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C3a induces versican V1 overexpression in tubular cells of focal segmental glomerulosclerosis

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Objectives: Chronic tubulointerstitial injury impacts prognosisof focal segmental glomerulosclerosis(FSGS), andversican is a large extracellular matrix proteoglycan. Relation between versican expressionand tubulointerstitial injury in FSGS patients has not been studied.

Methods: Tubulointerstitial tissues of FSGS patients and controls were isolated and analyzed by transcriptome chip. The expression level of versican was correlated with the decline rate of eGFR in FSGS patients. Biochemical techniques were used to analyze versican expression, Akt phosphorylation, β-catenin nuclear translocation, DNA binding of β-catenin and renal interstitial fibrosis in human renal tubular epithelial cells andadriamycin (ADR) mouse model.

Results: Analysis of transcriptome data and confirmation study in an independent cohort showed that the level of versican V1 mRNA was dominant in tubulointerstitial tissues and wascorrelated withthe decline rate of eGFR in FSGS patients.Versican V1 was upexpressed in renal tubular cells and accumulated in the interstitium of patients with FSGS. Treatment of tubular cells with patients' serum induced the expression of versican V1 in a time- and dose-dependent manner. The effect of patients' serum on versican V1 expression was obviously prevented by C3aR antagonist SB290157, and C3a treatment induced the expression of versican V1 in tubular cells. Inhibition of Akt prevented the binding of β-Catenin-TCF complex to versican promoter in tubular cells treated with C3a.In vivo, treatment with ADR caused an obvious increase inurinary C3a, versican V1 expression and interstitial fibrosisinmice. C3aR antagonist abolished the deposition of C3a on the tubular cells of ADR-treated mice. Blocking of C3aR also suppressed the activation of Akt/β-catenin signaling pathwayin the tubulointerstitialtissues of ADR-treated mice. As a result, the expression of versican V1 in tubulointerstitial tissuesand renal interstitialfibrosiswere decreased in the mice receiving C3aR antagonist.

Conclusions: C3a induces versican V1 overexpression through the activation of Akt/β-catenin signaling pathway, and the increased versican V1 in tubulointerstitial tissues predicts renal prognosis in focal segmental glomerulosclerosis patients.