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Inhibition of 5-lipoxygenase ameliorates diabetic kidney disease by attenuating proximal tubular cell ferroptosis

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Objectives : The enzyme 5-lipoxygenase plays a pivotal role in the formation of reactive oxygen species (ROS), which can lead to lipid peroxidation and subsequent ferroptosis. This study aims to elucidate the pathophysiological implications of 5-lipoxygenase in diabetic kidney disease (DKD), focusing on its impact on lipid peroxidation and tubular cell ferroptosis.
Methods : HKC-8 cells, a human-derived renal proximal tubular cell line, was used to perform in vitro experiments. Diabetes induction in male C57BL/6J mice was achieved through streptozotocin injection. Zileuton was used to inhibit 5-lipoxygenase activity.
Results : Hyperglycemic stimuli upregulated the expression of 5-lipoxygenase both in HKC-8 cells and mouse kidneys. The overexpression of 5-lipoxygenase aggravated hyperglycemia-induced increases in the expression of reactive oxygen species (ROS) and profibrotic cytokines production, while its suppression mitigated these detrimental effects. High glucose also led to downregulations of glutathione peroxidase 4 (GPX4) and upregulations of Acyl-CoA synthetase long chain family member 4 (ACSL4), ferritin heavy chain 1 (FTH-1), and malondialdehyde (MDA), indicating the activation of pro-ferroptotic pathways. The overexpression of 5-lipoxygenase exaggerated hyperglycemia-induced ferroptotic cell death, which is attenuated by the inhibition of 5-lipoxygenase or ferrostatin-1 treatment. Additionally, streptozotocin-induced diabetic mice exhibited worse kidney function and interstitial fibrosis in association with decreased GPX4 and increased ACSL4 and FTH-1 levels compared to normoglycemic mice. Zileuton administration or renal proximal tubule-specific knockout of 5-lipoxygenase significantly ameliorated hyperglycemia-induced kidney dysfunction and ferroptosis activation.
Conclusions : These findings demonstrate the central role of 5-lipoxygenase in intracellular lipid peroxidation and subsequent tubular cell ferroptosis under sustained hyperglycemic conditions. Inhibition of 5-lipoxygenase not only mitigates ferroptotic tubular cell death but also alleviates hyperglycemia-induced renal dysfunction. This suggests that 5-lipoxygenase could serve as a potential therapeutic target for the treatment of DKD.