Introduction and Aims: Endothelial progenitor cells (EPCs) are bone marrow-derived precursors known to reverse acute kidney injury (AKI) by paracrine mechanisms including the release of extracellular vesicles (EVs), small particles playing a role in intercellular communication through the transfer of proteins and RNA. Activation of the complement cascade in tubular epithelial and endothelial cells mediates kidney ischemia-reperfusion injury (IRI). The aim of this study was to evaluate whether the protective role of EPC-derived EVs in kidney IRI may be associated with complement inhibition.

Methods: EPCs were isolated from peripheral blood and EVs characterized by size, protein and RNA content. We evaluated the effects of EVs in a rat model of kidney IRI and in vitro in human tubular epithelial and endothelial cells cultured in hypoxia.

Results: EPC-derived EVs sized 60-130 nm and carried different subsets of mRNAs and microRNAs able to modulate cell proliferation and apoptosis. By RT-PCR, we found within EVs mRNAs coding for the complement inhibitors factor H, DAF and CD59. After i.v. infusion, EVs localized within peritubular capillaries and tubular cells exerting morphologic and functional protection from AKI by reducing tubular cell apoptosis and leukocyte infiltration. EV administration reduced C5b9 deposition and enhanced the expression of factor H, DAF and CD59 in the ischemic kidney. The reprotective effect of EVs was reduced after their treatment with RNase able to decrease mRNA expression of all complement inhibitors. In vitro, EVs reduced hypoxia-induced apoptosis of tubular epithelial and endothelial cells by decreasing the complement-dependent C5b9 activation and by up-regulating the expression of factor H, DAF and CD59, thus confirming the in vitro data. The role of factor H, DAF and CD59 mRNA transfer to injured renal cells was inferred by experiments using RNase-treated EVs or EVs released from EPCs engineered to knock-down all complement inhibitors by specific siRNA.

Conclusions: EPC-derived EVs protect the kidney from ischemic AKI by delivering mRNAs coding for factor H, DAF and CD59 to injured tubular epithelial and endothelial cells. These results confirmed previous data on the relevance of complement inhibition after kidney IRI and suggest the potential use of EPC-derived EVs as therapeutic option to avoid delayed graft function after kidney transplantation.

Introduction and Aims: Ischemia-reperfusion injury has been associated with the incidence of both acute and chronic rejection. To further characterize the protective effects, we treated the animals with tobramycin, an antibiotic known to reduce antibody-mediated injury, and observed the effects on renal function and morphology.

Results: Compared to scrambled controls, serum urea and creatinine levels were lower in treated groups. The histopathological analysis illustrated a successful treatment. The results suggest that tobramycin is a potential therapeutic agent for ischemia-reperfusion injury.

Conclusions: The findings of this study support the use of tobramycin as a potential therapeutic agent for ischemia-reperfusion injury.

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Results: Three miRNAs (miR-21, miR-17-5p and miR-106a) were significantly elevated in IR injury after 24 hours of reperfusion (3.0, 1.5 and 1.4 fold, respectively, p<0.05). Real-time PCR analysis demonstrated, that these miRNAs started to elevate after 24 hours of reperfusion, in the maintenance phase, further increasing at 48 hours (miR-21: 2.3 fold, p<0.01; miR-17: 2.2 fold, p<0.01; miR-106a, 1.9 fold, p<0.01). After sublethal ischemia miRNA levels normalized together with kidney damage markers in the recovery phase.

Conclusions: We identified three miRNAs with altered expression in the maintenance phase of IR injury. Validated targets of the identified miRNAs have mostly pro-apoptotic effects. Therefore our results suggest that these miRNAs may be involved in the regeneration processes and could represent possible therapeutic tools in the treatment of ATN. Support: OTKA: K81972, NF69278; ETT: 011-07/2009.

Introduction and Aims: The protective role of a novel pathway, the Sigma-1 receptor (S1R)-Akt-endothelial nitrogen monoxide synthase (eNOS) axis has been recently described in heart ischemia/reperfusion (IR) injury. In renal IR we previously showed that S1R agonists are protective, however the exact mechanism is still unknown. Here in renal IR we studied the effect of S1R agonist flavoxamine (FLU) and antagonist NE-100 on the S1R-Akt-eNOS signaling pathway.

Methods: Male Wistar rats were treated i.p. with FLU (20 mg/bwkg; FLU), FLU and NE-100 (20 mg/bwkg and 1 mg/bwkg; FN) or vehicle (VEH). 30 minutes after the treatment animals were harvested (T30’) or subjected to renal ischemia for 50 minutes followed by 2 (T2) or 24 (T24) hours of reperfusion. Sham-operated, untreated animals served as controls (C) (n=10/group). The renal S1R-Akt-eNOS proteins were analyzed by Western blot and immunofluorescence microscopy.

Results: 30 min after FLU treatment renal Akt and eNOS expression were elevated compared to C. After IR both proteins continually increased with time (C vs. T2 vs. T24). While at T2 there was no difference among the groups, at T24 renal Akt and eNOS protein levels were higher in the VEH group compared to FLU. NE-100 diminished all effects of FLU. S1R expression remained unchanged in the different groups. S1R-Akt-eNOS were co-localized in renal tubular cells. In C and after FLU treatment a nucleus-associated staining was observed, while in VEH and FN groups S1R-Akt-eNOS showed a more cytoplasmic localization.

Conclusions: The S1R-Akt-eNOS axis could be a novel pathway in the pathophysiology of renal IR injury. The S1R agonist FLU might exert its renoprotective effect by altering these proteins. This work was supported by LP2011-008/2012 Lendulet Research Grant; NIH grant R01 DK56843 and a. It was also supported by grants of OTKA PD83431, ETT 06-066/2009 and TÁMOP 4.2.4.A/1-11-1-2012-0001.