INTRODUCTION AND AIM

Diabetic nephropathy (DN) is a long-term complication of diabetes characterized by proteinuria and loss of kidney function. Up to one third of patients with diabetes develop DN, and no new therapies targeting DN have been introduced for more than a decade. The lack of treatment options may in part be caused by the scarcity of translatable rodent models. To address these challenges, we aimed to develop a novel surgery-induced rat model of DN by 70% pancreatectomy (Px) and uni-nephrectomy (UNx).

STUDY DESIGN AND GROUPS

Figure 1 | Male rats underwent 90% pancreatectomy (Px) alone or combined with unilateral nephrectomy (UNx) of the left kidney. Body weight and blood glucose was recorded for 11-12 weeks, with spot urine collected every other week. At termination, plasma was collected for biochemical analyses, while the right kidney was sampled for histological analyses and next generation RNA sequencing.

RESULTS

Figure 2 | Weekly blood glucose (non-fasted) and daily body weight throughout the study. Px and Px UNx rats were considered diabetic and included in study if non-fasted blood glucose was ≥12 mmol/l within 14 days after surgery. Data are mean ± SEM.

Figure 3 | Top panel | Urinary albumin-to-creatinine and NGAL-to-creatinine ratios. Kruskal-Wallis with Dunn’s post hoc: ***p<0.001 vs Ctrl; **p<0.01 vs Px 11 wks; *p<0.05 vs Px -UNx 11 wks. Bottom panel | Urinary creatinine concentration at termination. One-way ANOVA with Tukey’s post hoc test: ***p<0.001 vs Ctrl. Data are mean ± SEM.

Figure 4 | Stereological volume estimates of the right kidney and glomerulus. Data are mean ± SEM. One-way ANOVA with Tukey’s post hoc test: ***p<0.001 vs Ctrl; **p<0.01 vs Px 11 wks; *p<0.05 vs Px 11 wks.

Figure 5 | Relative and total fibrosis of right kidney at termination with representative images of fibrosis quantification on Picro-Sirius red stained kidney sections. Data are mean ± SEM. One-way ANOVA with Tukey’s post hoc test: **p<0.01, ***p<0.001 vs Ctrl; ***p<0.001 vs Px 11 wks; *p<0.05 vs Px 21 wks.

Figure 6 | Top panel | Principal component analysis (PCA) of the 50 most variable renal cortex genes as assessed by next generation sequencing. Bottom panel | Renal cortex expression of selected genes. Data are mean ± SEM; *p<0.05, **p<0.01, ***p<0.001 vs Ctrl after correction for gene-wise multiple testing.

CONCLUSION

We present a novel combined Px-UNx rat model of DN characterized by:

• Increased urinary albumin and NGAL excretion
• Renal hypertrophy, increased renal fibrosis, and clear evidence of glomerulosclerosis
• Altered gene expression in the renal cortex supporting a DN phenotype

This advanced surgical approach represents a strong and short-duration alternative to streptozotocin-induced diabetes and genetic models (e.g. ZDF rats) for preclinical studies of DN drug candidates.