Inhibition of the Activity of Omi/HtrA2 Attenuates Renal Fibrosis Induced by Ureteral Obstruction in Mice

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Omi/HtrA2 is a pro-apoptotic mitochondrial serine protease involved both in caspase-dependent as well as caspase-independent cell death. However, the role of Omi/HtrA2 in the apoptotic cell death associated with ureteral obstructive renal fibrosis is unknown. Here, we investigate the potential function of Omi/HtrA2 in the progression of renal fibrosis induced by ureteral obstruction in mice. Unilateral ureteral obstruction in BALB/c male mice results in severe hydronephrosis, the deposition of collagen, and the expression of -smooth muscle actin (-SMA) and fibronectin in the obstructed kidneys. Ureteral obstruction significantly alters the expression of Omi/HtrA2 in the tubular epithelial cells of obstructed kidneys. Furthermore, administration of ucf-101, a specific inhibitor of Omi/HtrA2 proteolytic activity, significantly alleviates the post-obstructive increase of collagen deposition and the expression of -SMA and fibronectin. Administration of ucf-101 results in a decrease of cytochrome c release from mitochondria following ureteral obstruction. The cleavage of poly (ADP-ribose) polymerase (PARP) and the numbers of terminal deoxynucleotidyl-transferase-mediated dUTP nick end labeling (TUNEL) positive cells after ureteral obstruction is significantly reduced by the administration of ucf-101. In conclusion, inhibition of the proteolytic activity of Omi/HtrA2 attenuates ureteral obstruction-induced apoptosis and significantly decrease renal fibrosis. These results suggest Omi/HtrA2 is a novel therapeutic target and its inhibition by ucf-101 or other similar pharmaceutical agents affords protection against the development and progression of renal fibrosis.