FINAL REPORT

„Role of cytokines of IL19 subfamily in the pathomechanism of chronic renal disease”

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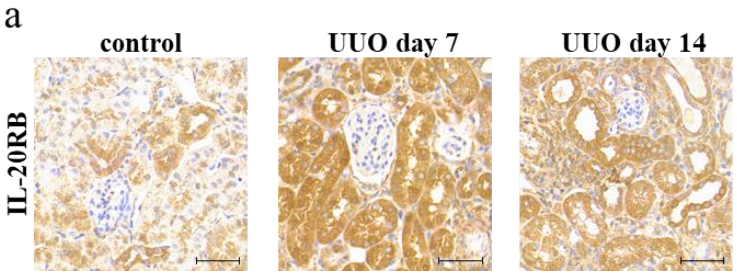
INTRODUCTION

Prevalence of chronic kidney disease (CKD) is estimated to be 8-16% worldwide, and rapidly increasing. The key risk factors of CKD are the chronic civilization diseases including hypertension, diabetes mellitus and autoimmune diseases but acute kidney injury can also lead to long-term renal damage. Despite the growing medical importance the pathomechanism of CKD is still not fully understood. The progression of CKD is characterized by the loss of renal cells and their replacement by extracellular matrix (ECM), independently of the associated disease. Recently, connection between IL-20 subfamily of cytokines including IL-19, IL-20 and IL-24 and tissue remodeling has been proposed but little is known about their involvement in development of renal diseases. Therefore, in the framework of this OTKA project we investigated the role of IL-20 subfamily cytokine in CKD.

MAIN RESULTS

Presence of IL-20RB in the kidney of mice underwent UUO and in human renal biopsies.

Previously, our research group identified *Il19* and *Il24*, the members of IL-20 subfamily, as one of the most abundantly expressed genes in the kidneys of new-born rats underwent unilateral ureteral obstruction (UUO). Within the subfamily IL-19, IL-20 and IL-24 form a distinct group as they exert their biological activity by binding to IL-20RA/IL-20RB and IL-22RA/IL-20RB receptor heterodimers. We demonstrated the presence of IL-20RB, the common subunit of the receptor heterodimers on tubular epithelial and glomerular cells of mice underwent UUO and also in human kidney biopsies of patients with CKD of different aetiology, including diabetic or IgA nephropathy and lupus nephritis. IL-20RB is a critical component of the receptor heterodimers, since it is responsible not only for ligand binding but also for the dimer formation and thus the biological activity of the receptors.



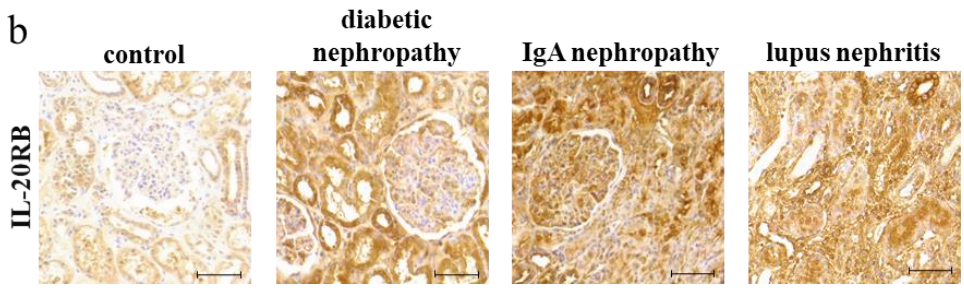
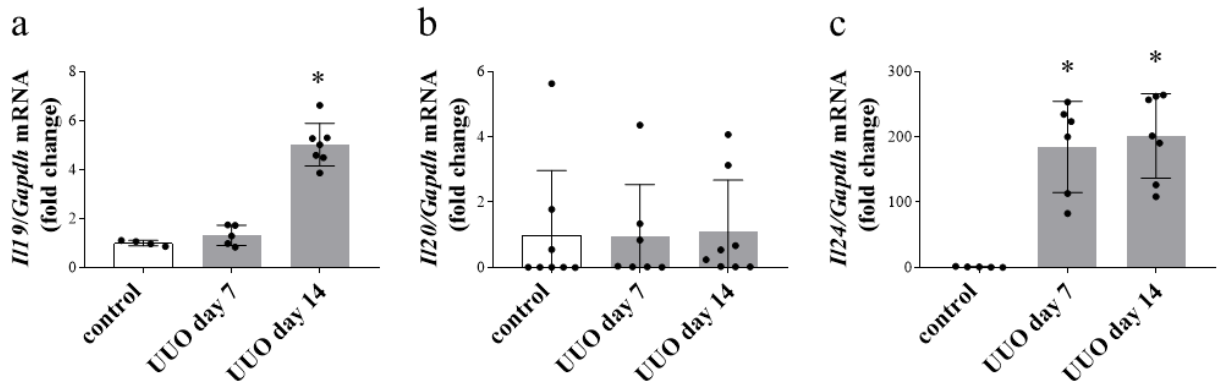


Figure 1. Localisation IL-20RB (d) was determined by immunohistochemical staining (brown) in the kidney of mice underwent UUO (a) and in that of controls or in kidney biopsy samples obtained from controls and patients with diabetic or IgA nephropathy and lupus nephritis (b). Scale bar: 50 μm (d).

Expression of *Il19, Il20* and *Il24* in the kidneys derived from different models of renal diseases

In line with our previous study on new-born rats we found markedly increased expression of *Il19* and *Il24* in kidneys of adult mice after the onset of UUO. We also demonstrated increased renal expression of *Il19*, *Il20* and *Il24* in ischemic reperfusion injury (I/R) induced rat model of acute renal failure and in streptozotocine (STZ) induced rat model of diabetic nephropathy, as well. However, only the renal expression of IL-24 increased in the mice model of lipopolysacharide (LPS) induced acute kidney injury. These *in vivo* experiments further strengthened the hypothesis about the unified importance of the investigated cytokines in the different renal pathologies leading to CKD.



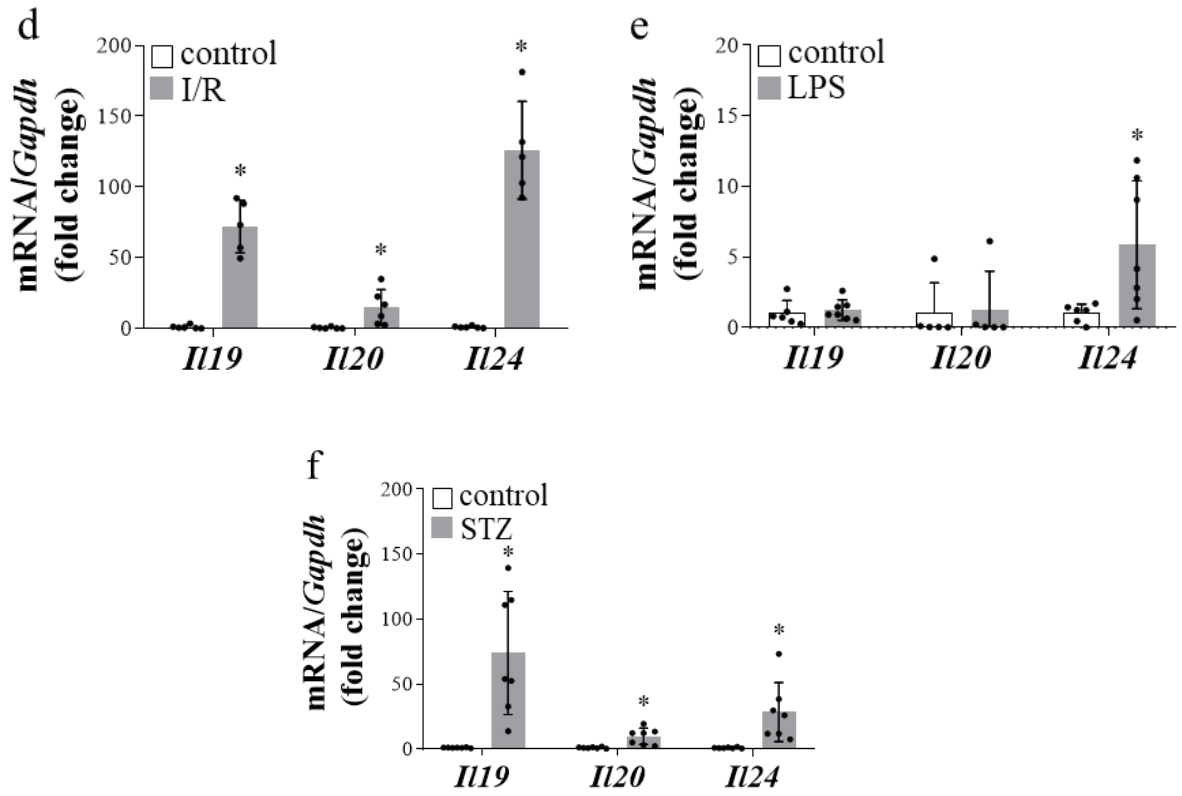


Figure 2. Renal mRNA expression of *Il19, Il20* and *Il24* of mice with UUO (a-c), I/R (d) or LPS (e) induced acute kidney disease or that of rats with STZ (f) induced diabetic was determined by real-time RT-PCR in comparison with glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) as internal control. Results were normalized over the mean for each experiment. *p<0.05 vs. control.

Effect of fibrosis related factors on the expression of *IL19 IL20* and *IL24* of PBMCs

Based on the literary data peripheral blood mononuclear cells (PBMCs), including monocytes and macrophages are the main source of IL-20 subfamily cytokines, however the factors regulate synthesis IL-19, IL-20 and IL-24 have not been previously clarified. Therefore, in the present study we investigated the role of those factors, including TGF-ß1, PDGF-B, IL-1ß, H_2O_2 and LPS, which play a central role in the pathomechanism of renal diseases.

We found that oxidative stress and LPS treatment increase the expression of *IL19, IL20* and *IL24* of PBMCs originated from healthy adults. On the other hand we found that core factors of tissue remodeling, including TGF-ß1 and PDGF-B decreased the *IL24* expression of healthy PBMCs. Interestingly, the regulation of the investigated cytokines showed different pattern in the PBMCs of patient with diabetic nephropathy. While the expression of IL-19 was increased

by several factors, including TGF-ß1, IL-1ß, LPS and H_2O_2, the expression of IL-20 or IL-24 remained mainly unchanged, only LPS treatment induced the expression of IL-24. Of particular interest is the response of PBMCs of different origin to TGF-β1 treatment. While TGF-β1 or PDGF-B treatment decreased the expression of IL-24 of healthy PBMCs, TGF-β1 increased the synthesis of IL-19 in the PBMCs of CKD patients. Our results demonstrate that PBMCs are capable to increasingly produce the cytokines of IL-20 subfamily in response to mediators of renal disease, however there is a clear difference between PBMCs of healthy adults and that of patients with CKD, which may be due to previous activation of the PBMCs originated from patients with CKD.

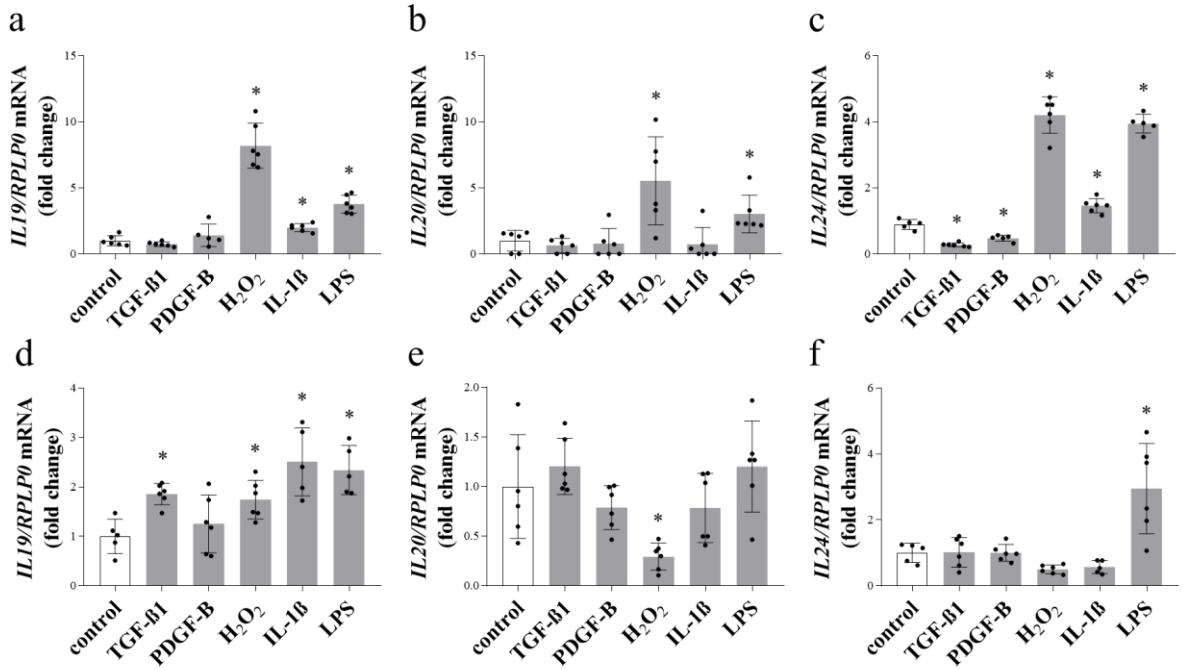
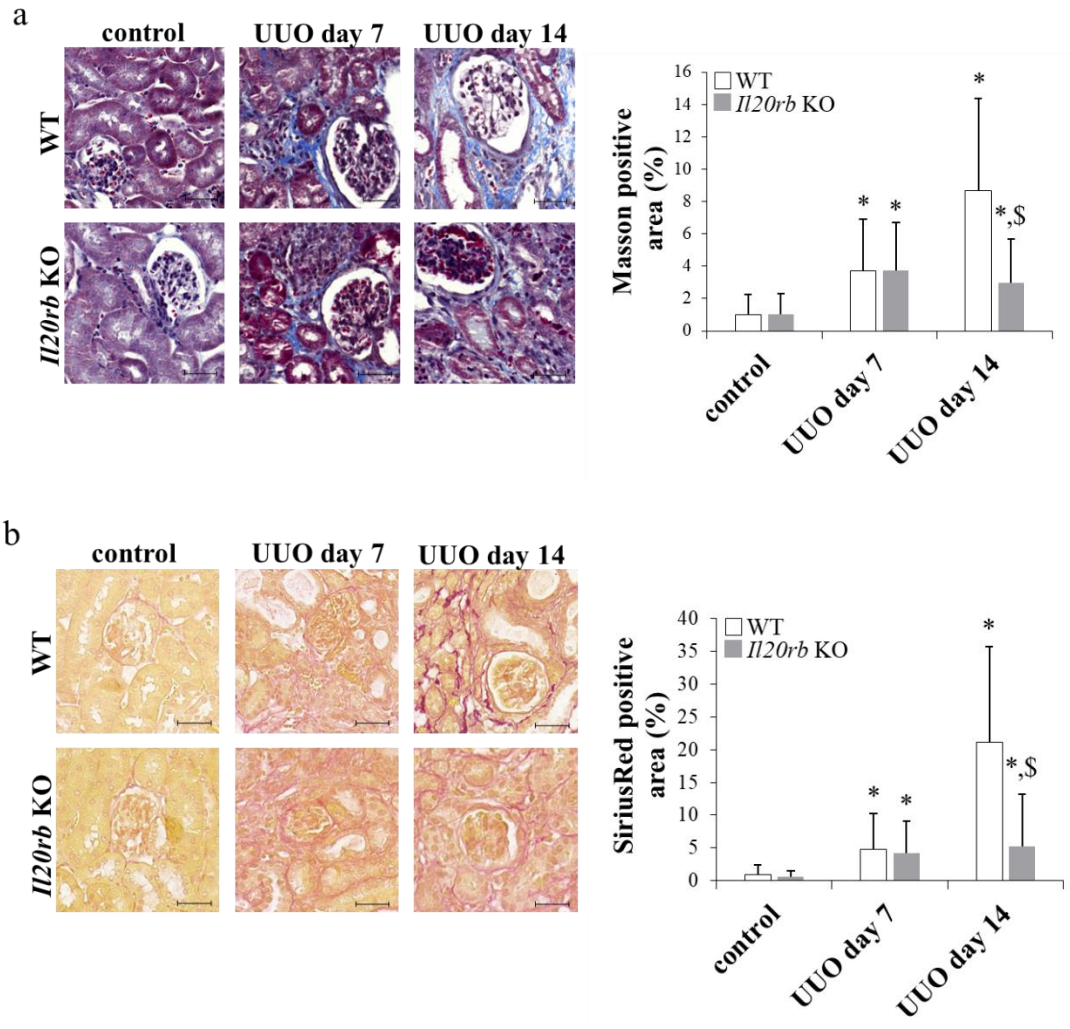


Figure 3. The mRNA expression of *IL19*, *IL20* and *IL24* in healthy (a, b and c) and CKD-derived PBMCs (d, e and f) was measured by real-time RT-PCR in a comparison with *RPLP0* as internal control. Results were normalized over the mean for each experiment. *p<0.05 vs. control.

Alteration of the markers of fibrosis in the kidney of WT and *Il20rb* KO mice

In the next set of experiments the effects of the investigated cytokines were further studied in mice lacking IL-20RB. Indeed, we found that protein level of α-SMA, which is a marker of the myofibroblasts (MFs), is lower in kidneys of *Il20rb* KO (kindly provided by Franz Oswald) compared to that of WT mice following UUO. The amount of α-SMA is proportional with the number of MFs, which are responsible for the increased production of ECM in the fibrotic

tissues. Accordingly, we found less increased ECM depositions in the kidneys of *Il20rb* KO than in that of WT mice underwent UUO, suggesting the pro-fibrotic role of the investigated cytokines. Our results are in line with the previous observations implying the role IL-19 in intestinal and the role of IL-24 in liver fibrosis and wound healing. Moreover, Van belle *et al.* who found that genetic deficiency of *Il20rb* resulted in less sever contact dermatitis, which is characterised by increased collagen depositions. Investigating the underlying molecular mechanisms we found decreased expression of *Tgfb1, Pdgfb* and *Ctgf*, the core factors of renal fibrosis, in the kidneys of *Il20rb* KO compared to WT mice underwent UUO. All these growth factors play well-known role in the regulation of tissue remodeling. TGF-ß1 and CTGF promote MF differentiation and induce the excessive production of ECM components, including collagens and fibronectin. Similarly, PDGF-B is mitogenic growth factor inducing proliferation of MFs. Therefore it's easy to accept that decreased deposition of ECM is closely related to the decreased amount of the investigated growth factors in *Il20rb* KO compared to WT mice.



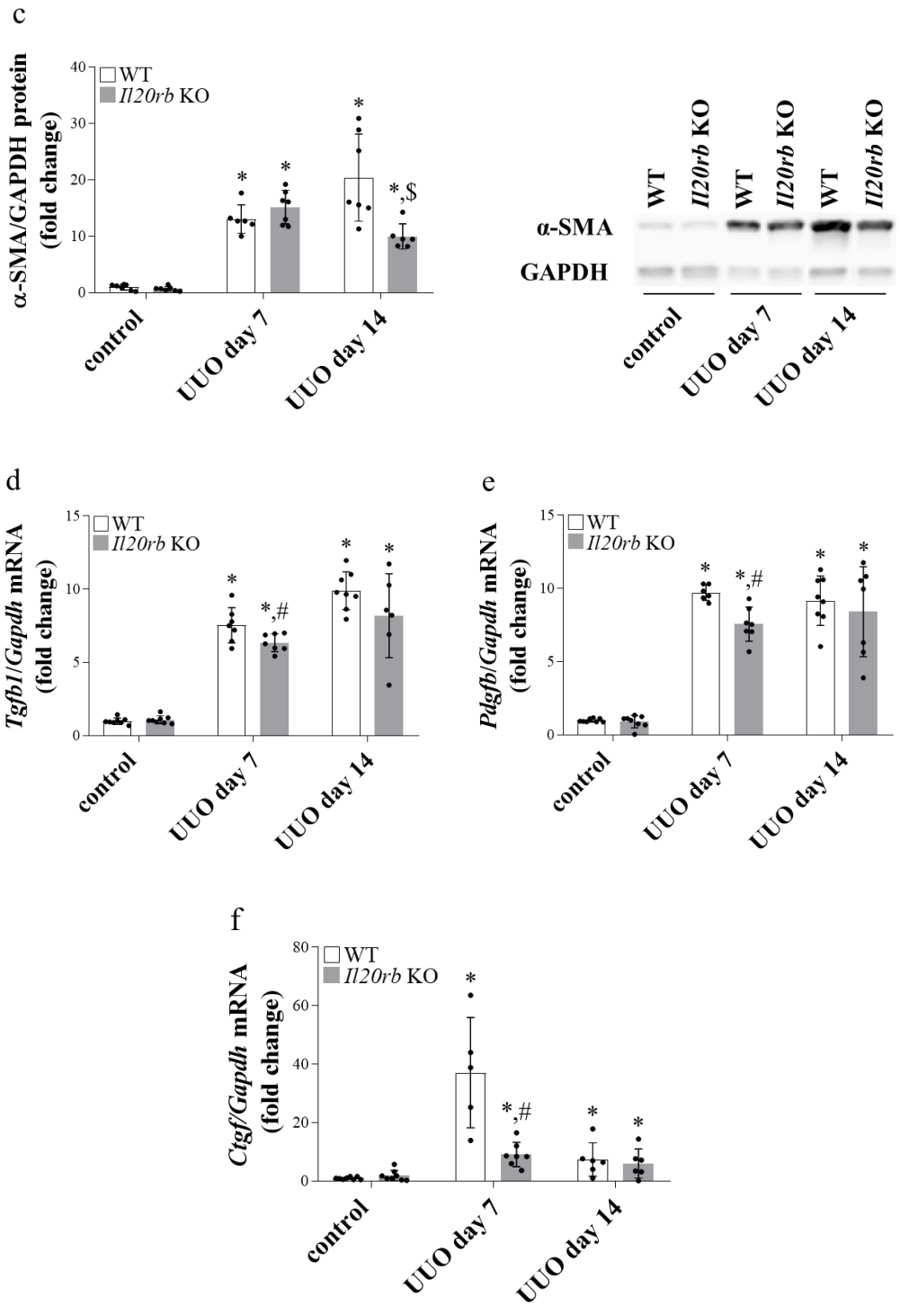
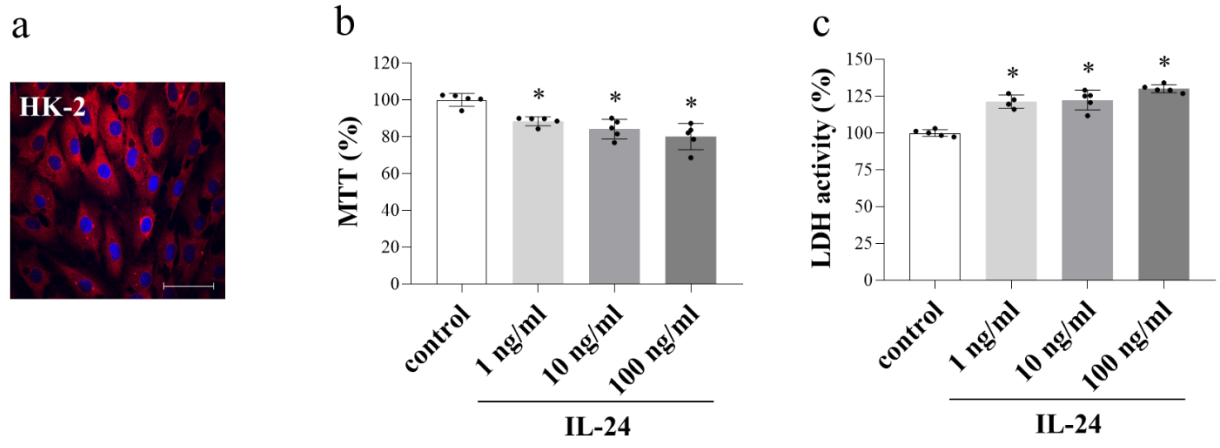


Figure 4. The red areas of the Masson's trichrome and blue areas of the SiriusRed stained kidney sections represent the collagen deposits of WT and *Il20rb* KO mice following the onset of UUO (Figure 3/a and b). Protein amount of *α-SMA* in kidney tissue of WT and *Il20rb* KO mice after UUO was measured by Western blot analysis in comparison with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as internal control (c). The renal mRNA expression of *Tgfb1* (d) *Pdgf* (e) and *Ctgf* (f) in kidney tissue of WT and *Il20rb* KO mice was determined by

real-time PCR in comparison with *Gapdh* as internal control. Results were normalized over the mean for each experiment. $^{*}p<0.05$ vs. control; $^{\#}p<0.05$ vs. WT UUO day 7; $^{\$}p<0.05$ vs. WT UUO day 14. Scale bar: 50 μm (a, b).

Effect of IL-24 treatment on the viability and pro-fibrotic growth factor production of HK-2 cells

Since IL-20RB is markedly present on renal tubular epithelial cells of different human biopsies and also on that of mice underwent UUO our further *in vitro* experiment were performed on HK-2 tubular epithelial cells expressing IL-20RB. In these experiment we focused to the effects of IL-24 the renal expression of which increased in the greatest extent in our *in vivo* experiments. We found that IL-24 treatment induce death of HK-2 cells in dose dependent manner as revealed by the MTT and LDH assays. Previously, the apoptosis inducing ability of IL-24 was thought to be specific to cancer cells only, however in line with our present experiment Hsu and Li *et al*., demonstrated that members of the subfamily including IL-19 and IL-20 induce apoptosis of HK-2 kidney epithelial and also M1 cortical duct cells. In their study they hypothesised a potential pro-fibrotic role of IL-19 and IL-20 based on their *in vitro* TGF-ß1 inducing ability in M1 and HK-2 cells. Similarly, we found that IL-24 treatment not only induces the TGF-ß1, but also the PDGF-B and CTGF expression of HK-2 tubular epithelial cells *in vitro*.



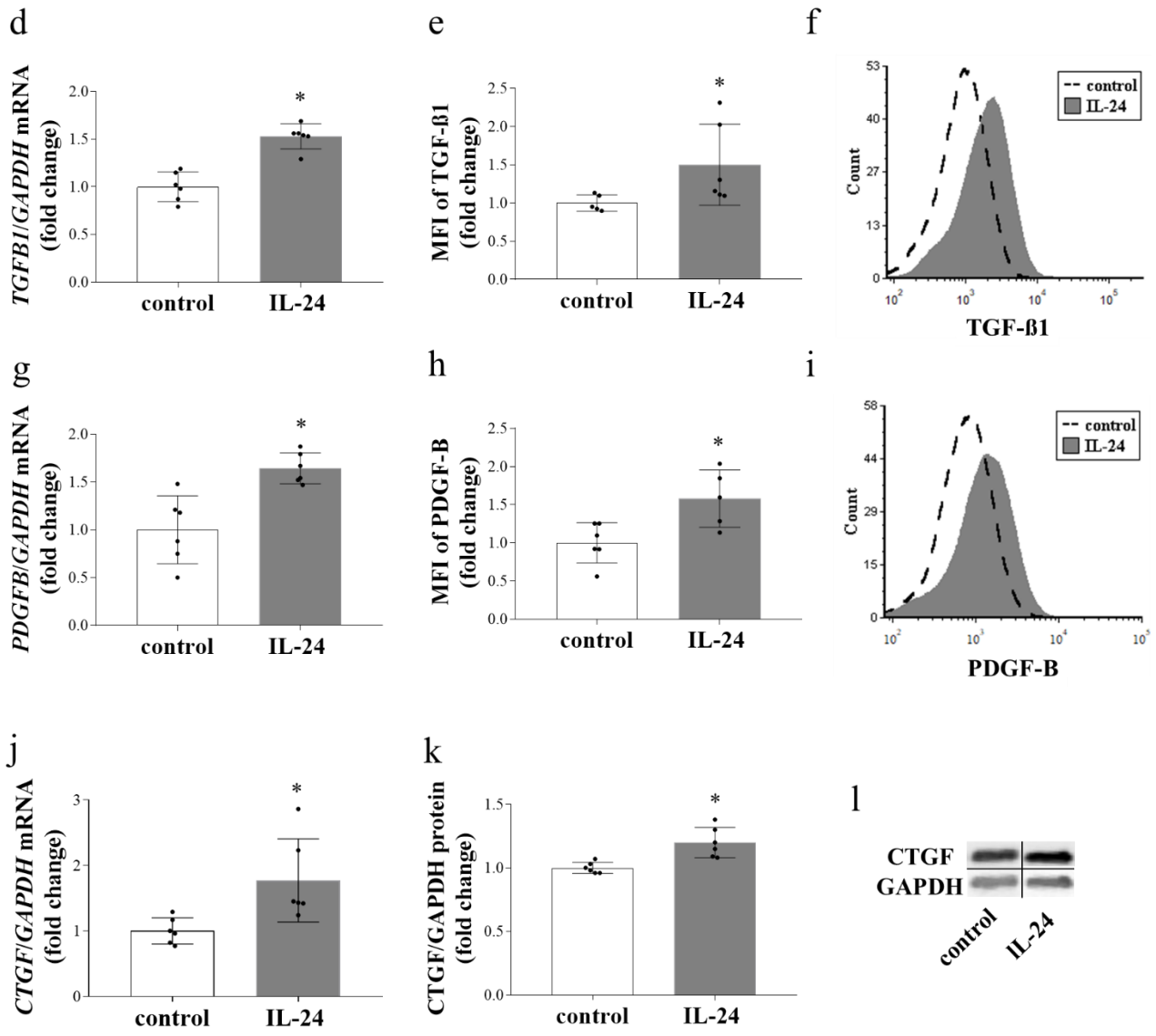


Figure 5. Effect of IL-24 treatment on HK-2 cells. Presence of IL-20RB (red) was determined by immunofluorescence staining on HK-2 cells (a). Cell nuclei were counterstained with Hoechst 33342 (blue). Cell viability was determined by MTT (b) and LDH (c) assays. The mRNA expression of TGFB1 (d) PDGFB (g) CTGF (j) after IL-24 treatment (100ng/ml) was measured by real-time RT-PCR in comparison with GAPDH as internal control. The protein level of TGF-ß1 (e, f) PDGF-B (h, i) after IL-24 treatment (100ng/ml) was measured by flow cytometry (g-h). The protein level of CTGF (k, l) after IL-24 treatment (100ng/ml) was measured by Western blot analysis in comparison with GAPDH as internal control. The results were normalized over the mean for each experiment. *p<0.05 vs. control; Scale bar: 50 µm (a).

OTHER RESULTS

Our knowledge about the role of IL-20 subfamily of cytokines in the pathomechanism of tissue remodeling is very limited, therefore to strengthen our observations regarding the injured kidney we also investigated the significance of the explored IL-24 related processes in the pathomechanism of intestinal remodeling, as well. We studied the role of IL-24 in the pathomechanism of inflammatory bowel disease (IBD) and in that of celiac disease (CD), as well. Indeed, the focus of our studies was to investigate the effect of IL-24 on the behaviour of the epithelial cell in all three studies.

Role of IL-24 in the maintenance of the epithelial integrity in the duodenal mucosa of IBD patients.

Finally, we also investigated the role of IL-24 in the pathomechanism of IBD. Our *in vivo* experiments using wild type and IL-20RB KO mice demonstrated that the IL-20 subfamily of cytokines significantly influence the activity of the DSS induced colitis of mice. Moreover, our data suggested that IL-24 may influence the IBD-associated tissue remodeling. Indeed, in accordance with our previous results on HK-2 renal tubular epithelial cells, we demonstrated that IL-24 induce the synthesis of TGF-β1 and PDGF-B of the colonic enterocytes *in vitro* and also that of the colonic mucosa *in vivo*. Similarly, we demonstrated that IL-24 enhance the expression of MMP-2 and-9 and also TIMP-1 and -2 of colon fibroblast further supporting the role of IL-24 in the remodeling of the inflamed colon. Currently anti-TNF drugs play a central role in the therapy of patients with IBD, however a significant number of the patients lose their sensitivity or do not respond to the therapy. Therefore, the better understanding of the molecular process of IBD may finally contribute to the identification of new drugs that can complete the current therapeutic options to treat IBD.

Role of IL-24 in the maintenance of the epithelial integrity in the duodenal mucosa of CD patients.

We demonstrated an increased expression of IL-24 in the duodenal mucosa of therapy naive children with celiac disease (CD), indicating its role in the disease pathomechanism. We described the regulatory role of IL-1ß, TNF-α, TGF-ß and IL-17 on the IL-24 production of FHs74Int duodenal epithelial cells, pdMFs and PBMCs. We showed that IL-24 can protect epithelial cells against oxidative damage, thus it may facilitate the maintenance of epithelial integrity. IL-24 also inhibited the proliferation of pdMFs and altered their stress fiber organization, thereby suggesting its role in the reconstitution of normal epithelial structure and

mucosal integrity. These results may contribute to the better understanding of the pathomechanism of CD and to the development of new therapeutic approaches.

SUMMARY

In the project we demonstrated the increased production of IL-19, IL-20 and IL-24 in the kidney samples from the different animal models of acute and chronic kidney disease. We also shown the presence of IL-20RB in the biopsy specimens of patients with lupus nephritis, IgA and diabetic nephropathy. Furthermore, we demonstrated the role of IL-20RB on the renal fibrosis *in vivo*. Moreover, our experiments described the role of IL-1ß, TGF-ß, PDGF-B, LPS and oxidative stress on the synthesis of IL-19, IL-20 and IL-24 of PBMCs. Finally, we have also shown the effect of IL-24 on the viability and TGF-ß, PDGF-B and CTGF production of the renal tubular epithelial cells *in vitro* and *in vivo*. Our observations suggest that increased IL-24 production of the immune cells activate the IL-20RB associated signalling pathway in the kidney leading to increased epithelial cell death and improved synthesis of pro-fibrotic factors. We hope that our work may contribute to the better understanding of the pathomechanism of CKD and to the development of new therapeutic approaches, which can help to treat or hinder kidney CKD.

PhD thesis in the framework of this OTKA project

- Domonkos Pap: „The role of IL-20 cytokine subfamily in the pathogenesis of kidney fibrosis" (2018)

PhD thesis that are in progress in the framework of this OTKA project

- Réka Rokonay: Role of IL-24 in the mucosal remodeling of children with coeliac disease (2020)
- Anna Ónody: Role of the IL-24 in the pathomechanism of IBD-associated tissue remodelling

Manuscripts under revision in the framework of this OTKA project

- Réka Rokonay, Apor Veres-Székely, Beáta Szebeni, Domonkos Pap, Rita Lippai, Nóra Béres, Andrea Fekete, Gábor Veres, Attila J. Szabó, Ádám Vannay. Role of IL-24 in the mucosal remodeling of children with coeliac disease
  -Under second revision at Journal of Translational Medicine-

Manuscripts prepared for publication in the framework of this OTKA project

- Domonkos Pap, Apor Veres-Székely, Beáta Szebeni, Réka Rokonay, Rita Lippai, István Márton Takács, Csenge Pajtók, András Tislér, Orsolya Cseprekál, Magdolna Kardos, Franz Oswald, Andrea Fekete, Attila J. Szabó, Ádám Vannay**.** Characterization of IL-19, -20 and -24 in acute and chronic kidney diseases reveals a pro-fibrotic role of IL-24
- Anna Ónody, Apor Veres-Székely, Erna Sziksz, Domonkos Pap, Réka Rokonay, Franz Oswald, Gábor Veres, Nóra Béres, Áron Cseh, Attila J. Szabó, Ádám Vannay. Role of the interleukin-24 in the pathomechanism of IBD-associated tissue remodeling

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