Nephrectomy induced renal repair after AKI prevents progression to CKD by an early immunosuppressive action

Lies MOONEN 1, Bart CUYPERS 2, Pieter MEYSMAN 2, Kris LAUKENS 2, Patrick C. D’HAES 1, Benjamin A. VERVAET 1

Background and Aim
Acute unilateral injury of sufficient severity leads to progressive renal deterioration (atrophy, fibrosis). Nonetheless, an acutely injured kidney demonstrates a remarkable degree of repair upon removal of the healthy contralateral kidney. If the latter kidney is left in place, repair is only marginal and the injured kidney chronically turns fibrotic. Yet, it is unclear by which molecular mechanism nephrectomy (Nx) is able to alter the fate of injured kidneys.

Materials and Methods
- Acute kidney injury was induced in R26R tdTomato 1 and C57BL/6J mice by left unilateral ischemia/reperfusion injury (IRI) at 34°C for 21 minutes, after which either right Nx or mock-Nx was performed 3 days later. Mice were euthanized at either 7 days or 6 weeks after IRI.
- Kidneys were examined macroscopically and weighed
- qPCR analysis of the profibrotic genes Col1, Col4, Tgfb and Ccn2 was performed.
- Masson/H&E stain was used to microscopically evaluate histopathology.
- RNA-Sequencing was used for differential gene expression analysis early in the progression (day 7).

Study setup

Results

Macroscopy
In the mock-Nx group, median left and right kidney-to-body weight ratio at week 6 was 2.8 (range 2.1-3.1) and 6.7 (range 6.4-7.0) respectively, indicating severe atrophy in the injured left kidney. In the Nx group, kidney-to-body weight ratio was 6.9 (range 6.0-7.3) and 6.5 (range 5.9-7.5) for left and right kidney respectively. *p<0.05 vs ischemic kidney.

Histopathology
Masson/H&E stain shows strongly attenuated atrophy and fibrosis in the recovered kidney (IRI+Nx). The recovered kidney also displays hypertrophy mainly in outer stripe of outer medulla.

Differential gene expression analysis
qPCR gene expression analysis of pro-fibrotic genes demonstrated an upregulation of Col1, Col4, TGFβ and CCN2 of 18-, 5-, 7-, and 3-fold compared to controls, respectively when no Nx was performed. In case of Nx, this decreased to a 5-, 2-, 2-, and 0-fold upregulation compared to controls, respectively. a= p<0.05 vs Sham (i.e. mock surgery), b=p<0.05 vs IRI without nephrectomy. Data are presented as mean±SD.

Gene set enrichment analysis
Gene set enrichment analysis of the differentially expressed genes demonstrated multiple down/upregulated pathways of which immune response and MAPK pathways were most significantly downregulated upon Nx.

Conclusion
Nephrectomy performed 3 days after unilateral ischemia/reperfusion injury attenuates renal atrophy and fibrosis. Nephrectomy leads to an early downregulation of inflammatory and immune response pathways. Although it can be suggested that nephrectomy-induced immunosuppression attenuates atrophy/fibrosis, it needs to be investigated whether the effect of nephrectomy is due to a direct or indirect action on proximal epithelial, immune, or other cells.