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Lysyl oxidase-like 2 inhibition ameliorates the progression of folic acid-induced renal tubulointerstitial fibrosis

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Objectives: Tubulointerstitial fibrosis is a common end point of chronic renal diseases. Preventing the progression of tubulointerstitial fibrosis is a key to prevent renal failure. Transforming growth factor-β (TGF-β) and accompanying molecules have been revealed to be responsible for tubulointerstitial fibrosis, but effective therapy has not been established yet. Lysyl oxidase-like 2 (LOXL2) is a molecule known to be related with invasive growth and metastasis of malignant neoplasm, and fibrosis of liver and lung. We recently showed that LOXL2 was expressed in podocytes and tubular epithelial cells and related with the progression of tubulointerstitial fibrosis induced by intraperitoneal folic acid injection. In this study, we evaluated the effect of a LOXL2 inhibitor on the progression of tubulointerstitial fibrosis.

Methods: Male CD1 mice were intraperitoneally injected with folic acid (240 μg/g body weight) to induce tubulointerstitial fibrosis. AB0023, an inhibitory monoclonal antibody of LOXL2 (Gilead Sciences) was intraperitoneally injected twice a week with a volume of 15 μg/g body weight. AB0023 injection was started 1 week before folic acid injection. Same volume of control IgG (Gilead Sciences) was injected to control mice. Mice were sacrificed 4 weeks after folic acid injection and harvested kidneys were stained with trichrome and the Sirius red. Total collagen analysis using fresh frozen tissue was also performed.

Results: Mice treated with AB0023 showed significantly decreased amount of tubulointerstitial fibrosis confirmed by morphometric analysis after trichrome and the Sirius red stainings. The amount of total collagen per total hydrolyzed protein was also decreased in AB0023-treated mice.

Conclusions: LOXL2 inhibitor has preventive effect on the progression of tubulointerstitial fibrosis induced by folic acid injection.