Investigation of macrophage iron stress in chronic kidney disease and renal senescence and development for a therapeutic strategy

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The importance of iron in the development and progression of kidney disease has been increasingly indicated. Macrophages are cells with active iron metabolism, and inflammatory M1 polarization is associated with increased H-ferritin (FTH) expression and intracellular iron content. Our previous study has demonstrated that macrophage-specific FTH knockout (FTHKO) mice, characterized by reduced iron levels, showed ameliorated inflammation in obesity-related diabetes models. In this study, we investigated the role of macrophage iron in folate-induced kidney injury using FTHKO mice. At day 14 (chronic phase), FTHKO mice exhibited significantly reduced kidney damage and fibrosis compared to wild-type (WT) controls, accompanied by suppressed expression of inflammatory and senescence-related genes. Similarly, at day 2 (acute phase), both kidney injury and oxidative stress were attenuated in FTHKO mice. Transcriptome analysis revealed the upregulation of antioxidant pathways and downregulation of inflammatory and senescence pathways in FTHKO mice. These findings suggest that reducing macrophage iron content may contribute to the suppression of renal pathology, potentially representing a novel therapeutic target for kidney disease.