Collecting duct cell specific mitochondrial dysfunction influence to inflammation and fibrosis in UUO mice.

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BACKGROUNDS

Unilateral ureteral obstruction (UUO) induced mitochondrial dysfunction resulting in increase of oxidative stress and inflammation in obstructed kidney. Although mitochondria play a role in UUO injury including tubulo-interstitial apoptosis, inflammation and fibrosis, the role of collecting duct cells was not evaluated. We evaluated whether collecting duct specific mitochondrial dysfunction affect the renal injury induced by UUO.

METHODS

For generation collecting duct specific mitochondrial injury mice, CRIF flox/flox mice were bred with Hoxb7-Cre mice. For evaluation of the phenotype of mice, we observed mitochondria using electron microscopy in mice. For evaluation of influence of CRIF1 deletion on mitochondrial function, we measured O2 consumption and membrane potential in control and silencing RNA treated mIMCD cells. For evaluation of effect on UUO induced renal injury, we divided mice into the following 4 groups: CRIF1flox/flox(WT) group; CRIF1 flox/flox-Hob7 Cre (CRIF1-KO) group; WT UUO group; and CRIF1-KO UUO group. I evaluated oxidative stress, inflammatory, and fibrosis marker in urine and kidney tissue.

RESULTS

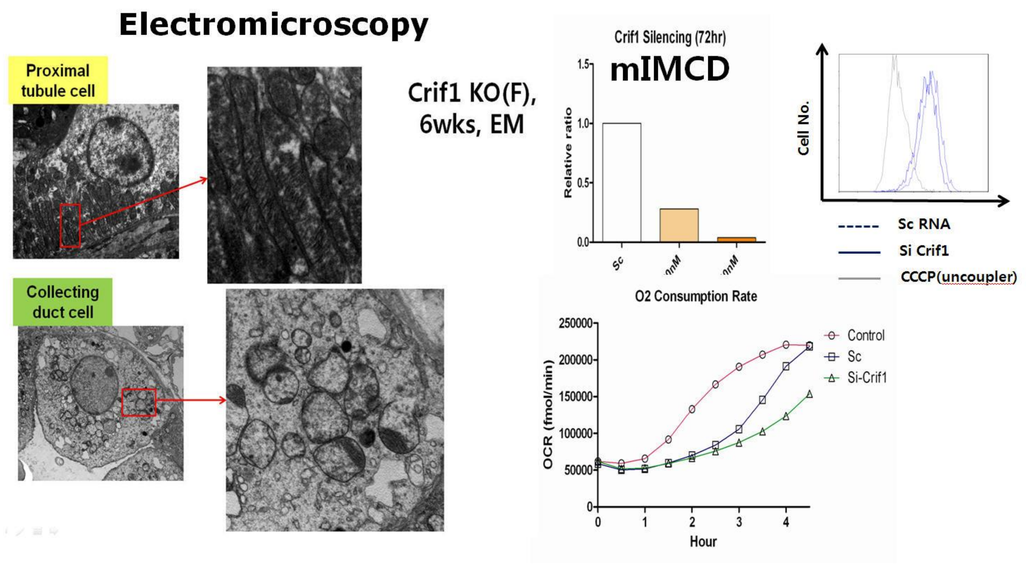

Figure 1. mitochondria in collecting duct cells in crif1KO kidney showed swelling and destruction of cristae compared to wild type kidney. silencing mRNA of crif1 in mIMCD cells(crif1-siRNA-mIMCD cells) significant decreased mitochondrial membrane potential and O2 consumption in crif1-siRNA-mIMCD cells compared to scRNA-mIMCD cells.

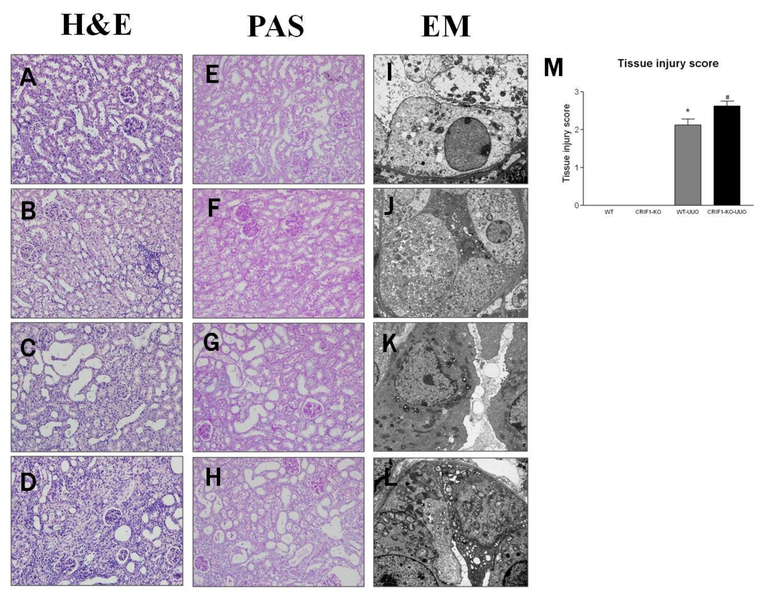

Figure 2. Photos of H & E stain, PAS stain, electron microscopy of WT and CRIF1-KO mouse kidney (A~L). WT-UUO kidney showed increase of tubular injury score compared with non-UUO kidney. CRIF1-KO-UUO kidney showed increase of tubular injury score compared with WT-UUO kidney (M). Although CRIF1-KO kidney showed severe mitochondrial injury, UUO did not alter significantly the mitochondrial morphology in WT kidney (I~L).

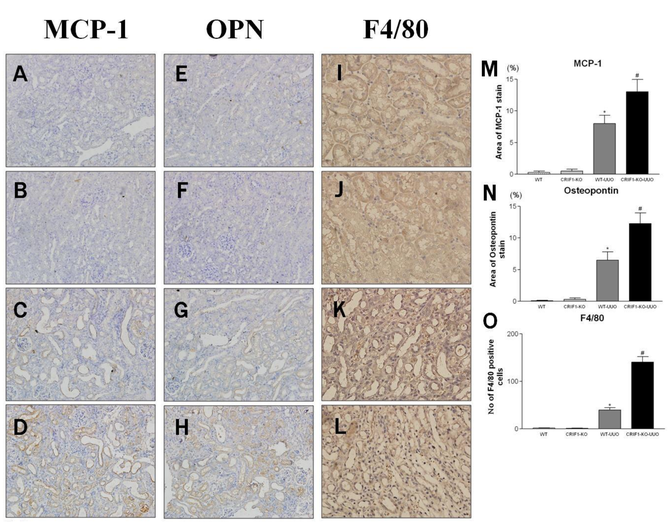

Figure 3. Photos of Immunohistochemical stain of MCP-1, osteopontin (OPN), and F4/80 (A~L). CRIF1-KO-UUO Kidney showed increase of stain area of MCP-1 and OPN and numbers of F4/80 positive cells compared with WT UUO kidney (M~O).

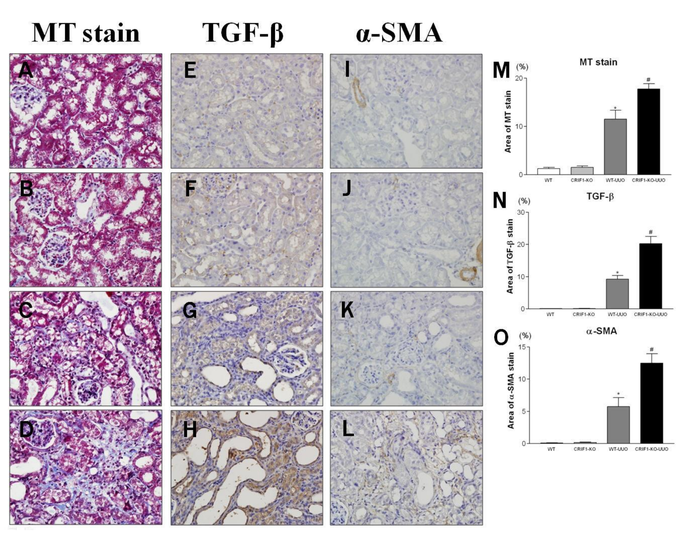

Figure 4. Photos of Masson trichrom stain and immunohistochemical stain of TGF-b and a-SMA (A~L). CRIF1-KO-UUO Kidney showed increase of stain area of TGF-b and a-SMA and Masson Trichrom stained area compared with WT UUO kidney (M~O).

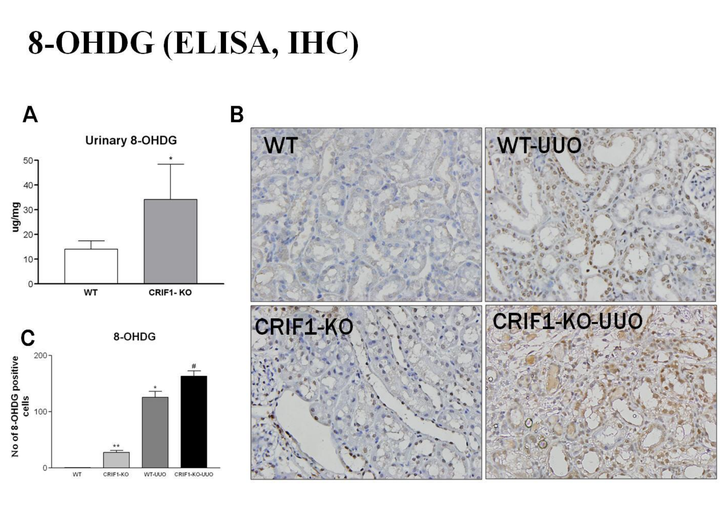

Figure 5. Uirnay 8-OHDG excretion of WT and CRIF1-KO-mouse (A). Photos of immunohistochemistry of 8-OHDG (B). CRIF1-KO mice had significantly increase of 8-OHDG-positive cell recruitment compared to WT mice. CRIF1-KO-UUO-kidneys were shown more increase recruitment of 8-OHDG-positive cells compared to WT-UUO-kindneys (C).

CONCLUSIONS

Collecting duct specific mitochondrial injury induced increase of oxidative stress, renal inflammation, and renal fibrosis in UUO mice.

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