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学位論文の内容の要旨

専　攻	分子情報制御医学	部　門	生体情報学
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論文題目	Roles of Na^+/H^+ exchanger type 1 and intracellular pH in angiotensin II-induced reactive oxygen species generation and podocyte apoptosis		

（論文要旨）

Podocytes are highly specialized, terminally differentiated, epithelial cells, play a key role both in maintenance of the glomerular filtration barrier and in glomerular structural integrity. Ang II induces podocyte apoptosis both in vivo and in vitro. The reactive oxygen species (ROS), especially superoxide anion, play an important role in cell survival and apoptosis. Activation of NHE-1 and subsequent alkalinization of cytosol generally precedes the activation of many cellular functions, including intracellular signaling pathways associated with apoptosis. It has been also reported that Ang II activates the NHE-1 in various tissues. NHE-1 predominately expresses in differentiated podocytes. In the present study, we hypothesized that Ang II induces podocyte apoptosis via NHE-1-induced pHi changes and NADPH oxidase-derived ROS production.

We examined the effects of Ang II (100 nmol/L) on apoptosis, superoxide anions, and cytosol pH in podocytes. For intracellular pH measurements, image analysis was conducted using confocal laser microscopy after incubation with carboxyseminaphthorhodafluor-1.

Superoxide anions and intracellular pH were elevated with Ang II treatment. Apoptotic cell numbers, as measured by TUNEL staining and caspase 3 activity, were also augmented in the Ang II–treated group. Pre-treatment with olmesartan (RNH-6270, an active form of olmesartan medoxomil, 100 nmol/L, an Ang II type 1–receptor blocker), apocynin (50 μmol/L, NADPH oxidase inhibitor), or 5-N, N-hexamethylene amiloride [HMA, 30 μmol/L, Na+/H+ exchanger type 1 (NHE-1) inhibitor] abolished Ang II–induced podocyte apoptosis, whereas NHE-1 MRNA and protein expression was not affected by Ang II treatment. Moreover, Ang II increased NHE-1 phosphorylation.

These results suggest that superoxide production, NHE-1 activation, and intracellular alkalization were early features prior to apoptosis in Ang II–treated mouse podocytes, and may offer new insights into the mechanisms responsible for Ang II–induced podocyte injury.

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