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## **Angiotensin II promotes podocyte apoptosis through the modulation of CD2AP and AMPK**

**Tae-Sun Ha**<sup>1</sup>, In-Wha Jeong<sup>2</sup>, Hye-Young Park<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Chungbuk National University College of Medicine, Korea, Republic of

<sup>2</sup>Department of College of Medicine, Chungbuk National University College of Medicine, Korea, Republic of

**Objectives:** Angiotensin II (Ang II) promotes the development and progression of proteinuria and renal diseases. CD2-associated protein (CD2AP) in podocytes serves as an adaptor protein binding to nephrin and podocin, anchoring these slit diaphragm proteins to actin filaments of podocyte cytoskeleton. In addition, CD2AP can facilitate the nephrin-induced PI3-K/AKT signaling, which protects podocytes from apoptosis. AMP-activated protein kinase (AMPK), as a sensor of cellular energy status, has been known to play an important role in the pathophysiology of metabolic diseases, including diabetes, and its renal complications. We investigated the role of AMPK on the changes of CD2AP and podocyte apoptosis by Ang II.

**Methods:** Mouse podocytes were incubated in media containing various concentrations of Ang II and AMPK-related agents. The changes of CD2AP and podocyte apoptosis were observed by confocal imaging, western blotting, and TUNEL assay according to the presence of Ang II.

**Results:** CD2AP and AMPK $\alpha$  were located diffusely but predominantly in peripheral cytoplasm and co-localized with nephrin. Ang II reduced AMPK $\alpha$  in time and dose-sensitive manners and also 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 AMPK $\alpha$  and CD2AP. Ang II also reduced (Thr172) phosphorylation of AMPK $\alpha$  and CD2AP in time- and concentration-dependent manners, which were significantly recovered by metformin and AICAR. Ang II type 1 receptor antagonist, losartan also recovered CD2AP suppressed by Ang II. LY294002, a PI3-K inhibitor, reduced CD2AP suppressed by Ang II. Ang II increased apoptosis in time- and concentration-dependent manners, which were ameliorated by AMPK activators and siCD2AP.

**Conclusions:** Our findings suggest that Ang II induces the relocation and suppression of podocyte CD2AP and AMPK $\alpha$  via Ang II type 1 receptor and through the inhibition of PI3-K signaling, which trigger podocyte apoptosis induced by Ang II.