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Peroxiredoxin III Deficiency Exacerbates Fibrosis in the Obstructed Kidneys

이화여자대학교 생명약학부 바이오융합과학과

황 인 아 · 하 헌 주

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Inah Hwang, Hunjoo Ha

Department of Bioinspired Sicence, Division of Life & Pharmaceutical Sciences
Ewha Womans University

Introduction : Renal injury resulting from unilateral urethral obstruction (UUO) is characterized by prominent interstitial fibrosis initiated by epithelial-mesenchymal transition (EMT). Reactive oxygen species (ROS) generated by mitochondria are signaling molecules necessary in physiological processes but excess ROS and loss of redox homeostasis contribute to chronic kidney disease (CKD) including obstructive nephropathy. Peroxiredoxins (Prx) are a family of thioredoxin-dependent peroxidases. Among six isoforms of mammalian Prx, Prx III has a mitochondrial targeting sequence. The present study was performed to investigate the role of endogenous Prx III in the progression of obstructive nephropathy using Prx III knockout mice.

Methods : Six-month-old male homozygous Prx III knockout (Prx3-/-) mice and wild-type (WT) mice (5 mice per group) were used. UUO was performed under pentobarbital-induced anesthesia: the left urethra was ligated with silk (6/0) at two locations and cut between ligatures to prevent urinary tract infection. At 14 days after the induction of UUO, mice were sacrificed and then kidneys were homogenized for mRNA and protein analysis.

Results : The kidney weight per body weight ratio was significantly increased in obstructed kidneys compared to sham kidneys. Markers of EMT (E-cadherin, α-SMA, and vimentin) as well as fibrosis (TGF-β1, CTGF, BMP7, collagen, and fibronectin) were significantly changed in obstructed kidneys compared to sham kidneys. However, the degree of injury in obstructed kidneys of Prx3-/- mice was significantly increased compared to that of WT mice: expression of TGF-β1, CTGF, collagen IVα1, collagen I, and fibronectin were increased and E-cadherin decreased. In addition, TGF-β1 and CTGF expression were significantly increased and BMP7 and E-cadherin decreased in sham kidneys of Prx3-/- mice compared to those of WT mice, implying accelerated renal injury in Prx3-/- mice.

Conclusions : Our study demonstrated that Prx III knockout accelerated obstructive nephropathy. These data suggest that Prx III may act as an important scavenger of ROS and that mitochodiral oxidative stress may be a major cause of renal fibrosis associated with UUO. Further mechanistic studies are required to elucidate the role of Prx III in the process of obstructive nephropathy. (Supported by R15-2006-020 and R31-2008-000-10010-0 from KOSEF and the second stage of Brain Korea 21 Project.)

Key Words : Peroxiredoxin 3, 편측요로폐쇄증, 만성신질환,
Peroxiredoxin III, Chronic kidney disease (CKD), Prx III knock