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Phosphatidylinositol-3 kinase (PI3-kinase) has a protective role at the early stage of angiotensin II-induced podocyte injury by inducing autophagy

Tae-Sun Ha[1], Dong-Soo Ha[2], Su-Bin Sung[1], In-Wha Jeong[1]
[1]Department of Pediatrics, Chungbuk National University College of Medicine, Korea, Republic of
[2]Department of Department of Biological Sciences, KAIST, Korea, Republic of

Objectives: PI3-kinase has distinct roles in cellular processes spanning from metabolism to cell motility and survival. Angiotensin II (Ang II) promotes the development and progression of proteinuria and renal diseases and induces podocyte apoptosis. Autophagy and apoptosis constitute the two processes through which injured/aged cells or organelles are eliminated. Autophagy is a highly regulated catabolic process that is involved in the turnover of unwanted cellular materials, on the other hand, apoptosis removes damaged or unwanted cells. We investigated the role of PI3-kinase in angiotensin II-induced podocyte injury.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and at different incubation times. Cell survival/death-modifying reagents and Atg5 siRNA were applied. The changes of podocyte autophagy and apoptosis were observed by confocal imaging, western blotting, realtime PCR, FACS and TUNEL assay according to the presence of Ang II.

Results: Ang II-treated podocytes showed an increase in autophagosomes compared with control cells at early phase in a dose-dependent manner. This pro-autophagic effect of Ang II was inhibited by pretreatment with 3-methyladenine (3-MA), an inhibitor of PI3-kinase class III. Atg5 siRNA reduced LC3 puncta levels and increased the number of apoptotic podocytes over that observed with Ang II treatment at 12 hours. Thereafter, Ang II reduced the expression of autophagy-related genes, such as, Atg3, Atg5, Atg7, and bcl-2 at 24 hours and induced podocyte apoptosis at later stages, 12 and 24 hours in concentration- and time-dependent manners in FACS and TUNEL assays. PI3-kinase inhibitors, 3-MA and LY294002, and Atg5 siRNA further increased Ang II-induced podocyte apoptosis. Thereafter, Ang II induced podocyte apoptosis significantly in concentration- and time-dependent manners in FACS and TUNEL assays. Therefore, autophagy precedes apoptosis for cytoprotection in angiotensin II-induced podocyte injury.

Conclusions: We suggest that PI3-kinase have a protective role in Ang II-induced podocyte injury by promoting autophagy and suppressing apoptosis.