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Inhibition of Rac1-GTPase attenuates renal ischemia/reperfusion-induced injury

Mi Ra Noh¹, Jee In Kim², Kwon Moo Park¹

¹Department of Anatomy, Kyungpook National University School of Medicine, Korea, Republic of

²Department of Molecular Medicine, Keimyung University School of Medicine, Korea, Republic of

Objectives: Migration of inflammatory cells is critical for ischemia/reperfusion (I/R) injury. Rac1, a member of the Rho-family of small GTPases, regulates cell migration through the control of actin cytoskeletal dynamics. Here, we investigated the role of Rac1 on I/R-induced mouse kidney injury.

Methods: Mice were intraperitoneally injected with either a single dose of NSC23766 (10 mg/kg body weight), an inhibitor of Rac1, or vehicle for 3 days before surgery and subjected to either ischemia or sham operation.

Results: When mice were subjected to 30 minutes of bilateral renal ischemia, kidney functions were significantly declined together with kidney tubule cell damage. This I/R insult increased the expression level of Rac1 in the kidney 4 hours after ischemia and then sustained until 21 days after ischemia. This post-I/R increase was relatively greater in the interstitium than in the tubules. Rac1-positive interstitial cells were most F4/80, a marker of macrophage, -positive. The treatment of NSC23766 significantly reduced post-I/R renal functional and structural damage accompanied with the inhibition in the post-I/R increase of F4/80-positive cell number. In vitro, NSC23766 treatment significantly reduced the migration of Raw 264.7, a mouse monocyte/macrophage, after treatment of MCP-1, a chemoattractant cytokine.

Conclusions: These results indicate that I/R increased Rac1 expression and Rac1 inhibition attenuates I/R-induced injury through suppressing macrophage infiltration into injured sites, suggesting that Rac1 represents a potentially useful target for the treatment of AKI.