Renal cells express a functional interleukin-15 receptor

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Abstract

Background. Interleukin (IL)-15 is a pleiotropic cytokine known to be involved in graft rejection and to serve as a survival factor for leukocytes and epithelial cells, including renal cells. It utilizes a heterotrimeric receptor complex that consists of the IL-2 receptor βγc subunits (IL-2/15Rβγc) and a unique high-affinity α-chain responsible for IL-15 specificity.

Methods. The cDNA of IL-15Rα main mRNA product was isolated from primary human tubular epithelial cells (TEC) and sequenced. IL-15R expression in TEC and in murine renal tissue was demonstrated using western blotting, ligand binding and flow cytometry. TEC were activated with combinations of IL-15, IL-2 and interferon-γ (IFN-γ), and mRNA and protein levels of IL-15R were determined. Jak–STAT tyrosine phosphorylation was assayed following IL-15 exposure.

Results. The full-length α-chain mRNA bearing exons 1–7 is expressed in TEC. IL-15Rα protein was detected on intact cells by flow cytometry and in extracts of human and mice renal cells using a specific anti-IL-15Rα antibody and by ligand-binding assay. The three subunits of the IL-15R were similarly expressed in cortex and medulla of mice kidney. Stimulation of TEC with IFN-γ upregulated the α-chain while IL-2 and IL-15 had no effect on its expression. A short IL-15 stimulation of TEC induced tyrosine phosphorylation of the main IL-15 signalling molecules (Jak-1, Jak-3, STAT-3 and STAT-5).

Conclusions. Our data demonstrate the presence of a functional IL-15 receptor in the kidney. Since renal cells produce IL-15, this cytokine may have an autocrine/paracrine regulatory role in the kidney.

Keywords: interleukin-15; interleukin-15 receptor; Jak; STAT; tubular epithelial cells

Introduction

Interleukin (IL)-15 is a pleiotropic cytokine known to be involved in a wide range of biological activities, including the activation and proliferation of T cells, differentiation of natural killer cells and secretion of cytokines by neutrophils and macrophages [1]. We have demonstrated previously the production of IL-15 by tubular epithelial cells (TEC) and its upregulation by IFN-γ and CD154 [2,3]. Evidence supporting the involvement of IL-15 in renal pathologies has been implicated by elevated IL-15 mRNA in renal transplant biopsies during acute cellular rejection [4]. In addition, IL-15 was shown to serve as a survival factor for kidney epithelial cells through an anti-apoptotic mechanism in a model of induced nephritis in IL-15-KO mice [5].

IL-15 mediates its biological activities by binding to the specific cell surface receptor IL-15R. IL-15R is composed of three different subunits, referred to as the α, β and common γ chains (γc). The γc-chain is shared with the receptors for IL-2, IL-4, IL-7, IL-9 and IL-21 [1]. Both IL-15 and IL-2 utilize the β and γc chains for signalling, which may explain why these two cytokines possess some redundant biological actions [1]. However, IL-2 and IL-15 sometimes have opposite roles. For example, IL-15 induced a protective effect against T-cell apoptosis mediated by anti-Fas, anti-CD3, dexamethasone and/or anti-immunoglobulin M, while under the same conditions IL-2 promoted apoptosis [6].

The IL-15 receptor α-subunit (IL-15Rα) is a 58–60 kDa type I transmembrane protein that includes an extremely high-affinity binding site (Kd = 10^-11) for IL-15 [1]. The IL-15Rα gene is composed of seven exons. Eight different transcripts corresponding to different combinations and exon deletions have been described.
Of the eight isoforms, two main transcripts can be distinguished by whether or not they contain the exon 2-coding sequence [7]. Exon 2 encodes a Sushi domain, which is a common motif in protein–protein interaction. It has been shown that this Sushi domain is critical for the functional activity of IL-15Rz [8]. The IL-15Rz protein is structurally related to IL-2Rz. However, in contrast to IL-2Rz, which is expressed mainly on leukocytes, IL-15Rz is distributed widely and was shown to be expressed in various cells, such as T cells [1], keratinocytes [9], fibroblasts, epithelial cells and brain tissue [1]. This widespread distribution of IL-15Rz may explain its broad range of effects.

The signalling pathways of IL-15 that are mediated by the β and γc chains involve the activation of Janus kinases (Jak-1/Jak-3) and the STAT factors (signal transducers and activators of transcription) STAT-3/STAT-5. When analysed in activated T cells, Jak-3 and Jak-1 were shown to be coupled functionally to the receptor systems that involve γc. Furthermore, ligand binding to the IL-15 or IL-2 receptor on T cells lead to phosphorylation and nuclear translocation of STAT-3 and STAT-5 [1]. IL-15Rz has been shown to induce Syk kinase activation in activated primary B cells as well as in a human B-lymphoblastoid cell line which expresses IL-15Rz and γc chains, but lacks the β-chain. The activated Syk phosphorylates IL-15Rz and phospholipase Cγ, which co-precipitates with Syk [10]. It has also been demonstrated in a murine fibroblast cell line that IL-15 activates nuclear factor κB and inhibits tumour necrosis factor-α-induced apoptosis by TRAF-2 recruitment to the IL-15Rz chain [11].

Since IL-15 is expressed in renal tissue and affects not only immune cells but also non-immune cells, we suggest that IL-15 may function in an auto/paracrine manner in the kidney. In order for renal tissue to respond to IL-15, it must bear a functional IL-15 receptor. There are several studies which support this idea. For example, Kobayashi et al. [12] found that labelled IL-15, rather than IL-2, significantly accumulates in murine kidneys. IL-15Rz as well as β- and γc-chain mRNA expression have been demonstrated in TEC [5]. Expression of β and γc chains has also been demonstrated using flow cytometry [5,13]. However, the high-affinity α-subunit of IL-15R in the kidney has not been characterized yet at the protein level, nor has its kidney specific isoform been identified. Therefore, the aim of the present study was to characterize the properties of IL-15Rz in the kidney and to demonstrate its function.

Subjects and methods

Mice

The generation and characterization of IL-15Rα−/− mice has been described [14]. B6;129-Il15ra1111Anm2 mice were purchased from JAX Laboratories (Bar Harbor, ME, USA). The 7–8-week-old B6;129-Il15ra1111Anm2 mice and Balb/C mice (Harlan, Jerusalem, Israel) were housed in the animal facility of Soroka University Medical Center (Beer-Sheva, Israel). Animal use conformed to the guidelines established by the Animal Care Committee in our institution.

Cell culture

Primary human cortical tubular epithelial cells (TEC) were prepared from normal cortex tissue of human kidneys from patients with hypernephroma as described previously [3].

Stimulation protocol

TEC were seeded in 25 cm² tissue flasks (Corning) and incubated for 24 h until confluent. Cells were washed and incubated with 2 ml culture medium supplemented with IL-2 (50 U/ml), IL-15 (1 ng/ml), IFN-γ (500 U/ml), a combination of IL-2 with IFN-γ and IL-15 with IFN-γ, or culture medium alone. Incubation time was 24 h for protein detection and 3 and 6 h for mRNA analysis. Experiments were performed on TEC from three different donors and repeated three times for each donor.

Flow cytometry analysis of IL-15Rα

Expression of IL-15Rα on primary TEC was analysed on unstimulated cells or on cells treated with IFN-γ (500 U/ml) for 24 h. TEC were harvested by trypsin–EDTA solution B (Biological Industries, Kibbutz Beit Haemek 25115, Israel), then washed and incubated in 100 μl phosphate-buffered saline (PBS) containing 0.5% bovine serum albumin and 0.05% sodium azide and stained for 1 h with either anti-IL-15Rα (Santa Cruz, Santa Cruz, CA, USA) or with a chimeric human IL-15–murine IgG fusion protein (hIL-15–mIgG) (kindly provided by Prof. Silvia Bulfone-Paus, Borstel, Germany). Incubation with anti-IL-15Rα was followed by staining with fluorescein isothiocyanate-conjugated donkey anti-goat IgG (Jackson Immunoresearch, Pennsylvania, PA, USA) and hIL-15–IgG incubation was followed by biotin conjugated anti-mouse and PE–streptavidin (Zymed Laboratories Inc., San Francisco, CA, USA). The antibodies were diluted to recommended concentrations according to the manufacturers’ instructions. For controls, we used isotype-matched IgG antibody. Analyses were conducted by a flow cytometer (FACS Calibur; Becton Dickinson, Mountain View, CA, USA). Fluorescence data were analysed by the Cell Quest program.

Messenger RNA analysis

Levels of IL-15 receptor subunits α, β and γc chains were determined by reverse transcription–polymerase chain reaction (RT–PCR) of total RNA extracted from TEC. Total RNA was extracted from cells with the RNeasy Mini Kit (Qiagen, Hilden, Germany) and cDNA was prepared as described previously [2].

The three subunits of IL-15R and β-actin cDNA were then amplified by PCR using specific primers. IL-15Rα sense: 5'-GCC GCG GCC ACC ACC CAC AGT AA-3', antisense: 5'-GCC AGC GGG GGA GTT TGC CTT GAC-3'; IL-15Rβ sense: 5'-CAC AGA TGC AAC ATA AGC TTG-3', antisense: 5'-ACT TCA GGA CCT TCT TCA GCC-3'; IL-15Rγ sense: 5'-AGC CCC AGC CTA CCA ACC TCA CT-3',
IL-15R levels were normalized according to corresponding agarose gels and quantified by video densitometry in the different samples.

Amplification, thus, permitting comparison of mRNA levels (15 min initial enzyme activation at 95°C). Standard cycling conditions for this instrument were used on a PCR machine (Corbett-Research, Nortlake, Australia). Reactions were carried out in the Rotor-Gene Real-Time Cleveland, OH, USA) was added to the reaction mixture. 

Mix (ABgene, Surrey, UK). SYBR green I dye (Amresco, USA) and mixed with primers (0.2 mM) and Thermo-Start master mix. 25 cycles for IL-15Rβ, 20 cycles for IL-15Rα, 35 cycles for IL-15Rβ and 30 cycles for IL-15Rγ were in the exponential phase of amplification, thus, permitting comparison of mRNA levels in the different samples.

Eight microlitres of PCR products were analysed on 1.5% agarose gels and quantified by video densitometry (ImageMaster VDS-CL; Amersharm, Freiburg, Germany). IL-15R levels were normalized according to corresponding values of β-actin cDNA.

Quantitative real-time PCR assays were carried out for IL-15Rα chain and β-actin. Templates (7 μl) were diluted 5-fold and mixed with primers (0.2 mM) and Thermo-Start master mix (ABgene, Surrey, UK). SYBR green I dye (Amresco, Cleveland, OH, USA) was added to the reaction mixture. Reactions were carried out in the Rotor-Gene Real-Time PCR machine (Corbett-Research, Northlake, Australia). Standard cycling conditions for this instrument were used (15 min initial enzyme activation at 95°C, then 40 cycles of 95°C for 10 s, annealing temperature according to the primers for 15 s and 72°C for 20 s).

Antibodies and reagents

Anti-hIL-15Rα and biotin-conjugated anti-hIL-15 were purchased from R&D Systems (Minneapolis, MN, USA). The latter does not cross-react with murine IL-15. Anti-mouse/human IL-15Rα (N-19), IL-15Rβ (M-20), IL-15Rγ (M-20), IL-15Rγ blocking peptide, STAT-5 (C-17) and STAT-3 (C-20) were purchased from Santa Cruz. Actin (Ab-1) kit was purchased from Oncogene (Darmstadt, Germany). Horseradish peroxidase (HRP)-conjugated streptavidin was obtained from Zymed (South San Francisco, CA, USA). Secondary antibodies were peroxidase-conjugated F(ab′)2 fragment donkey anti-goat IgG (Jackson, West Grove, PA, USA) and peroxidase-conjugated anti-rabbit (Dako, Glostrup, Denmark).

Immunoprecipitation, immunoblotting and ligand binding

TEC were incubated with 1 ng/ml IL-15 or left untreated as control for 7 min at 37°C. The cells were lysed at 4°C with RIPA buffer (150 mM NaCl, 50 mM Tris-HCl, pH 7.4, 1% NP40, 0.25% Na deoxycholate, 1 mM EGTA, proteinase inhibitor cocktail and phosphatase inhibitor; Sigma, Rehovot, Israel). The cell lysates were incubated with primary antibody for 1 h at 4°C and then with protein A-Sepharose beads (Santa Cruz) for another hour at 4°C. The resulting complex was washed three times with ice-cold PBS, resuspended in sample buffer, denatured by heat and separated through 8% sodium dodecyl sulphate–polyacrylamide gel. Separated proteins were transferred to a polyvinyl difluoride membrane (PVDF; Bio-Rad, Hercules, CA, USA).

The 7–8 week old Balb/C and B6;129-H15razm1Ama mice were sacrificed and their kidneys were removed. The kidneys were cut open and the cortex and medulla were separated carefully. The different parts of the kidney were homogenized in RIPA buffer. The insoluble materials were removed by centrifugation (30 min at 10,000 g at 4°C). Twenty-five microgram aliquots of protein were separated by SDS-PAGE (12% or 7%) and transferred to PVDF membranes (Bio-Rad). The membranes were blocked for 1 h with TBST buffer (20 mM Tris–HCl, pH 7.5, 150 mM NaCl, 0.05% Tween-20) with 5% (w/v) dry skim milk or 4% human serum albumin and then probed with primary antibodies anti-actin (Ab-1), anti-mouse/human IL-15Rα (N-19), IL-15Rβ (M-20), IL-15Rγ (M-20), IL-15Rγ blocking peptide, STAT-5 (C-17) and STAT-3 (C-20) or with 1 ng/ml rhIL-15 (R&D Systems) for 1 h at room temperature. The primary antibody reactions were detected using biotin-conjugated anti-human IL-15 (R&D Systems) and HRP-streptavidin (Zymed) or with other appropriate peroxidase-conjugated antibodies. Following analysis, membranes were stripped and reprobed with a specific primary anti-actin–mlgM antibody (Oncogene) followed by incubation with a secondary antibody. Visualization of specific proteins was conducted using chemiluminescence substrate (Renaissance; PerkinElmer, Waltham, MA, USA). As positive control for IL-15R subunits, protein was extracted from spleen mononuclear cells from Balb/C mice.

Statistical analysis

Results are expressed as means±SE. To compare levels between groups we used analysis of variance. P-values of <0.05 were considered significant.

Results

The IL-15Rα subunit is expressed in murine kidney and in human TEC

To investigate IL-15Rα expression in the kidney, murine kidneys and human TEC were isolated and analysed for IL-15Rα subunit expression. IL-15Rα mRNA was detected in murine kidney (Figure 1). To demonstrate IL-15Rα mRNA expression in human TEC, RT–PCR amplifications were carried out using oligonucleotide primers corresponding to the N-terminal end of exon 1 and the C-terminal end of exon 7 (Figure 2). The main RT–PCR product of 836 bp was sequenced and found to contain the full-length IL-15Rα cDNA, which contains all 7 exons. For mRNA levels analysis, we used a set of primers that produce a main PCR product of 401 bp. This product was sequenced and found to correspond to exons 3–6 of the full transcript containing exons 1–7.
The presence of the IL-15Rα protein in the medulla and cortex of mice kidneys was demonstrated by western blotting. Anti-IL-15Rα antibody revealed in murine renal extracts and in human TEC a major protein of ~60 kDa, comparable in size to the protein detected in spleen mononuclear cells, used as IL-15Rα-positive control (Figure 3A).

The presence of IL-15Rβ and the γc-chain was tested by western blotting in murine medulla and cortex and in human TEC (Figure 3B). We revealed a major product at the expected size of 75 kDa by using an anti-IL-15Rβ antibody and another at the expected size of 60 kDa protein (Figure 3C) in cortex, medulla and TEC by using the anti-IL-15Rγ antibody. No differences could be observed in the expression levels of the three subunits of the IL-15R between the cortex and the medulla.

To test for IL-15 binding proteins in the kidney, we performed ligand-binding assays in both murine extracts and human TEC. Immunoblots of kidney and TEC lysates were incubated with recombinant human IL-15 followed by the detection of IL-15 binding proteins by using anti-human IL-15 antibody. Two major IL-15 binding proteins were detected in renal extracts, one correlated with the 60 kDa protein detected using an IL-15Rα antibody and the second with the 75 kDa protein, which matches the size of IL-15Rβ (Figure 3D). Under the same experimental condition, no product was detected when we omitted IL-15 (data not shown). To further confirm our results we performed the same experiments on kidney extracts from IL-15Rα knockout mice (IL-15Rα−/−). As expected, the 60 kDa product of the α-chain was absent in kidneys of IL-15Rα−/−. IL-15 binding was detected on a 75 kDa protein in both wild-type and IL-15Rα−/− mice (Figure 4A). Since the 75 kDa protein corresponds to the size of IL-15Rβ, it is possible that we detected the low-affinity binding of IL-15 to IL-15Rβ. The possibility that the 60 kDa protein is the α-chain is further supported by its absence in IL-15Rα−/− kidney extract, as demonstrated by anti-IL-15Rα antibody (Figure 4B).

**IL-15Rα is upregulated by IFN-γ in TEC**

We tested the effect of IL-15, IL-2 and IFN-γ on mRNA levels of IL-15R subunits in human primary TEC. IFN-γ was also examined in combination with IL-2 or IL-15. Initially, we analysed the receptor subunits by semi-quantitative PCR and found that IFN-γ induced a 2-fold increase in expression levels of IL-15Rα, but not in IL-15Rβ and IL-15Rγ chains (Figure 5A). IL-2 and IL-15, however, did not affect
IL-15Rα levels, whether administered alone or in combination with IFN-γ. These results were confirmed by real-time PCR and revealed comparable results (Figure 5B). Protein levels of IL-15Rα were also upregulated by IFN-γ while IL-15Rβ and IL-15Rγ chain levels were unaffected (Figure 6). Membrane expression of IL-15Rα by flow cytometry (Figure 7) revealed the presence of IL-15Rα on intact quiescent TEC membranes. Following IFN-γ stimulation, TEC labelled with IL-15 fusion protein (hIL-15-mIgG) exhibited an 80% increase in their net mean fluorescence. Similar results were obtained by flow cytometry using an anti-IL-15Rα antibody (data not shown).

**IL-15 induces Jak/STAT activation in TEC**

Jak-1/Jak-3 and STAT-3/STAT-5 are known to mediate IL-15 signalling pathways in lymphocytes [1]. We stimulated TEC with IL-15 and immunoprecipitated Jak-1/Jak-3 and STAT-3/STAT-5 from cell lysates. We then performed western blotting using an anti-phosphotyrosine antibody (Figure 8A) and found that IL-15 induced Jak-1/Jak-3 and STAT-3/STAT-5 tyrosine phosphorylation. Uniform loading of STAT-3 and STAT-5 was confirmed by western analysis of the same blots (Figure 8B). We could not confirm equal loading of Jak-1 and -3, since the antibodies used for immunoprecipitation were not suitable for western analysis of denatured proteins. However, we did observe strong tyrosine phosphorylation signalling on Jak molecules following IL-15 stimulation.

**Discussion**

We characterized the specific, high-affinity IL-15Rα in the kidney and also demonstrated the presence of a major IL-15 binding protein with a molecular weight of 60 kDa and an mRNA transcript that includes the full-length IL-15Rα sequence containing exons 1-7. Our results indicated that all three IL-15R subunits are expressed constitutively in the cortex and medulla of murine kidneys and in primary cultures of human TEC. In addition, we demonstrated that the IL-15R in the kidney is functional, since IL-15 binding induced typical IL-15R signalling.

IL-15Rα expression was depicted using different techniques. We performed a ligand-binding assay, in which we incubated the membranes of murine kidney lysates with IL-15 and then probing for IL-15 with a specific antibody. This assay revealed two major IL-15 binding proteins in wild-type mice: a 75 kDa protein and an ~60 kDa protein. In contrast, IL-15Rα–/– mice exhibited only the 75 kDa protein. This 75 kDa protein was undetectable when stripping and reprobing the blots with an anti-IL-15Rα antibody. Since IL-15Rβ is a 75 kDa protein, we suggest that the 75 kDa IL-15 binding protein found here is the β-chain of the IL-15R. This suggestion is supported by a report which...
demonstrated low-affinity IL-15 binding by the β-chain [14].

We examined the regulatory effect of IFN-γ, IL-15 and IL-2 on the expression of the three IL-15R subunits in TEC. In contrast to IL-15 and IL-2, which had no apparent effect on IL-15R subunits, IFN-γ induced a 2-fold increase in mRNA and protein levels of the specific high-affinity IL-15R α-chain. On the other hand, IFN-γ did not alter the expression of IL-15Rβ and IL-15Rγ chains. The inducible effect that IFN-γ exerts on both IL-15 [3] and its receptor can be explained by the presence of IFN regulatory factor response elements (IRF-E) on both the promoter of IL-15 and IL-15Rα genes [15]. This upregulation of both IL-15Rα and its ligand by the same factor in TEC suggests that IL-15 has an autocrine/juxtacrine activity in the kidney.

Induction of IL-15 and IL-15Rα expression may be significant in the context of allograft rejection, acting as a graft-derived recruiter and supporter of the immune system. On the other hand, because IL-15 signalling also mediates anti-apoptotic effects, an increase in IL-15 signalling may render renal cells more resistant to T cell-induced apoptosis. However, it has been shown that IL-15 expression correlates with acute graft rejection, as demonstrated in biopsies from rejected human renal grafts [4] and that IL-15-Rα or IL-15Rβ blockers and IL-15 antagonists inhibit allograft rejection (reviewed in [16]). Consequently, during acute rejection, IL-15 may function more as an immunostimulatory mediator than as an anti-apoptotic mediator.

Binding to IL-15Rα was not only evident in whole cell lysates of TEC but also on intact TEC membranes, as demonstrated by the binding of a chimeric fusion protein composed of human IL-15 and murine IgG (hIL-15–mIgG) to TEC. Similar to our findings in mRNA and protein from whole cell lysate, we found that the outer TEC membrane exhibits both basal and IFN-γ-induced binding of hIL-15–mIgG. This increase is similar in magnitude to that detected by ligand binding to IL-15Rα. In our experimental system, IL-15Rα was the only regulated subunit of the IL-15 receptor complex. Its extremely high affinity to IL-15 makes it relevant as a limiting factor for IL-15 binding. We now emphasize the fact that since the other subunits are shared by other receptors, it may be implied that the specific regulation of IL-15 signalling would most likely be due to IL-15Rα levels.

An additional indication for the importance of IL-15Rα inducibility was described by Dubois et al. [17], who showed that IL-15 and IL-15Rα can form stable complexes on the surface of activated monocytes, by which the IL-15/IL-15Rα complex is presented to neighbouring cells that bear the intermediate affinity IL-15Rβγ. This creates a complete and potent IL-15R complex in a juxtacrine manner. Supporting this possibility is a recent publication showing that trans-presentation of IL-15 by IL-15Rα on bone marrow-derived cells mediates the basal proliferation of memory CD8+ T cells [18] and that a population of infiltrating CD8+ T cells express IL-15Rα receptor during acute rejection [19]. Based on these findings, renal cells might present the IL-15/IL-15Rα complex...
to neighbouring cells or infiltrating leukocytes. Thus, the induction of IL-15α may promote local IL-15 activity in neighbouring cells.

We also examined the downstream events of IL-15 ligation in TEC. Short exposure to IL-15 induced tyrosine phosphorylation of Jak-1 and Jak-3 and transcription factors STAT-3 and STAT-5, indicating that the signalling pathway of IL-15 is functional in renal cells. The presence of a functional IL-15 receptor complex in the kidney raises the question of its role there. One possibility is that it eliminates local IL-15 in order to prevent its unwanted systemic effect. However, if this were the case, the presence of IL-15Rα would suffice and there would be no need for IL-15β and IL-15γ signalling, which are functional in TEC. Another possible role is its regulation of the apoptotic threshold. IL-15 has been identified as a survival factor for different cell types, e.g. keratinocytes [9], fibroblasts [11], hepatocytes [6] and haematopoietic cells, such as T cells, B cells, neutrophils, natural killer cells and mast cells [1,20]. In support of this idea, the recent study of Shinozaki et al. [5] showed that TEC of IL-15<sup>−/−</sup> mice are highly susceptible to anti-Fas and actinomycin D induced apoptosis. They also demonstrated that kidneys from IL-15<sup>−/−</sup> mice were substantially sensitive to cell-dependent immunological insult.

It is possible that basal IL-15 and IL-15R levels in the kidney increase the apoptotic threshold of TEC. This protection against apoptosis by IL-15 might be specifically important for renal cells, since they are continuously exposed to toxic inducers of apoptosis and extreme pH conditions. In addition, IL-15 may be involved in renal immune responses by supporting and activating T cells during immune reactions. It has been shown that levels of IL-15 mRNA are significantly high in biopsies from acutely rejected renal transplants in patients [4]. Therefore, during an immune response, a positive feedback loop between the kidney parenchyma and the lymphocyte infiltrate can progress. Specifically, it has been shown that IL-15 expression in TEC is upregulated by IFN-γ and CD40 ligand (CD40L) [3], which are the products of activated T-helper cells and mononuclear cells, respectively.

In summary, the presence of both IL-15 and its complete and functional receptor in the kidney, as well as their upregulation by immune mediators suggest that IL-15 is an important mediator in both renal physiology and pathology. On the one hand, during normal renal physiological functions, the anti-apoptotic effect of IL-15 and its receptor may help overcome renal damage caused by extreme physiological conditions. On the other hand, during inflammation IL-15 acts as a pro-inflammatory cytokine that supports lymphocyte proliferation and activation. In such cases, it is important to try to find a way of blocking IL-15/IL-15R. Undoubtedly, the mechanism of the anti-apoptotic effects of IL-15/IL-15Rα and the means to upregulate IL-15 signalling are important issues that need to be investigated further in relation to renal damage.

In conclusion, IL-15 and its receptor may have an important role within a variety of normal and pathological conditions of the kidney.

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