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Necrox-7 Improves Kidney Tissue Damage Caused by Fibrosis During Renal Ischemia-Reperfusion

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Introduction: Ischemia-reperfusion injury (IRI) is a well-known cause of progression to renal fibrosis, a major pathologic symptom of chronic kidney disease (CKD). Ischemia-reperfusion (IR) increases inflammatory stimuli as CKD progresses, leading to ferroptosis and fibrosis. NecroX-7 was demonstrated to protect against necrosis and inflammation in virous organ injuries. In the present study, we evaluated whether NecroX-7 improves CKD-induced renal fibrosis through an anti-inflammatory response and reduction of reactive oxygen species in an IRI mouse model, and we investigated the mechanisms involved. Methods: C57BL/6 mice (eight weeks old, male) were divided into groups according to IR and NecroX-7 administration. IR was induced via 24-h renal IRI. One (1d), three (3d), or seven days (7d) after NecroX-7 treatment, kidney tissue and blood were collected. HK2 cell with TGF-β treatment are used for invitro studies. Results: Blood urea nitrogen and serum creatinine were both decreased in NecroX-7-treated IRI 3d and 7d mice compared with IRI 3d and 7d mice. Expression of F4/80, collagen IV, alpha smooth muscle actin, and transforming growth factor beta were all decreased and expression of E-cadherin was increased in the kidneys of NecroX-7-treated IRI 3d and 7d mice compared with IRI 3d and 7d mice. Anti-inflammatory, anti-ferroptosis, and antifibrotic protein expression were all increased in NecroX-7-treated IRI 3d and 7d mice compared with IRI 3d and 7d mice. In addition, lower levels of HMGB1 and nuclear factor kappa B were found in the kidneys of NecroX-7-treated IRI 3d and 7d mice than in IRI 3d and 7d mice. Conclusion: Our results confirmed that IR damages the kidneys and causes fibrosis. NecroX-7 functions as a protector against IRI-induced renal fibrosis in IRI mice.

Keywords: NecroX-7, Fibrosis, Ischemia-reperfusion, Ferroptosis