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Loss of KLF15 promotes chronic podocyte injury

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Objectives : Krüppel-like factor 15 (KLF15), kidney-enriched transcription factor, is known to participate in the differentiation of podocyte. However, the implication of KLF15 in chronic podocyte injury remains unresolved, particularly in the relationship with the infiltrated macrophage.

Methods : 5/6 nephrectomized and C-C chemokine receptor type 5 (CCR5)-/- mouse models were used to determine chronic podocyte injury and explore exclusive role of M1 macrophage in the KLF15 expression, respectively. Human primary podocytes were flow-cytometically isolated and cultured to emulate the injury process in the in vitro system. Biopsied kidney tissues were obtained from the patients with diabetic nephropathy (n=21) and primary membranous nephropathy (n=26) to elucidate the relationship between glomerular KLF15 expression and subsequent outcomes.

Results : When 5/6 nephrectomy was predisposed to progressive kidney damage, the fibrosis markers increased, but the KLF15 expressions decreased in the site of podocytes. The KLF15 expression was further reduced by the infiltration of M1 macrophage using CCR5-/- mice, which resulted in more intense fibrosis [Figure]. We also observed corresponding trends in human primary podocytes, such as increase in fibrosis markers and decrease in KLF15 production after 2-day treatment of TGF-β. These trends were reversed when cyclosporine or tacrolimus were treated in cultured podocytes. When patients were categorized based on the KLF15 expression levels in kidney tissues, the low expression groups suffered worse kidney events such as end-stage renal disease and non-remission of disease.

Conclusions : Low KLF15 expression in podocytes is associated with chronic kidney injury.

Keywords : chronic kidney disease; cyclosporine; Krüppel-like factor 15; podocyte