외국 연수회원 발표

사구체 간질 세포에서 TGF-β1에 의한 autophagy의 유도가 PI3K/Akt signaling 경로를 통해 세포 생존에 미치는 영향

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Induction of Autophagy by TGF-β1 may Serve as a Cell Survival Factor Via PI3K/Akt Signaling Pathway in Mesangial Cells

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Introduction : In glomerular injury, counterbalancing of mesangial cell death and cell survival plays an important role in the pathogenesis of progressive glomerulosclerosis. Autophagy is a highly conserved process that cells use to degrade and recycle cellular proteins and remove damaged organelles for cell survival, and is thought to be an essential function for tissue homeostasis. Thus, autophagy can be a major cytoprotective pathway and represents a cell survival factor. In contrast, excessive autophagic activity can lead to type II programmed cell death. TGF-1 is a key mediator of glomerular injury response in progressive kidney diseases and regulates both cell growth and celldeath. Here we investigated the role of TGF-1 in the induction of autophagy for mesangial cell survival and protection from apoptosis.

Results : Serum deprivation induced caspase-3 activation as determined by increased levels of cleaved caspase-3 in mouse mesangial cells in a time-dependent manner. Treatment with exogenous TGF-1 prevented the induction of cleaved caspase-3 by serum deprivation, but led to the activation of the serine/threonine protein kinase Akt implicated in mediating survival signals, and the induction of LC3B-II, the autophagic form of LC3B, as well as Autophagy Protein 7 (APG7). Treatment with the phosphoinositide 3-kinase (PI3K) inhibitor LY294002 suppressed the induction of LC3B-II by TGF-1 under serum deprivation, and led to the induction of cleaved caspase-3 upon serum deprivation even in the presence of TGF-1 treatment. These findings suggest that TGF-1-induced autophagy is PI3K-dependent and inhibition of autophagy may allow for apoptosis to proceed. Interestingly, in MMC from MKK3 deficient ($Mkk3^{-/-}$) mice, serum deprivation failed to induce LC3B-II expression, suggesting that the MKK3 pathway is required for serum deprivation-induced autophagy in MMC. Moreover, TGF-1-induced Akt phosphorylation was significantly increased in the $Mkk3^{-/-}$ MMC compared to the wild-type MMC.

Conclusion : Our data indicate that TGF-1 is an inhibitor of serum deprivation-induced apoptosis in mesangial cells and the induction of autophagy by TGF-1 may serve as a cell survival factor via PI3K-dependent Akt signaling pathway.