Introduction and Aims: Genetic background has a strong influence on the progression of chronic kidney disease. We recently found that Rowett black hooded rats were resistant to renal fibrosis. We aimed to investigate the role of sustained inflammation and oxidative/nitrative damage in renal fibrosis progression using this new model. Our previous data suggested the involvement of podocytes, thus we investigated renal fibrosis initiated by doxorubicin-induced podocyte damage.

Methods: Rats were treated with Doxorubicin (5 mg/kg) and observed for 8 weeks. Survival was assessed in a separate cohort. Renal function was assessed as urinary protein and neutrophil gelatinase-associated lipocalin excretion and histologic analysis following periodic acid-Schiff and Picro-Sirius-red staining and nephrin and fibronectin immunohistochemistry and profibrotic factors (TGF-β, CTGF, collagen type I alpha 1), and inflammatory (MCP1) mRNA expression were detected by PCR. Oxidative and nitrative stress was evaluated by p47phox (neutrophil cytosol factor 1) p91-phox (NADPH oxidase-2) expression on western blot and 4-hydroxynonenal (HNE) and nitrotyrosine (NT) staining.

Results: Doxorubicin reduced bodyweight and induced progressive loss of renal function during the observation period. Compared to fibrosis-sensitive, Charles Dawley rats the fibrosis-resistant, Rowett black hooded rats had longer survival, better renal function, reduced loss of the slit diaphragm protein, nephrin, less glomerulosclerosis, tubulointerstitial fibrosis and matrix deposition and reduced profibrotic proteins. Milder inflammation demonstrated by histology was confirmed by less MCP1 expression. Less oxidative and nitrative stress was obvious on HNE and NT staining.

Conclusions: Thus, mediators of fibrosis, inflammation and oxidative/nitrative stress were suppressed in doxorubicin nephropathy in fibrosis-resistant BH rats underlying the importance of these pathomechanisms in the progression of renal fibrosis.