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The kidney-protective effects of lysyl-tRNA Synthetase 1(KARS1) modulation in chronic kidney disease

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Objectives : Lysyl-tRNA synthetase 1 (KARS1) is an enzyme that links lysine to tRNA. Notably, secreted KARS1 functions as a signaling molecule that activates monocytes and macrophages, inducing an immune response. Given that chronic inflammation plays a key role in chronic kidney disease (CKD) progression, understanding the role of KARS1 in CKD pathology is crucial. This study investigates the effect of KARS1 modulation on kidney function, inflammation, and fibrosis in a CKD model.
Methods : CKD was induced in mice by feeding a 0.2% adenine diet (AD). Mice were divided into three groups (n = 6-8 per group): Control, AD (CKD model), and AD + KARS1 modulator (treatment group). KARS1 expression was analyzed using immunostaining, and its cell-specific localization was determined using macrophage (F4/80) and proximal tubular cell (Lotus tetragonolobus lectin) markers. To assess the therapeutic potential of KARS1 modulation, a KARS1 modulator (Zymedi Co., Ltd.) was orally administered once daily, and kidney function was evaluated by measuring serum blood urea nitrogen (BUN) and cystatin C levels. In addition, immunostaining and qPCR were used to evaluate the damaged tubular, inflammation markers and fibrosis markers
Results : KARS1 was highly expressed in F4/80 and Lotus tetragonolobus lectin in AD mice. BUN and cystatin C levels were significantly elevated in AD mice but were markedly reduced following KARS1 modulation. Moreover, VCAM-1, a marker of damaged tubular cells, was significantly elevated in AD mice but was markedly reduced in KARS1 modulator-treated AD mice. Furthermore, the expression levels of KARS1, inflammatory markers, and fibrotic markers were increased in AD mice but significantly decreased after KARS1 modulator treatment.
Conclusions : Our results indicate for the first time that KARS1 expression is elevated in CKD mice. Moreover, KARS1 modulation effectively inhibits inflammation and fibrosis, suggesting that targeting KARS1 may be a promising therapeutic strategy for CKD treatment.