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Fabry disease exacerbates renal interstitial fibrosis after unilateral ureteral obstruction via impaired autophagy

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Objectives: Fabry disease is a rare X-linked genetic lysosomal disorder caused by mutations in the GLA gene, encoding the acid hydrolase α-galactosidase A (α-Gal A). Since the kidney is one of the main target organs in subjects with Fabry disease, all kinds of renal cells can be affected by abnormal globotriaosylceramide (Gb3) deposition resulting from deficient α-Gal A activity. Despite some data showing that some pro-fibrotic and pro-inflammatory cytokines could be involved in renal inflammation, the pathogenic link between the metabolic derangement within cells and renal injury is still unclear.

Methods: To investigate the pathogenic mechanism leading to fibrosis in kidneys of Fabry disease, renal fibrosis in Fabry disease model mice (B6;129-Gla^{tm1}Kul/J) was triggered by unilateral ureteral obstruction (UUO) and then compared with those of sham-operated or obstructed kidneys of control wild-type mice.

Results: Compared to kidneys of wild-type mice, Gb3-containng myeloid bodes were recognized in proximal tubules in mice with Fabry disease but not increased by UUO. Significant increases in fibrosis area measured by Sirius red and trichrome stainings were observed in obstructed kidneys and more prominent in kidneys of Fabry disease mice. The mRNA levels of IL-1β, IL-6, TNFα, MMP-2, MMP-9, α-SMA, fibronectin, vimentin, TGF-β1 and COL4A1 were increased in all UUO kidneys compared to sham-operated kidneys but those of VE-cadherin and α-SMA were not different between sham-operated kidneys and obstructed Fabry kidneys. The protein content of LC3-II to LC3-I and protein expressions of Beclin 1 and HO-1 were significantly decreased in UUO kidneys of Fabry disease mice than in those of wild-type mice, while the SQSTM1/p62 expression was elevated in obstructed kidneys of mice with Fabry disease.

Conclusions: These findings suggest that the impaired autophagy could be one of mechanisms by which renal fibrosis is enhanced under the stimulus of persistent UUO in Fabry disease.