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CD2AP/PI3-kinase 경로를 통한 angiotensin II의 족세포사멸기전

충북대학교 의과대학 소아청소년과

하태선, 박혜영

Angiotensin II Induces Podocyte Apoptosis by the Downregulation of CD2AP/PI3-kinase Pathway

Tae-Sun Ha, Hye-Young Park

Department of Pediatrics, College of Medicine, Chungbuk National University

Objective: Angiotensin II (Ang II) promotes podocytes dysfunction directly or indirectly, causing proteinuria. The glomerular slit diaphragm (SD), a slit between interdigitating foot processes of podocytes, serves as a size-selective barrier and is linked to the actin-based cytoskeleton by adaptor proteins, including CD2-associated protein (CD2AP). Therefore, damages to CD2AP affect not only the function of the SD, but also directly disrupt the podocyte cytoskeleton, leading to pathological features including proteinuria. In addition, CD2AP can facilitate the nephrin-induced phosphoinositide 3-kinase (PI3-K)/Akt signaling, which protects podocytes form apoptosis. We investigated the changes of CD2AP and podocyte apoptosis by Ang II, a major vascular injury inducer.

Research Design and Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and signal-related agents. The changes of CD2AP by Ang II were observed by confocal imaging and Western blotting and podocyte apoptosis by TUNEL assay and FACS.

Results: Ang II decreased CD2AP stainings diffusely and induced spatial separation from concentrated nephrin, similar to those of compound C-treated condition. AICAR and metformin, AMPK activators, ameliorated the abnormal distributional changes of CD2AP. In Western blot analysis, Ang II notably reduced CD2AP in time- and concentration-dependent manners, which were recovered significantly by AMPK activators and Ang II type 1 receptor (AT1R) antagonist, losartan. LY294002, a PI3-kinase inhibitor, further reduced CD2AP protein suppressed by Ang II. Ang II increased the intracellular ROS level of podocytes via Nox4 and also induced podocyte apoptosis in FACS and TUNEL assay in time- and concentration-dependent manners, which were also recovered significantly by AMPK activators and losartan in TUNEL assay.

Conclusions: We suggest that Ang II induces the relocalization and reduction of CD2AP protein in podocytes via AT1R, which would cause podocyte apoptosis by the suppression of AMPK and PI3-K signalings and the oxidative stress.

Key Words: 안지오텐신 II, 세포사멸, 족세포
Angiotensin II, Apoptosis, Podocyte