GENETIC SUSCEPTIBILITY TO TGF-BETA INDUCED RENAL FIBROSIS IS ASSOCIATED WITH ALTERED MIR-199 EXPRESSION

Miklos Mozses, Agnes Nemeth, Krisztina Fazekas, Gabor Kokenyi

1Dept of Pathophysiology, Semmelweis University, Budapest, Hungary and 2Dept of Pathophysiology, Semmelweis University, Budapest, Hungary

INTRODUCTION AND AIMS: Several microRNAs (miR) have been associated with kidney fibrosis. Increased miR-199 has been reported in UUO kidneys and fibrotic liver. Moreover, TGF-β can induce miR-199 in lung fibroblasts in vitro. We have shown that allb/TGF-beta1 transgenic mice (TGFb) on C57Bl6/J (B6) and CBAx6 genetic background develop mild or severe renal fibrosis, respectively (Kokenyi et al. Clin Kidney J 2011;4(S2):421–429). We hypothesized that genetically determined profibrotic microRNA response to TGF-β might influence the development of renal fibrosis.

METHODS: We analyzed male B6-TGFb and CBAx6-TGFb transgenic mice and wild type B6 and CBAx6 controls at the age of 14 days (n=5/group). Kidneys were investigated for histology, and mRNA and miRNA expressions. Data are presented as mean±SD and statistical significance was evaluated using Kruskal-Wallis test.

RESULTS: Compared to B6-TGFb mice, CBAx6-TGFb kidneys depicted significant glomerulosclerosis (histology score B6: 0.1±0.1; CBAx6: 0.1±0.1; B6-TGFb: 0.1±0.1; CBAx6-TGFb: 2.3±0.4, p<0.01) accompanied by markedly increased TIMP-1 mRNA levels (B6: 1.0±0.5; CBAx6: 1.5±0.3; B6-TGFb: 3.6±0.6 vs CBAx6-TGFb: 87.6±38.8, p<0.01). The expression of miR-199 was significantly elevated in fibrotic CBAx6-TGFb kidneys as compared to B6-TGFb (B6: 1.0±0.2; CBAx6: 1.1±0.2; B6-TGFb: 2.0±0.3 vs CBAx6-TGFb: 3.3±0.4, p<0.05), showing a strong correlation to TIMP-1 (R-square: 0.85, p=0.002).

CONCLUSIONS: In our transgenic model of TGF-β induced kidney fibrosis, genetic background determines the expression of profibrotic miR-199, which correlates to TIMP-1 and might influence the progression. Funding: Hungarian Scientific Research Fund (OTKA PD 112960).