monocytes into DCs bearing features of potent antigen-presenting Langerhans cells able to promote CD4 $^{+}$ T-cell proliferation [122], and to prime robust CD8 $^{+}$ T-cell responses with high levels of Th1 cytokines *in vivo* [123,124]. In addition, results from two distinct delayed-type hypersensitivity (DTH) mouse models have invited the postulate that DC-derived IL-15 is an absolute requirement for the initiation of DTH response: an autocrine IL-15/IL-15R α signaling loop in DCs is essential for inducing CD8 $^{+}$ -mediated Th1 immune responses in paracrine or juxtacrine fashion [125]. In fact, IL-15-expressing DCs stimulate the expansion and differentiation of memory CD8 $^{+}$ cells [123,125], and proliferation and activation of NK cells [126]. A particularly intriguing question in this context is whether the activities exerted on NK and T cells by IL-15 which is produced by dendritic cells or monocytes/macrophages require a *trans*-presentation [16,95,96] or simply a stabilization of cytokine-binding via shed IL-15R α .

5.1.4. B lymphocytes

Since genetically modified mice which are deficient for IL-15 or IL-15R α do not reveal significant abnormalities in B cell responses [127,128], it was long thought that IL-15 plays little, if any, role in B cell biology. This concept is

changing rapidly, as several lines of evidence now indicate an essential role of IL-15 in modulating B cell activities.

While IL-15 exerts no activity on resting B cells, it does stimulate proliferation of anti-IgM- and PMA-activated B cells and, in combination with recombinant CD40L, the production and secretion of IgA, IgG1 and IgM [129]. In addition, IL-15 induces proliferation of lymphoblasts from patients with B-cell chronic lymphocytic leukemia [130], supports HIV-1-driven polyclonal B cell responses [131] and contributes to tumor propagation in multiple myeloma [132]. Moreover, IL-15 potently inhibits apoptosis induced by anti-Fas, anti-IgM or anti-IgM and dexamethason of activated human B lymphocytes *in vitro* and mouse B lymphocytes *in vivo* [12]. In the human B lymphoblastoid cell line, Raji, IL-15 stimulation induces the recruitment of Syk, a non-receptor protein-tyrosine kinase, to the IL-15R α chain; this protects Raji cells from ceramide-induced apoptosis [82]. IL-15 effectively supports growth of IL-3-dependent BA/F3 cells expressing functional IL-15R α in the absence of IL-3 [63].

Finally, IL-15 has been shown to be active in germinal center reactions since it is produced by follicular DCs, which are contained within the germinal centers and are key cellular components in the regulation of B cell survival and proliferation [98]. IL-15 is here biologically active in the membrane-bound form and supports germinal center B cell proliferation via a cell–cell contact-dependent mechanism [98]. At the same time, this may help to understand why IL-15 can promote the development of B-cell lymphoma [132,133].

5.2. IL-15 and non-immune cells

Perhaps, one of the most defining functional differences between IL-2 and IL-15 is that IL-15 is increasingly being recognized as a major modulator of many different types of non-immune cells, while the characteristic functions of IL-2 are almost exclusively restricted to T cells. Interestingly, IL-15 mRNA is found to be highly expressed in mesenchymal stem cells and their differentiated cell types, including osteoblasts, adipocytes, endothelial cells and myoblasts [46,134–136]. The role of the IL-15 cytokine transcript enrichment in these cells as well as its significance for the regulation of hematopoietic stem cell localization, self-renewal and differentiation is still largely unexplored. The effects of IL-15 on non-immune cells are summarized in Fig. 4.

5.2.1. Fibroblasts

Fibroblasts from human spleen, gingiva and skin constitutively express IL-15 [43,137,138]. In patients with RA, fibroblasts expressing elevated levels of IL-15 are considered as a main source of the increased levels of IL-15 in the synovium [139]. Interestingly, IL-15 also inhibits apoptosis of synovial fibroblasts [140]. Spleen-derived, membrane IL-15-expressing fibroblasts induce NK cell differentiation from CD34 $^{+}$ progenitors [137], while dermal

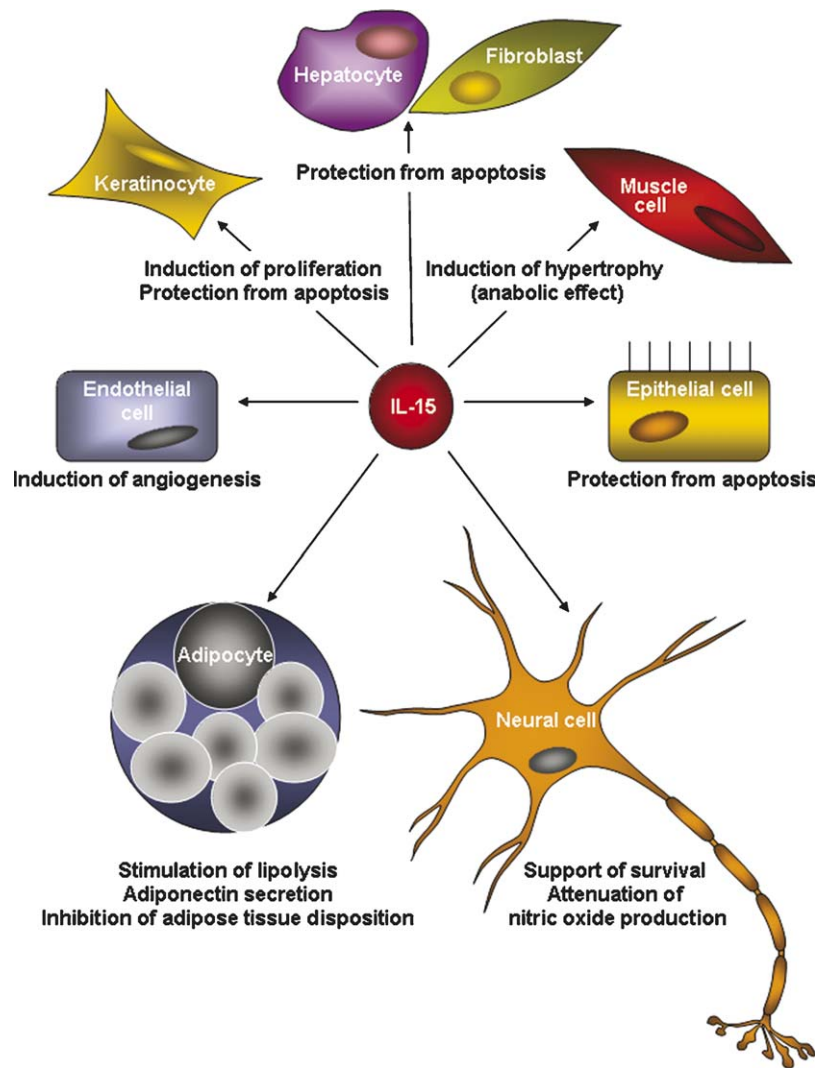


Fig. 4. Functional properties of IL-15. Schematic diagram of the IL-15-mediated effects in different non-immune cell types.

fibroblasts expressing membrane-bound IL-15 support proliferation of activated T cells [43]. IL-15 is able to protect mouse L929 fibroblasts from TNF α -induced apoptosis. Stimulation of IL-15R α by IL-15 induces recruitment of TRAF2 to the IL-15R α , NF- κ B activation [88], and transactivates Axl receptor tyrosine kinase pathway, which results in the activation of PI3K/Akt and upregulation of Bcl-2 and Bcl-x_L [93]. IL-15-mediated Axl transactivation is also essential to sustain the survival of serum-deprived mouse embryonic fibroblasts [93]. Thus, while fibroblasts can be a significant source of IL-15, at least defined fibroblast subpopulations also are important IL-15 targets, *e.g.* by exploiting IL-15 as a suppressor of apoptosis.

5.2.2. Osteoclasts

The elevated levels of IL-15 found in the synovial fluid of patients with rheumatoid arthritis (RA) [141] raised the question whether IL-15 is not only involved in bone pathology, but also in bone development and physiology. Indeed, IL-15 stimulates the formation of osteoclast-like

cells in rat bone-marrow culture *in vitro* [142]. Simultaneously, IL-15 induces expression of calcitonin receptor mRNA in preosteoclasts. The effects of IL-15 on generation of mononuclear preosteoclast-like cells are direct and not mediated by combination of M-CSF, IL-3 and CSF or TNF α [142]. Moreover, IL-15 expressed on the surface of lymphocytes from patients with RA effectively promotes osteoclastogenesis in autologous monocytes [143]. Therefore, it is conceivable that IL-15, in addition to its well-documented pro-inflammatory properties as a key pathogenesis promoter in RA [141], aggravates bone destruction by stimulating excessive bone resorption by osteoclasts [142,143].

5.2.3. Epithelial cells

Human keratinocytes and HaCaT cells line express both IL-15 and IL-15R α [42]. IL-15 inhibits methylcellulose-, anti-Fas- and UVB-induced keratinocyte apoptosis [42,144] and induces their proliferation through the activation of ERK1/2, PI3K and Akt pathways [144]. Inhibition of

physiological keratinocyte apoptosis may be involved in mediating epidermal hyperplasia in psoriasis [42].

Peritoneal mesothelial cells and renal tubular epithelial cells (TECs) express IL-15 at mRNA level [47,145]. This is upregulated by CD40 ligation [47,145] and IFN γ [145], whereas IFN γ also upregulated IL-15R α in TECs [61]. Thus, TECs are rich sources of IL-15, which have been shown to stimulate intratubular CD8 $^{+}$ T cells [146]. Recently, a synergy between TGF- β and IL-15 was demonstrated, resulting in chronic expansion and anti-apoptotic maintenance of allospecific CD8 $^{+}$ CD103 $^{+}$ T cells *in vitro* [147]. Such accumulation of intraepithelial cells occurs during renal allograft rejection [147]. Conversely, IL-15 is an autocrine survival factor for TECs, protects them from apoptosis and inhibits manifestation of nephrotoxic serum-induced glomerulonephritis by downregulation of nephritogenic chemokine MCP-1 expression [45]. TECs derived from IL-15 $^{-/-}$ mice are highly susceptible to anti-Fas and actinomycin D-induced apoptosis [45]. IL-15-mediated signaling in TECs involves activation of Jak1/Jak3 and STAT3/STAT5 molecules [61].

5.2.4. Endothelial cells

Human umbilical cord endothelial cells (HUVEC) and human intestinal microvascular endothelial cells (HIMEC) express IL-15R α and IL-15 mRNA [136,148], and IL-15 stimulates angiogenesis *in vivo* and *in vitro* [140,148]. IL-15 induces hyaluronan expression by endothelial cells, whereas CD44/hyaluronan interaction is important for T-cell adhesion and recruitment to the blood vessel wall, promoting extravasation of activated T cells [149]. Endothelial cell-derived IL-15, furthermore, induces transendothelial migration of T cells by activating the binding capacity of LFA-1 integrin, and increases T-cell motility [150]. Therefore, IL-15 has both direct effects on endothelial cell biology and angiogenesis, and promotes immunocyte extravasation.

5.2.5. Myocytes

IL-15 is highly expressed in skeletal muscle at mRNA level [3] and has muscle anabolic effects *in vitro*, like another potent anabolic cytokine insulin growth factor-1 (IGF-1) [46]. IL-15 stimulates the muscle-specific myosin heavy chain accumulation by differentiated myocytes and muscle fibers and is able to slow muscle wasting in rats with cancer cachexia [46,151]. Overexpression of IL-15 induces skeletal muscle hypertrophy *in vitro* [152]. The main mechanism involved in the anabolic effects of IL-15 on skeletal muscle may rely on a general reduction of proteolysis [153].

5.2.6. Adipocytes

Studies investigating the effect of IL-15 on skeletal muscle demonstrated that IL-15 administration induces a 33% reduction of adipose tissue in growing rats, with no reduction in food intake [154]. This anti-adipose effect of

IL-15 depends on the expression of IL-15R α on adipocytes [155]. Experimental evidence sustains the hypothesis that IL-15 functions in modulating fat:lean body composition and insulin sensitivity through a muscle-to-fat endocrine axis [154,156]. However, not all adipocyte subpopulations appear to be IL-15-responsive, while IL-15-sensitive adipocytes differ in their functional responses to IL-15 stimulation. Also, there are species- and differentiation-dependent differences: for example, while primary porcine adipocytes express IL-15, which is upregulated by IFN γ , murine 3T3-L1 adipocytes express little or no IL-15 at any differentiation stage [135,156]. IL-15 inhibits lipid deposition in murine 3T3-L1 preadipocytes, and this effect declines with progressing differentiation so that IL-15 has no effect on lipid deposition in fully differentiated 3T3-L1 cells; however, in these adipocytes, IL-15 stimulates adiponectin secretion [156].

5.2.7. Neuronal and glia cells

IL-15 and all three subunits of the IL-15R are widely expressed in the central nervous system of mice and human, including the frontal and parietal cortex, hippocampus, medulla oblongata, thalamus and cerebellum [157,158]. Recent cell culture studies in the human system showed the expression of IL-15 mRNA in microglia, astrocytes and neuronal cell lines [44,157,159]. In low doses, IL-15 supports microglial cell growth, attenuates their nitric oxide production and induces the phosphorylation of Jak1 [157]. Interestingly, it has recently been shown that IL-15 production and IL-15R α expression of murine microglia cells are inhibited by low concentrations of the ganglioside GD3 [160]. Therefore, this may become exploitable as a new class of IL-15 inhibitors.

6. Clinical relevance

That signaling through the IL-15/IL-15R system is of profound clinical importance has become amply clear in RA, where IL-15 antibodies have already been tested in Phase I/II trials (reviewed in [161]). However, there are several other important clinical fields where IL-15/IL-15R signaling has recently become a focus of interest, and has been explored as a potential target for therapeutic intervention. For example, a number of other autoimmune diseases such as inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), inflammatory synovitis, psoriasis, diabetes mellitus, asthma bronchiale and autoimmune vasculitis are associated with an increase in serum IL-15 levels [42,162–166]. Such areas of potential clinical relevance of IL-15 beyond the RA horizon are briefly sketched below.

6.1. Rheumatoid arthritis

RA is an autoimmune disorder characterized by synovial inflammation and the erosion of bone and cartilage,

ultimately leading to the destruction of affected joints. The dysregulated expression of synovial and systemic IL-15 in patients with active RA was initially suggested by McInnes *et al.* [141], a finding since then confirmed by many other groups [139,165,167–170]. IL-15 is present in the synovium of RA patients and in RA joint lesions, and may act as a chemotactic and proliferation-inducing factor for synovial cells, thereby increasing synovial macrophages activation via a process requiring direct contact between macrophages and T cells [141,170,171]. These findings were extended by the demonstration that endothelial-, macrophage- and fibroblast-derived IL-15 recruits, activates and increases the transendothelial migration of synovial T cells [139,141,150].

Our recent data suggest that IL-15 may trigger both the differentiation and the priming function of macrophages at sites of chronic inflammation (Ruckert *et al.*, submitted for publication). The progression of RA is accompanied by recruitment and expansion of oligoclonal CD4+CD28[−] T cells, which are currently thought to represent autoreactive lymphocytes that promote not only joint destruction, but also the enhanced atherosclerosis in RA patients (as opposed to patients with psoriatic arthritis [172]). These cells are CD45RA⁺ cells, which is suggestive of a memory phenotype. They produce high amounts of IFN γ and TNF α as well as perforin and express adhesion markers as CD18 but also CD57 which is found on NK cells as well, and intracytoplasmatic perforin, suggesting that they represent Th1 cytotoxic T cells and may promote monocyte accumulation and granuloma formation in Wegener's granulomatosis [173]. The nature of these cells, the antigen and the factors which drive their expansion in RA are still a matter of debate. Moreover, Yamamura *et al.* recently demonstrated that peripheral T lymphocytes from RA patients significantly increase the production of IL-6 and IL-8 by synovial fibroblasts [174]. This suggests that positive, pro-inflammatory feedback loops in the inflamed joints reflect tripartite interactions among T cells, macrophages and synovial fibroblasts.

Based on these findings, IL-15 is now widely considered as one of the key instigators of RA pathogenesis, together with other cytokines such as IL-1 β , TNF α , IL-6 and IL-18 [161,175].

6.2. Inflammatory bowel disease

IBD is characterized by severe inflammation of lower intestine mucosa caused by infiltration of activated T, B lymphocytes and macrophages and by local pro-inflammatory cytokine production [176]. IL-15, which is normally not detectable in serum, was demonstrated in the sera of patients with moderate and severe ulcerative colitis (UC)—but not in patients with Crohn's disease (CD), while the number of IL-15-positive cells was increased in the inflamed mucosa of IBD patients [177,164]. Expression of IL-15 mRNA was also found significantly increased in the inflamed rectal

mucosa from IBD patients [178]. Isolated from lamina propria mononuclear cells actively produce IL-15 upon stimulation with LPS or IFN γ , and lamina propria T cells isolated from IBD patients are more responsive to IL-15 as compared with controls [164]. IL-15 significantly increases the production of TNF α and IFN γ in such lamina propria T cells, whereas these T cells induce CD40–CD40 ligand-dependent production of TNF α and IL-12 by monocytes *in vitro* [164]. These data suggest that IL-15 plays an important role in the pathogenesis of IBD.

6.3. Systemic lupus erythematosus

SLE is characterized by the deposition of immune complexes and the presence of characteristic inflammatory patterns that ultimately cause tissue destruction, mainly in the kidney, skin, blood vessels and central nervous system [179]. IL-15 can be detected in the serum of up to 40% of patients with SLE [163,180]. High IL-15 concentrations were correlated with the expression of the anti-apoptotic protein Bcl-2 and CD25 in lymphocytes derived from these patients [163]. However, unlike TNF α , whose levels are significantly associated with disease severity [181], IL-15 is not directly associated with the disease activity. The IFN γ +LPS-induced synthesis and release of IL-15 by monocytes *in vitro* as well as the amount of membrane-bound IL-15-positive monocytes were increased in SLE patients with active phase of disease [180]. Despite the fact that IL-15 is a powerful anti-apoptotic cytokine, T lymphocytes from SLE patients showed a poor anti-apoptotic response to IL-15 treatment [180]. Though these data raise the possibility that IL-15, likely in conjunction with IL-2, may contribute to SLE pathogenesis, its exact contribution remains to be dissected.

6.4. Other autoimmune diseases

The concentration of IL-15 is increased in serum of the patients with type I diabetes mellitus and correlates with long-term metabolic control (HbA_{1c}) [162]. The correlation between these two parameters suggests that IL-15 may contribute to microangiopathy development in type I diabetes mellitus. The increased level of IL-15 transcripts in rat pancreatic islet cells after IL-1 β , IFN γ and/or TNF α exposure [182] suggests that IL-15 may contribute to the development of insulinitis in early type I diabetes. However, the treatment of non-obese diabetic (NOD) mice with the (agonistic) IL-15–IgG_{2b} fusion protein actually reduces the incidence of diabetes, probably due to downregulation of immune-mediated β -cell apoptosis, while it does not affect the extent and severity of insulinitis [183]. Therefore, IL-15 may play a dual role in type I diabetes mellitus, namely as a promoter of autoaggressive inflammation, and as a blocker of β cell apoptosis—perhaps loosely related to the “protective autoimmunity” principle previously demonstrated for neurotrophin-secreting autoaggressive T cells in experimental autoimmune encephalomyelitis [184].

Psoriasis represents a chronic inflammatory, hyperproliferative skin disease characterized by epidermal hyperplasia and infiltration with mononuclear cells including T lymphocytes and monocytes whose autoimmune nature is still hotly debated [185]. Psoriatic epidermal lesions display high expression of IL-15 mRNA and protein in/on epidermal keratinocytes and enhanced IL-15-binding activity compared to the healthy skin [42]. IL-15 is also upregulated in psoriatic arthritis synovium [186]. IL-15 blockade in a murine model of psoriasis leads to the suppression of typical psoriatic skin features [187].

6.5. Hypertension and atherosclerosis

Enhanced IL-15 mRNA steady-state levels were found in fibroblast and lipid-rich atherosclerotic plaques, and IL-15 transcripts levels are elevated in the atherosclerotic aorta of ApoE-deficient mice [188,189]. The main IL-15 sources here are infiltrating macrophages that are positive for oxidized low-density lipoprotein (oxLDL) [188]. This macrophage-derived IL-15 may recruit T cells into lesional sites [189]. IL-15 may also influence the migration and activation of mast cells which are prominently found in human coronary atheromas at sites of atheromatous erosion or rupture [190]. Importantly, serum levels of IL-15 are significantly increased in patients with essential hypertension and severe organ damage and this systemic IL-15 concentration increase was related to the cardiovascular disease [191].

6.6. Muscle disease

Inflammatory stimuli increase IL-15 protein production of muscle cells in polymyositis and dermatomyositis, and IL-15 may contribute to the immunopathogenesis by augmenting recruitment and activation of T cells [192]. Here, blocking of IL-15 activity may be useful in the treatment of the disease. IL-15 administration, however, awards relative protection from muscle degeneration in a mouse model for Duchenne type muscular dystrophy [193]. Therefore, IL-15 likely also operates as a potent anti-apoptotic parameter in myocyte biology and pathology.

6.7. IL-15 in tumor growth

The powerful anti-apoptotic properties of IL-15 point to a role of this cytokine in the propagation of tumor cell clones and raise the question which biological importance the IL-15/IL-15R α system may have in tumor cell growth, expansion and metastasis. Both IL-15 and IL-15R α mRNA are expressed in several neoplastic cell types, including T cell leukemia, cutaneous T-cell lymphoma, melanoma and solid tumors such as small cell lung carcinoma, renal and colon cell carcinomas, glioblastoma, neuroblastoma, mesothelioma, etc. [28,87,132,194–197]. Such abundant expression of IL-15 and IL-15R α in malignant tumor cells

invites the speculation that this may reflect the establishment of autocrine/paracrine/juxtacrine loops that promote tumor growth [195]. We have recently shown that membrane-bound IL-15 promotes tumor cell migration of prostate carcinoma cells *in vitro* [101]. Expression of IL-15 plays a role in colon cancer progression by promoting cell growth, invasion, mucosal hyperplasia and metastasis [196,197]. IL-15 also enhances cell motility and invasion in a highly metastatic colon cancer cell line [196].

Additional tumor growth-promoting effects of IL-15 may arise from its effects on angiogenesis: IL-15 is an effective angiogenic factor, stimulates proliferation of HUVEC and stimulates angiogenesis *in vivo* [140,148].

The existence of an autocrine/paracrine/juxtacrine loop was recently shown in several models including multiple myeloma and melanoma [132,198]. Autocrine IL-15 decreases spontaneous apoptosis in primary myeloma cells while exogenous IL-15 protects myeloma cell lines from spontaneous, Fas-, vincristine- or doxorubicin-induced apoptosis [132]. IL-15 is a growth and anti-apoptotic factor for cutaneous T-cell lymphoma [195], it supports survival of malignant T cells isolated from patients with Sezary syndrome via activation of different STAT factors, c-myc, JunD, c-myc activation and Bcl-2 expression [199,200]. Finally, that IL-15 stimulates germinal center B cell proliferation via a cell–cell contact-dependent mechanism [98] may be related to the apparent promotion of the development of B cell lymphoma by IL-15.

7. Conclusions and therapeutic perspectives

IL-15 is a pleiotropic cytokine which regulates the proliferation, survival, secretory activities and differentiation of many more distinct cell types than originally postulated at the time of its identification. IL-15 is a very broadly expressed bioregulator which serves not only as prototypic cytokine of innate immunity but modulates as well selected adaptive immune responses and, in fact, links both. Largely because of its unusually potent anti-apoptotic properties, IL-15 controls the homeostasis and growth of different non-immune cell types and tissues.

A very intriguing (yet, still rather ill-defined) feature of this cytokine is its unusual pattern of expression and secretion, namely the contrast between the widespread IL-15 mRNA expression and the virtually undetectable extracellular release of IL-15 under physiological conditions. This indicates the presence of an extremely tightly controlled regulation of IL-15 translation, transport and secretion, which appears to be unique in the cytokine family. The detection of IL-15/IL-15R α complexes on cell membranes and in cell supernatants (Bulanova *et al.*, submitted for publication) suggests that not only signal transduction, but also storage, stabilization and regulation of this cytokine depend on its high affinity receptor chain.

Finally, another most intriguing characteristic of this cytokine, which puts it into striking contrast to IL-2, is the diverse and promiscuous usage of receptor chains (IL-2R β , IL-2R γ , IL-15R α , Axl and IL-15RX)—which depends not only on the individual cell type in question, but also on the activation state of the target cell.

This variety and promiscuity of receptor chain usage has important therapeutic implications that one needs to keep in mind when designing pharmacological strategies that target IL-15/IL-15R signaling: (a) an overall stimulatory or inhibitory effect is most likely when the cytokine itself is administered or targeted (*e.g.* by IL-15, anti-IL-15 antibodies or soluble IL-15R α [12,57,161,183,201–204]); (b) instead, by targeting individual IL-15R chains, an unusually high degree of target cell and/or activation status selectivity is obtainable.

Systemic administration of IL-15 antagonists such as antibodies directed against IL-15 or alternatively against IL-2R/IL-15R subunits, recombinant sIL-15R α and IL-15R-Fc fusion protein [57,201–206] allows to effectively manipulate IL-15 bioactivity *in vivo*. For example, recombinant soluble IL-15R α prevents collagen-mediated arthritis in mice [201] and even in primate models [175], inhibits carrageenan-induced acute inflammation [57], prevents the induction of allergen-specific T cells and allergic inflammation *in vivo* [207], inhibits inflammatory and allogenic responses *in vitro* and *in vivo* [57] and enhances cardiac allograft survival [202].

Another example of an IL-15 antagonist is an IL-15 mutant/Fc γ 2a fusion protein (CRB-15) that was produced by mutating glutamine residues to aspartic acid within the C-terminus of IL-15 [206,208]. This mutant binds IL-15R α with a high affinity but does not induce signaling, thereby acting as a specific IL-15 antagonist. Administration of this chimeric protein inhibits pancreatic islet cell allograft rejection [205], delayed type of hypersensitivity responses and alloantigen-induced T cell proliferation *in vivo* [208] and prevents the development of collagen-induced arthritis in mouse model [206].

Finally, antibodies against IL-15 have been used effectively in murine models of psoriasis [187]. Reportedly, such antibodies have already shown efficacy in a Phase I/Phase II in patients with RA [161,209]. Humanized MiK β 1 antibodies directed against the IL-2R/IL-15R β chain have been proven to be effective when used as a single agent to prolong cardiac allograft survival in monkeys [210].

Vice versa, administration of IL-15 agonists such as recombinant IL-15, IL-15-Fc fusion protein and IL-15 cDNA [183,211–213] is extremely successful in anti-tumor adjuvant therapy. Adenocarcinoma engineered to highly secrete IL-15 was rejected completely when injected into syngeneic BALB/c mice [212]. The human small lung cancer cell line N592 and adenocarcinoma TS/A engineered to secrete IL-15 showed a reduced tumor growth rate [213,214]. Furthermore, human prostate carcinoma cell line

(PC-3) and human pancreatic cancer cells (AsPC-1) transfected with highly secretable form of IL-15 showed retarded growth in nude mice [215,216]. IL-15 was also successfully used as an adjuvant in anti-tumor therapy of melanoma. Vaccination with IL-12-secreting melanoma cells and the combined systemic treatment with IL-15 caused eradication of established tumors in all treated mice. This combined treatment activated not only a local response, but also induced systemic anti-tumor immunity [217].

Thus, a wide range of well-targeted and relatively selective agonistic or antagonistic pharmacological interventions in IL-15/15R signaling are already available and have been successfully tested at the *in vivo* level. This availability of potential therapeutic tools renders it particularly important and attractive to systematically dissect the increasing number of clinical conditions beyond RA in whose pathogenesis IL-15/IL-15R signaling has recently become implicated (see above), including diseases such as muscular dystrophy, atherosclerosis, acute hepatic failure and neurodegenerative diseases, where the blockade of apoptosis and/or the stimulation of tissue regeneration are of predominant importance.

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References

- [1] Bazan JF. Hematopoietic receptors and helical cytokines. *Immunol Today* 1990;11:350–4.
- [2] Burton JD, Bamford RN, Peters C, Grant AJ, Kurys G, Goldman CK, et al. 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 USA* 1994;91:4935–9.
- [3] Grabstein KH, Eisenman J, Shanebeck K, Rauch C, Srinivasan S, Fung V, et al. Cloning of a T cell growth factor that interacts with the beta chain of the interleukin-2 receptor. *Science* 1994;264:965–8.
- [4] Bamford RN, Battista AP, Burton JD, Sharma H, Waldmann TA. 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 R region/IL-15 fusion message that lacks many upstream AUGs that normally attenuate IL-15 mRNA translation. *Proc Natl Acad Sci USA* 1996;93:2897–902.
- [5] Giri JG, Ahdieh M, Eisenman J, Shanebeck K, Grabstein K, Kumaki S, et al. Utilisation of the β and γ chains of the IL-2 receptor by the novel cytokine IL-15. *EMBO J* 1994;13:2822–30.
- [6] Leonard WJ, Shores EW, Love PE. Role of the common cytokine receptor gamma chain in cytokine signaling and lymphoid development. *Immunol Rev* 1995;148:97–114.
- [7] Bullfong-Paus S, Dürkop H, Paus R, Krause H, Pohl T, Onu A. Differential regulation of human T lymphoblasts functions by IL-2 and IL-15. *Cytokine* 1997;9:507–13.

- [8] Ohteki T, Suzue K, Maki C, Ota T, Koyasu S. Critical role of IL-15–IL-15R for antigen-presenting cell functions in the innate immune response. *Nat Immunol* 2001;2:1138–43.
- [9] Van Belle T, Grooten J. IL-15 and IL-15R α in CD4+ T cell immunity. *Arch Immunol Ther Exp* 2005;53:115–26.
- [10] Lodolce JP, Burkett PR, Koka RM, Boone DL, Ma A. Regulation of lymphoid homeostasis by interleukin-15. *Cytokine Growth Factor Rev* 2002;13:429–39.
- [11] Becknell B, Caligiuri MA. Interleukin-2, interleukin-15, and their roles in human natural killer cells. *Adv Immunol* 2005;86:209–39.
- [12] Bulfone-Paus S, Ungureanu D, Pohl T, Lindner G, Paus R, Rückert R, et al. Interleukin-15 protects from lethal apoptosis *in vivo*. *Nat Med* 1997;3:1124–8.
- [13] Antony PA, Restifo NP. CD4+CD25+ T regulatory cells, immunotherapy of cancer, and interleukin-2. *J Immunother* 2005;28:120–8.
- [14] Granucci F, Feau S, Angeli V, Trottein F, Ricciardi-Castagnoli P. Early IL-2 production by mouse dendritic cells is the result of microbial-induced priming. *J Immunol* 2003;170:5075–81.
- [15] Bulfone-Paus S, Bulanova E, Budagian V, Paus R. The interleukin-15/interleukin-15 receptor system as a model for juxacrine and reverse signaling. *Bioessays* 2006;28:362–77.
- [16] Schluns KS, Stoklasek T, Lefrançois L. The roles of interleukin-15 receptor α : *trans*-presentation, receptor component, or both? *Int J Biochem Cell Biol* 2005;37:1567–71.
- [17] Ma A, Koka R, Burkett P. Diverse functions of IL-2, IL-15, and IL-7 in lymphoid homeostasis. *Annu Rev Immunol* 2006;24:657–79.
- [18] Giri JG, Kumaki S, Ahdieh M, Friend DJ, Loomis A, Shanabek K, et al. Identification and cloning of a novel IL-15 binding protein that is structurally related to the α chain of the IL-2 receptor. *EMBO J* 1995;14:3654–63.
- [19] Anderson DM, Kumaki S, Ahdieh M, Bertles J, Tometsko M, Loomis T, et al. Functional characterization of the human interleukin-15 receptor α chain and close linkage of *IL15RA* and *IL2RA* genes. *J Biol Chem* 1995;270:29862–9.
- [20] Canals A, Grimm DR, Gasbarre LC, Lunney JK, Zarlenga DS. Molecular cloning of cDNA encoding porcine interleukin-15. *Gene* 1997;195:337–9.
- [21] Anderson DM, Johnson L, Glaccum MB, Copeland NG, Gilbert DJ, Jenkins NA, et al. Chromosomal assignment and genomic structure of *IL15*. *Genomics* 1995;25:701–6.
- [22] Xiong C, Hixson PM, Mendoza LH, Smith CW. Cloning and expression of rabbit interleukin-15. *Vet Immunol Immunopathol* 2005;107:131–41.
- [23] Dean GA, Barger A, Lavoy A. Cloning and expression of feline interleukin 15. *Cytokine* 2005;29:77–83.
- [24] Wang B, Lohrengel B, Lu Y, Meng Z, Xu Y, Yang D, et al. Molecular characterization of woodchuck interleukin 15 (wIL-15) and detection of its expression in liver samples of woodchuck infected with woodchuck hepatitis virus (WHV). *Cytokine* 2005;32:296–303.
- [25] Choi KD, Lillehoj HS, Song KD, Han JY. Molecular and functional characterization of chicken IL-15. *Dev Comp Immunol* 1999;23:165–7.
- [26] Krause H, Jandrig B, Wernicke C, Bulfone-Paus S, Pohl T, Diamantstein T. Genomic structure and chromosomal localization of the human *interleukin-15* gene (IL-15). *Cytokine* 1996;8:667–74.
- [27] Seigel LJ, Harper ME, Wong-Staal F, Gallo RC, Nash WG, O'Brien SJ. Gene for T-cell growth factor: location on human chromosome 4q and feline chromosome B1. *Science* 1984;223:175–8.
- [28] Meazza R, Verdiani S, Biassoni R, Coppolecchia M, Gaggero A, Orengo AM, et al. Identification of a novel interleukin-15 (IL-15) transcript isoform generated by alternative splicing in human small cell lung cancer cell lines. *Oncogene* 1996;12:2187–92.
- [29] Prinz M, Hanisch UK, Kettenmann H, Kirchhoff F. Alternative splicing of mouse IL-15 is due to the use of internal splice site in exon 5. *Brain Res Mol Brain Res* 1998;63:155–62.
- [30] Onu A, Pohl T, Krause H, Bulfone-Paus S. Regulation of IL-15 secretion via the leader peptide of two IL-15 isoforms. *J Immunol* 1997;158:255–62.
- [31] Tagaya Y, Kurys G, Thies TA, Losi JM, Azimi N, Hanover JA, et al. Generation of secretable and nonsecretable interleukin 15 isoforms through alternate usage of signal peptides. *Proc Natl Acad Sci USA* 1997;94:14444–9.
- [32] Nishimura H, Yajima T, Naiki Y, Tsunobuchi H, Umemura M, Itano K, et al. Differential roles of interleukin 15 mRNA isoforms generated by alternative splicing in immune responses *in vivo*. *J Exp Med* 2000;191:157–69.
- [33] Pettit DK, Bonnert TP, Eisenman J, Srinivasan S, Paxton R, Beers C, et al. Structure–function studies of interleukin 15 using site-specific mutagenesis, polyethylene glycol conjugation, and homology modeling. *J Biol Chem* 1997;272:2312–8.
- [34] Kurys G, Tagaya Y, Bamford R, Hanover JA, Waldmann TA. The long signal peptide isoform and its alternative processing direct the intracellular trafficking of interleukin-15. *J Biol Chem* 2000;275:30653–9.
- [35] Gaggero A, Azzarone B, Andrei C, Mishal Z, Meazza R, Zappia E, et al. Differential intracellular trafficking, secretion and endosomal localization of two IL-15 isoforms. *Eur J Immunol* 1999;29:1265–74.
- [36] Pereno R, Giron-Michel J, Gaggero A, Cazes E, Meazza R, Monetti M, et al. IL-15/IL-15R α intracellular trafficking in human melanoma cells and signal transduction through the IL-15R α . *Oncogene* 2000;19:5153–62.
- [37] Dubois S, Magrangeas F, Lehours P, Raher S, Bernard J, Boisteau O, et al. Natural splicing of exon 2 of human interleukin-15 receptor α -chain mRNA results in shortened form with a distinct pattern of expression. *J Biol Chem* 1999;274:26978–84.
- [38] Nishimura H, Fujimoto A, Tamura N, Yajima T, Wajjwalku W, Yoshikai Y. 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* 2005;19:19–28.
- [39] Musso T, Calosso L, Zucca M, Millesimo M, Ravarino D, Giovarelli M, et al. Human monocytes constitutively express membrane-bound, biologically active, and interferon- γ -upregulated interleukin-15. *Blood* 1999;93:3531–9.
- [40] Doherty TM, Seder RA, Sher A. Induction and regulation of IL-15 expression in murine macrophages. *J Immunol* 1996;156:735–41.
- [41] Mattei F, Schiavoni G, Belardelli F, Tough DF. 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* 2001;167:1179–87.
- [42] Rückert R, Asadullah K, Seifert M, Budagian V, Arnold R, Trombotto C, et al. Inhibition of keratinocyte apoptosis by IL-15: a new parameter in the pathogenesis of psoriasis? *J Immunol* 2000;165:2240–50.
- [43] Rappi G, Kapsokafalou A, Heuser C, Rossler M, Ugurel S, Tilgen W, et al. Dermal fibroblasts sustain proliferation of activated T cells via membrane-bound interleukin-15 upon long-term stimulation with tumor necrosis factor- α . *J Invest Dermatol* 2001;116:102–9.
- [44] Satoh J, Kurohara K, Yukitake M, Kuroda Y. Interleukin-15, a T-cell growth factor, is expressed in human neural cell lines and tissues. *J Neurol Sci* 1998;155:170–7.
- [45] Shinozaki M, Hirahashi J, Lebedeva T, Liew FY, Salant DJ, Maron R, et al. IL-15, a survival factor for kidney epithelial cells, counteracts apoptosis and inflammation during nephritis. *J Clin Invest* 2002;109:951–60.
- [46] Quinn LS, Haug KL, Grabstein KH. IL-15: a novel anabolic cytokine for skeletal muscle. *Endocrinology* 1995;136:3669–72.
- [47] Basok A, Shnaider A, Man L, Chaimovitz C, Douvdevani A. CD40 is expressed on human peritoneal mesothelial cells and upregulates the production of interleukin-15 and RANTES. *J Am Soc Nephrol* 2001;12:695–702.
- [48] Azimi N, Brown K, Bamford RN, Tagaya Y, Siebenlist U, Waldmann TA. Human T cell lymphotropic virus type I Tax protein transactivates interleukin 15 gene transcription through an NF- κ B site. *Proc Natl Acad Sci USA* 1998;95:2452–7.
- [49] Lindstein T, June CH, Ledbetter JA, Stella G, Thompson CB. Regulation of lymphokine messenger RNA stability by a surface-mediated T cell activation pathway. *Science* 1989;244:339–43.

- [50] Waldmann TA, Tagaya Y. 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* 1999;17:19–49.
- [51] Ohteki T, Yoshida H, Matsuyama T, Duncan GS, Mak TW, Ohashi PS. The transcription factor interferon regulatory factor 1 (IRF-1) is important during the maturation of natural killer 1.1+ T cell receptor- α/β + (NK1+ T) cells, natural killer cells, and intestinal intraepithelial T cells. *J Exp Med* 1998;187:967–72.
- [52] Vázquez N, Walsh TJ, Friedman D, Chanock SJ, Lyman CA. Interleukin-15 augments superoxide production and microbicidal activity of human monocytes against *Candida albicans*. *Infect Immunol* 1998;66:145–50.
- [53] Flamand L, Stefanescu I, Menezes J. Human herpesvirus-6 enhances natural killer cell cytotoxicity via IL-15. *J Clin Invest* 1996;97:1373–81.
- [54] Bamford RN, DeFilippis AP, Azimi N, Kurys G, Waldmann TA. 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* 1998;160:4418–26.
- [55] Wang X, Rickert M, Garsia KC. Structure of the quaternary complex of interleukin-2 with its α , β and γ c receptors. *Science* 2005;310:1159–63.
- [56] Perkins SJ, Haris PI, Sim RB, Chapman D. A study of the structure of human complement component factor H by Fourier transform infrared spectroscopy and secondary structure averaging methods. *Biochemistry* 1988;27:4004–12.
- [57] Wei X, Orchardson M, Gracie JA, Leung BP, Gao B, Guan H, et al. The Sushi domain of soluble IL-15 receptor α is essential for binding IL-15 and inhibiting inflammatory and allogenic responses *in vitro* and *in vivo*. *J Immunol* 2001;167:277–82.
- [58] Bernard J, Harb C, Mortier E, Quémener A, Meloen RH, Vermot-Desroches C, et al. Identification of an interleukin-15 α receptor-binding site on human interleukin-15. *J Biol Chem* 2004;279:24313–22.
- [59] Lorenzen I, Dingley AJ, Jacques Y, Grötzinger J. The structure of the IL-15 α -receptor and its implication for ligand binding. *J Biol Chem* 2006;281:6642–7.
- [60] Fehninger TA, Caligiuri MA. Interleukin 15: biology and relevance to human disease. *Blood* 2001;97:14–32.
- [61] Tejman-Yarden N, Zlotnik M, Lewis E, Etzion O, Chaimovitz C, Douvdevani A. Renal cells express a functional interleukin-15 receptor. *Nephrol Dial Transplant* 2005;20:516–23.
- [62] Schluns KS, Klonowski KD, Lefrançois L. Transregulation of memory CD8 T-cell proliferation by IL-15R α + bone marrow-derived cells. *Blood* 2004;103:988–94.
- [63] Bulanova E, Budagian V, Orinska Z, Krause H, Paus R, Bulfone-Paus S. Mast cells express novel functional interleukin-15 receptor α isoforms. *J Immunol* 2003;170:5045–55.
- [64] Carson WE, Giri JG, Lindemann MJ, Linett ML, Ahdieh M, Paxton R, et al. Interleukin (IL) 15 is a novel cytokine that activates human natural killer cells via components of IL-2 receptor. *J Exp Med* 1994;180:1395–403.
- [65] Hatakeyama M, Tsudo M, Minamoto S, Kono T, Doi T, Miyata T, et al. Interleukin-2 receptor β chain gene: generation of three receptor forms by cloned human α and β chain cDNA. *Science* 1989;244:551–6.
- [66] Takeshita T, Asao H, Ohtani K, Ishii N, Kumaki S, Tanaka N, et al. Cloning of the γ chain of the human IL-2 receptor. *Science* 1992;257:379–82.
- [67] Cosman D. The hematopoietin receptor superfamily. *Cytokine* 1993;5:95–106.
- [68] Budagian V, Bulanova E, Orinska Z, Ludwig A, Rose-John S, Saftig P, et al. Natural soluble interleukin-15R α is generated by cleavage that involves the tumor necrosis factor- α -converting enzyme (TACE/ADAM17). *J Biol Chem* 2004;279:40368–75.
- [69] Mortier E, Bernard J, Plet A, Jacques Y. Natural, proteolytic release of a soluble form of human IL-15 receptor α -chain that behaves as a specific, high affinity IL-15 antagonist. *J Immunol* 2004;173:1681–8.
- [70] Rose-John S. Interleukin-6 biology is coordinated by membrane bound and soluble receptors. *Acta Biochem Pol* 2003;50:603–11.
- [71] Mortier E, Quémener A, Vusio P, Lorenzen I, Boublik I, Grötzinger J, et al. Soluble IL-15R α sushi as a selective and potent agonist of IL-15 action through IL-15R β/γ : hyper-agonist IL-15-IL-15R α fusion proteins. *J Biol Chem* 2005;281:1612–9.
- [72] Johnston JA, Bacon CM, Finbloom DS, Rees RC, Kaplan D, Shibuya K, et al. Tyrosine phosphorylation and activation of STAT5, STAT3, and Janus kinases by interleukins 2 and 15. *Proc Natl Acad Sci USA* 1995;92:8705–9.
- [73] Leonard WJ. Role of JAK kinases and STATs in cytokine signal transduction. *Int J Hematol* 2001;73:271–7.
- [74] Gaffen SL, Goldsmith MA, Green WC. Interleukin-2 and the interleukin-2 receptor. San Diego: Academic; 1998.
- [75] Leonard WJ. Cytokines and immunodeficiency diseases. *Nat Rev Immunol* 2001;1:200–8.
- [76] Teglund S, McKay C, Schuetz E, van Deursen JM, Stravopodis D, Wang D, et al. Stat5a and Stat5b proteins have essential and nonessential, or redundant, roles in cytokine responses. *Cell* 1998;93:841–50.
- [77] Imada K, Bloom ET, Nakajima H, Horvath-Arcidiacono JA, Udy GB, Davey HW, et al. Stat5b is essential for natural killer cell-mediated proliferation and cytotoxic activity. *J Exp Med* 1998;188:2067–74.
- [78] Nosaka T, van Deursen JMA, Tripp RA, Thierfelder WE, Witthuhn BA, McMickle AP, et al. Defective lymphoid development in mice lacking Jak3. *Science* 1995;270:800–2.
- [79] Zhu X, Suen K-L, Barbacid M, Bolen JB, Fargnoli J. Interleukin-2-induced tyrosine phosphorylation of Shc proteins correlates with factor-dependent T cell proliferation. *J Biol Chem* 1994;269:5518–22.
- [80] Miyazaki T, Liu Z-J, Kawahara A, Minami Y, Yamada K, Tsujimoto Y, et al. Three distinct IL-2 signaling pathways mediated by *bcl-2*, *c-myc*, and *lck* cooperate in hematopoietic cell proliferation. *Cell* 1995;81:223–31.
- [81] Gu H, Maeda H, Moon JJ, Lord JD, Yoakim M, Nelson BH, et al. New role for Shc in activation of the phosphatidylinositol 3-kinase/Akt pathway. *Mol Cell Biol* 2000;20:7109–20.
- [82] Bulanova E, Budagian V, Pohl T, Krause H, Dürkop H, Paus R, et al. The IL-15R α chain signals through association with Syk in human B cells. *J Immunol* 2001;170:5045–55.
- [83] McDonald PP, Russo MP, Ferrini S, Cassatella MA. Interleukin-15 (IL-15) induces NF- κ B activation and IL-8 production in human neutrophils. *Blood* 1998;92:4828–35.
- [84] Bianchi T, Gasser S, Trumpp A, MacDonald HR. c-Myc acts downstream of IL-15 in the regulation of memory CD8 T cell homeostasis. *Blood* 2006;107:3992–9.
- [85] Goebel J, Forrest K, Morford L, Roszman TL. Differential localization of IL-2- and -15 receptor chains in membrane rafts of human T cells. *J Leukoc Biol* 2002;72:199–206.
- [86] Vámosi G, Bodnár A, Vereb G, Jenei A, Goldman CK, Langowski J, et al. IL-2 and IL-15 receptor α -subunits are coexpressed in a supramolecular receptor cluster in lipid rafts of T cells. *Proc Natl Acad Sci USA* 2004;101:11082–7.
- [87] Stevens AC, Matthews J, Andres P, Baffis V, Zheng XX, Chae DW, et al. Interleukin-15 signals T84 colonic epithelial cells in the absence of the interleukin-2 receptor beta chain. *Am J Physiol Gastrointest Liver Physiol* 1997;272:G1201–8.
- [88] Bulfone-Paus S, Bulanova E, Pohl T, Budagian V, Dürkop H, Rückert R, et al. Death deflected: IL-15 inhibits TNF α -mediated apoptosis in fibroblasts by TRAF2 recruitment to the IL-15R α chain. *FASEB J* 1999;13:1575–85.
- [89] Rathé C, Girard D. Interleukin-15 enhances human neutrophil phagocytosis by a Syk-dependent mechanism: importance of the IL-15R α chain. *J Leukoc Biol* 2004;76:162–8.
- [90] Tagaya Y, Burton JD, Miyamoto Y, Waldmann TA. Identification of a novel receptor/signal transduction pathway for IL-15/T in mast cells. *EMBO J* 1996;15:4928–39.

- [91] Masuda A, Matsuguchi T, Yamaki K, Hayakawa T, Yoshikai Y. Interleukin-15 prevents mouse mast cell apoptosis through STAT6-mediated Bcl-x_L expression. *J Biol Chem* 2001;276:26107–13.
- [92] Masuda A, Matsuguchi T, Yamaki K, Hayakawa T, Kubo M, LaRoche W, et al. Interleukin-15 induces rapid tyrosine phosphorylation of STAT6 and the expression of interleukin-4 in mouse mast cells. *J Biol Chem* 2000;275:29331–7.
- [93] Budagian V, Bulanova E, Orinska Z, Thon L, Mamat U, Bellosta P, et al. A promiscuous liaison between IL-15 receptor and Axl receptor tyrosine kinase in cell death control. *EMBO J* 2005;24: 4260–70.
- [94] Gschwind A, Zwick E, Prenzel N, Leserer M, Ullrich A. Cell communication networks: epidermal growth factor receptor transactivation as the paradigm for interreceptor signal transmission. *Oncogene* 2001;20:1594–600.
- [95] Dubois S, Mariner J, Waldmann TA, Tagaya Y. IL-15R α recycles and presents IL-15 in *trans* to neighboring cells. *Immunity* 2002;17:537–47.
- [96] Kobayashi H, Dubois S, Sato N, Sabzevari H, Sakai Y, Waldmann TA, et al. Role of *trans*-cellular IL-15 presentation in the activation of NK cell-mediated killing, which leads to enhanced tumor immunosurveillance. *Blood* 2005;105:721–7.
- [97] Sandau MM, Schluns KS, Lefrançois L, Jameson SC. Cutting edge: transpresentation of IL-15 by bone marrow-derived cells necessitates expression of IL-15 and IL-15R α by the same cells. *J Immunol* 2004;173:6537–41.
- [98] Park C-S, Yoon S-O, Armitage RJ, Choi YS. Follicular dendritic cells produce IL-15 that enhances germinal center B cell proliferation in membrane-bound form. *J Immunol* 2004;173:6676–83.
- [99] Burkett PR, Koka R, Chien M, Chai S, Chan F, Ma A, et al. IL-15R α expression on CD8⁺ T cells is dispensable for T cell memory. *Proc Natl Acad Sci USA* 2003;100:4724–9.
- [100] Dubois SP, Waldmann TA, Müller J. Survival adjustment of mature dendritic cells by IL-15. *Proc Natl Acad Sci USA* 2005;102:8662–7.
- [101] Budagian V, Bulanova E, Orinska Z, Pohl T, Borden EC, Silverman R, et al. Reverse signaling through membrane-bound interleukin-15. *J Biol Chem* 2004;279:42192–201.
- [102] Neely GG, Epelman S, Ma LL, Colarusso P, Howlett CJ, Amankwah EK, et al. Monocytes surface-bound IL-15 can function as an activating receptor and participate in reverse signaling. *J Immunol* 2004;172:4225–34.
- [103] Eissner G, Kolch W, Schneurich P. Ligands working as receptors: reverse signaling by members of the TNF superfamily enhance the plasticity of the immune system. *Cytokine Growth Factor Rev* 2004;15:353–66.
- [104] Cassatella MA, McDonald PP. Interleukin-15 and its impact on neutrophil function. *Curr Opin Hematol* 2000;7:174–7.
- [105] Musso T, Calosso L, Zucca M, Millesimo M, Puliti M, Bulfone-Paus S, et al. Interleukin-15 activates proinflammatory and antimicrobial functions in polymorphonuclear cells. *Infect Immun* 1998;66:2640–7.
- [106] Girard D, Paquet M-E, Paquin R, Beaulieu AD. Differential effects of interleukin-15 (IL-15) and IL-2 on human neutrophils: modulation of phagocytosis, cytoskeleton rearrangement, gene expression, and apoptosis by IL-15. *Blood* 1996;88:3176–84.
- [107] Pelletier M, Rathé C, Girard D. Mechanisms involved in interleukin-15-induced suppression of human neutrophils apoptosis: role of the anti-apoptotic Mcl-1 protein and several kinases including Janus kinase-2, p38 mitogen-activated protein kinase and extracellular signal-regulated kinase-1/2. *FEBS Lett* 2002;532:164–70.
- [108] Bouchard A, Rathé C, Girard D. Interleukin-15 delays human neutrophils apoptosis by intracellular events and not via extracellular factors: role of Mcl-1 and decreased activity of caspase-3 and caspase-8. *J Leukoc Biol* 2004;75:893–900.
- [109] Hoontrakoon R, Chu WH, Gardai SJ, Wenzel SE, McDonald P, Fadok VA, et al. Interleukin-15 inhibits spontaneous apoptosis in human eosinophils via autocrine production of granulocyte macrophage-colony stimulation factor and nuclear factor- κ B activation. *Am J Respir Cell Mol Biol* 2002;26:404–12.
- [110] Watson RWG, Rotstein OD, Padolo J, Bitar R, Marshall JC. The IL-1 β -converting enzyme (caspase-1) inhibits apoptosis of inflammatory neutrophils through activation of IL-1 β . *J Immunol* 1998;161:957–62.
- [111] Ottonello L, Frumento G, Arduino N, Bertolotto M, Dapino P, Mancini M, et al. Differential regulation of spontaneous and immune complex-induced neutrophil apoptosis by proinflammatory cytokines. Role of oxidants, Bax and caspase-3. *J Leukoc Biol* 2002;72:125–32.
- [112] Means-Markwell M, Burgess T, deKeraty D, O'Neil K, Mascola J, Fleisher T, et al. Eosinophilia with aberrant T cells and elevated serum levels of interleukin-2 and interleukin-15. *N Engl J Med* 2000;342:1568–71.
- [113] Galli SJ, Nakae S, Tsai M. Mast cells in the development of adaptive immune responses. *Nat Immunol* 2005;6:135–42.
- [114] Neely GG, Robbins SM, Amankwah EK, Epelman S, Wong H, Spurrell JCL, et al. Lipopolysaccharide-stimulated or granulocyte-macrophage colony-stimulating factor-stimulated monocytes rapidly express biologically active IL-15 on their cell surface independent of new protein synthesis. *J Immunol* 2001;167:5011–7.
- [115] D'Agostino P, Milano S, Arcoleo F, Di Bella G, La Rosa M, Ferlazzo V, et al. Interleukin-15, as interferon-gamma, induces the killing of *Leishmania infantum* in phorbol-myristate-acetate-activated macrophages increasing interleukin-12. *Scand J Immunol* 2004;60:609–14.
- [116] Maeurer MJ, Trinder P, Hommel G, Walter W, Freitag K, Atkins D, et al. Interleukin-7 or interleukin-15 enhances survival of *Mycobacterium tuberculosis*-infected mice. *Infect Immun* 2000;68:2962–70.
- [117] Badolato R, Negro Ponzi A, Millesimo M, Notarangelo LD, Musso T. Interleukin-15 (IL-15) induces IL-8 and monocyte chemotactic protein production in human monocytes. *Blood* 1997;90:2804–9.
- [118] Krutzik SR, Tan B, Li H, Ochoa MT, Liu PT, Sharfstein SE, et al. TLR activation triggers the rapid differentiation of monocytes into macrophages and dendritic cells. *Nat Med* 2005;11:653–60.
- [119] Liu T, Nishimura H, Matsuguchi T, Yoshikai Y. Differences in interleukin-12 and -15 production by dendritic cells at the early stage of *Listeria monocytogenes* infection between BALB/c and C57 BL/6 mice. *Cell Immunol* 2000;202:31–40.
- [120] Jinushi M, Takehara T, Tatsumi T, Kanto T, Groh V, Spies T, et al. Autocrine/paracrine IL-15 that 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* 2003;171:5423–9.
- [121] Feau S, Facchinetti V, Granucci F, Citterio S, Jarrossay D, Seresini S, et al. Dendritic cell-derived IL-2 production is regulated by IL-15 in humans and in mice. *Blood* 2005;105:697–702.
- [122] Mohamadzadeh M, Berard F, Essert G, Chalouni C, Pulendran B, Davoust J, et al. Interleukin 15 skews monocyte differentiation into dendritic cells with features of Langerhans cells. *J Exp Med* 2001;194:1013–20.
- [123] Pulendran B, Dillon S, Joseph C, Curiel T, Banchereau J, Mohamadzadeh M. Dendritic cells generated in the presence of GM-CSF plus IL-15 prime potent CD8⁺ Tc1 responses *in vivo*. *Eur J Immunol* 2004;34:66–73.
- [124] Brandt K, Bulfone-Paus S, Foster DC, Rückert R. Interleukin-21 inhibits dendritic cell activation and maturation. *Blood* 2003;102: 4090–8.
- [125] Rückert R, Brandt K, Bulanova E, Mirghomizadeh F, Paus R, Bulfone-Paus S. Dendritic cell-derived IL-15 controls the induction of CD8 T-cell immune responses. *Eur J Immunol* 2003;33:3493–503.
- [126] Ferlazzo G, Pack M, Thomas D, Paludan C, Schmid D, Strowig T, et al. Distinct roles of IL-12 and IL-15 in human natural killer cell activation by dendritic cells from secondary lymphoid organs. *Proc Natl Acad Sci USA* 2004;101:16606–11.
- [127] Kennedy MK, Glaccum M, Brown SN, Butz EA, Viney JL, Embers M, et al. Reversible defects in natural killer and memory CD8 T cell lineage in interleukin 15-deficient mice. *J Exp Med* 2000;191: 771–80.

- [128] Lodolce JP, Boone DL, Chai S, Swain RE, Dassopoulos T, Trettin S, et al. IL-15 receptor maintains lymphoid homeostasis by supporting lymphocyte homing and proliferation. *Immunity* 1998;9:669–76.
- [129] Armitage RJ, MacDuff BM, Eisenman J, Paxton R, Grabstein KH. IL-15 has stimulatory activity for the induction of B cell proliferation and differentiation. *J Immunol* 1995;154:483–90.
- [130] Trentin L, Cerutti A, Zambello R, Sancetta R, Tassarini C, Facco M, et al. Interleukin-15 promotes the growth of leukemic cells of patients with B-cell chronic lymphoproliferative disorders. *Blood* 1996;87:3327–35.
- [131] Kacani L, Sprinzl GM, Erdei A, Dierich MP. Interleukin-15 enhances HIV-1-driven polyclonal B-cell response *in vitro*. *Exp Clin Immunogenet* 1999;16:162–72.
- [132] Tinhofe I, Marschitz I, Henn T, Egle A, Greil R. Expression of functional interleukin-15 receptor and autocrine production of interleukin-15 as mechanisms of tumor propagation in multiple myeloma. *Blood* 2000;95:610–8.
- [133] Trentin L, Zambello R, Facco M, Sancetta R, Agostini C, Semenzato G. Interleukin-15: a novel cytokine with regulatory properties on normal and neoplastic B lymphocytes. *Leuk Lymphoma* 1997;27:35–42.
- [134] Silva Jr WA, Covas DT, Panepucci RA, Proto-Suqueira R, Siufi JL, Zanette DL, et al. The profile of gene expression of human marrow mesenchymal stem cells. *Stem Cells* 2003;21:661–9.
- [135] Ajuwon KM, Jacobi SK, Kuske JL, Spurlock ME. Interleukin-6 and interleukin-15 are selectively regulated by lipopolysaccharide and interferon- γ in primary pig adipocytes. *Am J Physiol Regul Integr Comp Physiol* 2004;286:R547–53.
- [136] Nilsen EM, Johansen F-E, Jahnsen FL, Lundin KEA, Scholz T, Brandtzaeg P, et al. Cytokine profiles of cultured microvascular endothelial cells from the human intestine. *Gut* 1998;42:635–42.
- [137] Briard D, Brouty-Boyé D, Azzarone B, Jasmin C. Fibroblasts from human spleen regulate NK cell differentiation from blood CD34⁺ progenitors via cell surface IL-15. *J Immunol* 2002;168:4326–32.
- [138] Ozawa A, Tada H, Sugawara Y, Uehara A, Sasano T, Shimauchi H, et al. Endogenous IL-15 sustains recruitment of IL-2R β and common γ and IL-2-mediated chemokine production in normal and inflamed human gingival fibroblasts. *J Immunol* 2004;173:5180–8.
- [139] Miranda-Carús M-E, Balsa A, Benito-Miguel M, Péres de Ayala C, Martín-Mola E. IL-15 and the initiation of cell contact-dependent synovial fibroblast-T lymphocytes cross-talk in rheumatoid arthritis: effect of methotrexate. *J Immunol* 2004;173:1463–86.
- [140] Yang L, Thornton S, Grom AA. Interleukin-15 inhibits sodium nitroprusside-induced apoptosis of synovial fibroblasts and vascular endothelial cells. *Arthritis Rheum* 2002;46:3010–4.
- [141] McInnes IB, Al-Mughales J, Field M, Leung BP, Huang F, Dixon R, et al. The role of interleukin-15 in T-cell migration and activation in rheumatoid arthritis. *Nat Med* 1996;2:175–82.
- [142] Ogata Y, Kukita A, Kukita T, Komine M, Miyahara A, Miyazaki Z, et al. A novel role of IL-15 in the development of osteoclasts: inability to replace its activity with IL-2. *J Immunol* 1999;162:2754–60.
- [143] Miranda-Carús M-E, Benito-Miguel M, Balsa A, Cobo-Ibáñez T, Péres de Ayala C, Pascual-Salcedo D, et al. Peripheral blood T lymphocytes from patients with early rheumatoid arthritis express RANKL and interleukin-15 on the cell surface and promote osteoclastogenesis in autologous monocytes. *Arthritis Rheum* 2006;54:1151–64.
- [144] Yano S, Komine M, Fujimoto M, Okochi H, Tamaki K. Interleukin 15 induces the signals of epidermal proliferation through ERK and PI3-kinase in a human epidermal keratinocyte cell line, HaCaT. *Biochem Biophys Res Commun* 2003;301:841–7.
- [145] Weiler M, Rogashev B, Einbinder T, Hausmann MJ, Kaneti J, Chaimovitz C, et al. Interleukin-15, a leukocyte activator and growth factor, is produced by cortical tubular epithelial cells. *J Am Soc Nephrol* 1998;9:1194–201.
- [146] Robertson H, Kirby JA. Post-transplant renal tubulitis: the recruitment, differentiation and persistence of intra-epithelial T cells. *Am J Transplant* 2003;3:3–10.
- [147] Wong WK, Robertson H, Carroll HP, Ali S, Kirby JA. Tubulitis in renal allograft rejection: role of transforming factor-beta and interleukin-15 in development and maintenance of CD103⁺ intraepithelial T cells. *Transplantation* 2003;75:505–14.
- [148] Angiolillo AL, Kanegane H, Sgadari C, Reaman GH, Tosato G. Interleukin-15 promotes angiogenesis *in vivo*. *Biochem Biophys Res Commun* 1997;233:231–7.
- [149] Estess P, Nandi A, Mohamadze M, Siegelman MH. Interleukin 15 induces endothelial hyaluronan expression *in vitro* and promotes activated T cell extravasation through a CD44-dependent pathway *in vivo*. *J Exp Med* 1999;190:9–19.
- [150] Oppenheimer-Marks N, Brezinschek RI, Mohamadze M, Vita R, Lipsky PE. 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* 1998;101:1261–72.
- [151] Furmanczyk PS, Quinn LS. Interleukin-15 increases myosin accretion in human skeletal myogenic cultures. *Cell Biol Int* 2003;27:845–51.
- [152] Quinn LS, Anderson BG, Drivdahl RH, Alvarez B, Argilés JM. Overexpression of interleukin-15 induces skeletal muscle hypertrophy *in vitro*: implication for treatment of muscle wasting disorders. *Exp Cell Res* 2002;280:55–63.
- [153] Busquets S, Figueras MR, Meijnsing S, Carbo N, Quinn LS, Almendro V, et al. Interleukin-15 decreases proteolysis in skeletal muscle: a direct effect. *Int J Mol Med* 2005;16:471–6.
- [154] Carbo N, López-Soriano J, Costelli P, Alvarez B, Busquets S, Baccino FM, et al. Interleukin-15 mediates reciprocal regulation of adipose and muscle mass: a potential role in body weight control. *Biochim Biophys Acta* 2001;1526:17–24.
- [155] Alvarez B, Carbó N, López-Soriano J, Drivdahl RH, Busquets S, López-Soriano FJ, et al. Effects of interleukin-15 (IL-15) on adipose tissue mass in rodent obesity models: evidence for direct IL-15 action on adipose tissue. *Biochim Biophys Acta* 2002;1570:33–7.
- [156] Quinn LS, Strait-Bodey L, Anderson BG, Argilés JM, Havel PJ. Interleukin-15 stimulates adiponectin secretion by 3T3-L1 adipocytes: evidence for a skeletal muscle-to-fat signaling pathway. *Cell Biol Int* 2005;29:449–57.
- [157] Hanisch U-K, Lyons SA, Prinz M, Nolte C, Weber JR, Kettenmann H, et al. Mouse brain microglia express interleukin-15 and its multimeric receptor complex functionally coupled to Janus kinase activity. *J Biol Chem* 1997;272:28853–60.
- [158] Kurowska M, Rudnicka W, Maślińska D, Maśliński W. Expression of IL-15 and IL-15 receptor isoforms in select structures of human fetal brain. *Ann N Y Acad Sci* 2002;966:441–5.
- [159] Lee YB, Satoh J, Walker DG, Kim SU. Interleukin-15 gene expression in human astrocytes and microglia in culture. *Neuroreport* 1996;7:1062–6.
- [160] Gomez-Nicola D, Doncel-Perez E, Nieto-Sampedro M. Regulation by GD3 of the proinflammatory response of microglia mediated by interleukin-15. *J Neurosci Res* 2006;83:754–62.
- [161] Waldmann TA. Targeting the interleukin-15/interleukin-15 receptor system in inflammatory autoimmune diseases. *Arthritis Res Ther* 2004;6:174–7.
- [162] Kuczyński S, Winiarska H, Abramczyk M, Szczawińska K, Wiersz-Wysocka B, Dworacka M. IL-15 is elevated in serum patients with type 1 diabetes mellitus. *Diabetes Res Clin Pract* 2005;69:231–6.
- [163] Aringer M, Stummvoll GH, Steiner G, Köller M, Steiner CW, Hoffer E, et al. Serum interleukin-15 is elevated in systemic lupus erythematosus. *Rheumatology (Oxford)* 2001;40:876–81.
- [164] Liu Z, Geboes K, Colpaert S, D'Haens GR, Rutgeerts P, Ceppens JL. IL-15 is highly expressed in inflammatory bowel disease and regulates local T cell-dependent cytokine production. *J Immunol* 2000;164:3608–15.

- [165] McInnes IB, Gracie JA, Harnett M, Harnett W, Liew FY. New strategies to control inflammatory synovitis: interleukin 15 and beyond. *Ann Rheum Dis* 2003;62:51–4.
- [166] Muro S, Taha R, Tsicopoulos A, Olivenstein R, Tonnel A-B, Christodoulouopoulos P, et al. Expression of IL-15 in inflammatory pulmonary diseases. *J Allergy Clin Immunol* 2001;108:970–5.
- [167] Cho M-L, Yoon C-H, Hwang S-Y, Park M-K, Min S-Y, Lee SH, et al. Effector function of type II collagen-stimulated T cells from rheumatoid arthritis patients. *Arthritis Rheum* 2004;50:776–84.
- [168] Kurowska M, Rudnicka W, Kontny E, Janicka I, Chorzay M, Kowalczewski J, et al. Fibroblast-like synoviocytes from rheumatoid arthritis patients express functional IL-15 receptor complex: endogenous IL-15 in autocrine fashion enhances cell proliferation and expression of Bcl-x_L and Bcl-2. *J Immunol* 2002;169:1760–7.
- [169] Ernestam S, Af Klint E, Catrina AI, Sundberg E, Engström M, Klareskog L, et al. Synovial expression of IL-15 in rheumatoid arthritis is not influenced by blockade of tumor necrosis factor. *Arthritis Res Ther* 2005;8:R18.
- [170] Thirkow EW, van der Heijden IM, Breedveld FC, Smeets TJM, Daha MR, Kluin PM, et al. Increased expression of IL-15 in the synovium of patients with rheumatoid arthritis compared with patients with *Yersinia*-induced arthritis and osteoarthritis. *J Pathol* 1997;181:444–50.
- [171] Wilkinson PC, Liew FY. Chemoattraction of human blood T lymphocytes by interleukin-15. *J Exp Med* 1995;181:1255–9.
- [172] Waase I, Kayser C, Carlson PJ, Goronzy JJ, Weyand CM. Oligoclonal T cell proliferation in patients with rheumatoid arthritis and their unaffected siblings. *Arthritis Rheum* 1996;39:904–13.
- [173] Komosci A, Lamprecht P, Csernok E, Mueller A, Holl-Ulrich K, Seitzer U, et al. Peripheral blood and granuloma CD4+CD28– T cells are a major source of interferon- γ and tumor necrosis factor- α in Wegener's granulomatosis. *Am J Pathol* 2002;160:1717–24.
- [174] Yamamura Y, Gupta R, Morita Y, He X, Pai R, Endres J, et al. Effector function of resting T cells: activation of synovial fibroblasts. *J Immunol* 2001;166:2270–5.
- [175] Liew FY, McInnes IB. Role of interleukin 15 and interleukin 18 in inflammatory response. *Ann Rheum Dis* 2002;61:100–2.
- [176] Papadakis KA, Targan SR. Current theories on the causes of inflammatory bowel disease. *Gastroenterol Clin North Am* 1999;28:283–96.
- [177] Kirman I, Nielsen OH. Increased numbers of interleukin-15-expressing cells in active ulcerative colitis. *Am J Gastroenterol* 1996;91:1789–94.
- [178] Sakai T, Kusugami K, Nishimura H, Ando T, Yamaguchi T, Ohsuga M, et al. Interleukin 15 activity in the rectal mucosa of inflammatory bowel disease. *Gastroenterology* 1998;114:1237–43.
- [179] Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. *J Clin Pathol* 2003;56:481–90.
- [180] Baranda L, de la Fuente H, Layseca-Espinosa E, Portales-Pérez D, Niño-Moreno P, Valencia-Pacheco G, et al. IL-15 and IL-15R in leucocytes from patients with systemic lupus erythematosus. *Rheumatology* 2005;44:1507–13.
- [181] Aringer M, Feierl E, Steiner G, Stummvoll GH, Höfler E, Steiner CW, et al. Increased bioactive TNF in human systemic lupus erythematosus: associations with cell death. *Lupus* 2002;11:102–8.
- [182] Cardozo AK, Proost P, Gysemans C, Chen M-C, Mathieu C, Eizirik DL. IL-1 β and IFN- γ 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* 2003;46:255–66.
- [183] Signore A, Annovazzi A, Giacalone P, Beales PE, Valorani MG, Vestri AR, et al. Reduced cumulative incidence of diabetes but not insulin following administration of chimeric human IL-15-murine IgG2b in NOD mice. *Diabetes Metab Res Rev* 2003;19:464–8.
- [184] Wekerle H. Myelin specific, autoaggressive T cell clones in the normal immune repertoire: their nature and their regulation. *Int Rev Immunol* 1992;9:231–41.
- [185] Schön MP, Boehncke W-H. Psoriasis. *N Engl J Med* 2005;352:1899–912.
- [186] McInnes IB. Cytokine targeting in psoriasis and psoriatic arthritis: beyond TNF α . Ernst Schering Res Found Workshop 2006;56:29–44.
- [187] Villadsen LS, Schuurman J, Beurskens F, Dam TN, Dagnaes-Hansen F, Skov L, et al. Resolution of psoriasis upon blockade of IL-15 biological activity in a xenograft mouse model. *J Clin Invest* 2003;112:1571–80.
- [188] Houtkamp MA, van der Wal AC, de Boer OJ, van der Loos CM, de Boer PAJ, Moorman AFM, et al. Interleukin-15 expression in atherosclerotic plaques: an alternative pathway for T-cell activation in atherosclerosis? *Atheroscler Thromb Vasc Biol* 2001;21:1208–13.
- [189] Wuttge DM, Eriksson P, Sirsjo A, Hansson GK, Stemme S. Expression of interleukin-15 in mouse and human atherosclerotic lesions. *Am J Pathol* 2001;159:417–23.
- [190] Kovanen RT, Kaartinen M, Paavonen T. Infiltrates of mast cells at the site of coronary atheromatous erosion of rupture of myocardial infarction. *Circulation* 1995;92:1084–8.
- [191] Kaibe M, Ohishu M, Ito N, Yuan M, Takagi T, Terai M, et al. Serum interleukin-15 concentration in patients with essential hypertension. *Am J Hypertension* 2005;18:1019–25.
- [192] Sugiura T, Harigai M, Kawaguchi Y, Takagi K, Fukasawa C, Ohsako-Higami S, et al. Increased IL-15 production of muscle cells in polymyositis and dermatomyositis. *Int Immunol* 2002;14:917–24.
- [193] Harcourt LJ, Holmes AG, Gregorevic P, Schertzer JD, Stupka N, Plant DR, et al. Interleukin-15 administration improves diaphragm muscle pathology and function in dystrophic *mdx* mice. *Am J Pathol* 2005;166:1131–41.
- [194] Trinder P, Seitzer U, Gerdes J, Seliger B, Maeurer M. Constitutive and IFN- γ regulated expression of IL-7 and IL-15 in human renal cell cancer. *Int J Oncol* 1999;14:23–31.
- [195] Döbbling U, Dummer R, Laine E, Potoczna N, Qin JZ, Burg G. Interleukin-15 is an autocrine/paracrine viability factor for cutaneous T-cell lymphoma cells. *Blood* 1998;92:252–8.
- [196] Kuniyasu H, Oue N, Nakae D, Tsutsumi M, Denda A, Tsujiuchi T, et al. Interleukin-15 expression is associated with malignant potential in colon cancer cells. *Pathobiology* 2001;69:86–95.
- [197] Kuniyasu H, Ohmori H, Sasaki T, Sasahira T, Yoshida K, Kitada Y, et al. Production of interleukin 15 by human colon cancer cells is associated with induction of mucosal hyperplasia, angiogenesis, and metastasis. *Clin Cancer Res* 2003;9:4802–10.
- [198] Barzegar C, Meazza R, Pereno R, Pottin-Clemenceau C, Scudeletti M, Brouty-Boyé D, et al. IL-15 is produced by a subset of human melanomas, and is involved in the regulation of markers of melanoma progression through juxtacrine loops. *Oncogene* 1998;16:2503–12.
- [199] Qin J-Z, Dummer R, Burg G, Döbbling U. Constitutive and interleukin-7/interleukin-15 stimulated DNA binding of Myc, Jun, and novel Myc-like proteins in cutaneous T-cell lymphoma cells. *Blood* 1999;93:260–7.
- [200] Qin J-Z, Zhang C-L, Kamarashev J, Dummer R, Burg G, Döbbling U. Interleukin-7 and interleukin-15 regulate the expression of the *bcl-2* and *c-myc* genes in cutaneous T-cell lymphoma cells. *Blood* 2001;98:2778–83.
- [201] Ruchatz H, Leung BP, Wei X, McInnes IB, Liew FY. Soluble IL-15 receptor α -chain administration prevents murine collagen-induced arthritis: a role for IL-15 in development of antigen-induced immunopathology. *J Immunol* 1998;160:5654–60.
- [202] Smith XG, Bolton EM, Ruchatz H, Wei X, Liew FY, Bradley JA. Selective blockade of IL-15 by soluble IL-15 receptor α -chain enhances cardiac allograft survival. *J Immunol* 2000;165:3444–50.
- [203] Morris JC, Janik JE, White JD, Fleisher TA, Brown M, Tsudo M, et al. Preclinical and phase I clinical trial of blockade of IL-15 using Mik1 β monoclonal antibody in T cell large granular lymphocyte leukemia. *Proc Natl Acad Sci USA* 2006;103:401–6.
- [204] Amlong CA, Nardelli DT, Peterson SH, Warner TF, Callister SM, Schell RF. Anti-interleukin-15 prevents arthritis in *Borrelia*-vaccinated and -infected mice. *Clin Vaccine Immunol* 2006;13:289–96.
- [205] Ferrari-Lacraz S, Zheng XX, Kim YS, Li Y, Maslinski W, Li XC, et al. An antagonist IL-15/Fc protein prevents costimulation blockade-resistant rejection. *J Immunol* 2001;167:3478–85.

- [206] Ferrari-Lacraz S, Zanelli E, Neuberg M, Donskoy E, Kim YS, Zheng XX, et al. 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* 2004;173: 5818–26.
- [207] Rückert, Brandt K, Braun A, Hoymann H-G, Herz U, Budagian V, et al. Blocking IL-15 prevents the induction of allergen-specific T cells and allergic inflammation *in vivo*. *J Immunol* 2005;174: 5507–15.
- [208] Kim YS, Maslinski W, Zheng XX, Stevens AC, Li XC, Tesch GH, et al. Targeting the IL-15 receptor with an antagonist IL-15 mutant/Fc γ 2a protein blocks delayed-type hypersensitivity. *J Immunol* 1998;160:5742–8.
- [209] Baslund B, Tvede N, Danneskiold-Samsøe B, Petersen J, Petersen LJ, Schuurman J, et al. A novel human monoclonal antibody against IL-15 (humax-IL15) in patients with active rheumatoid arthritis (RA): results of a double-blind, placebo-controlled phase I/II trial. *Arthritis Rheum* 2003;(Suppl. S):1706.
- [210] Tinubu SA, Hakimi J, Kondas JA, Bailon P, Familletti PC, Spence C, et al. A humanized antibody directed to the interleukin-2 receptor β -chain prolongs primate cardiac allograft survival. *J Immunol* 1994; 153:4330–8.
- [211] Sun A, Wei H, Sun R, Xiao W, Yang Y, Tian Z. Human interleukin-15 improves engraftment of human T cells in NOD-SCID mice. *Clin Vaccine Immunol* 2006;13:227–34.
- [212] Araki A, Hazama S, Yoshimura K, Yoshino S, Iizuka N, Oka M. Tumor secreting high levels of IL-15 induces specific immunity to low immunogenic colon adenocarcinoma via CD8 $^{+}$ T cells. *Int J Mol Med* 2004;14:571–6.
- [213] Orenge AM, Di Carlo E, Comes A, Fabbi M, Piazza T, Cilli M, et al. Tumor cells engineered with IL-12 and IL-15 genes induce protective antibody responses in nude mice. *J Immunol* 2003;171:569–75.
- [214] Meazza R, Lollini P-L, Nanni P, De Giovanni C, Gaggero A, Comes A, et al. Gene transfer of a secretable form of IL-15 in murine adenocarcinoma cells: effects on tumorigenicity, metastatic potential and immune response. *Int J Cancer* 2000;87:574–81.
- [215] Suzuki K, Nakazato H, Matsui H, Hasumi M, Shibata Y, Ito K, et al. NK cell-mediated anti-tumor immune response to human prostate cancer cell, PC-3: immunogene therapy using a highly secretable form of interleukin-15 gene transfer. *J Leukoc Biol* 2001;69:531–7.
- [216] Yoshida Y, Tasaki K, Miyauchi M, Narita M, Takenaga K, Yamamoto H, et al. Impaired tumorigenicity of human pancreatic cancer cells retrovirally transduced with interleukin-12 or interleukin-15 gene. *Cancer Gene Ther* 2000;7:324–31.
- [217] Lasek W, Basak G, Switaj T, Jakubowska AB, Wysocki PJ, Mackiewicz A, et al. Complete tumour regressions induced by vaccination with IL-12 gene-transduced tumour cells in combination with IL-15 in a melanoma model in mice. *Cancer Immunol Immunother* 2004;53:363–72.