Effect of NK-104 on proliferation of cells

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Objective: Products of intracellular mevalonate metabolism are essential for cell growth and proliferation. Inhibition of mevalonate synthesis by statins has been shown to suppress mesangial cell proliferation associated with various glomerular diseases. In this study, we investigated the effect of a new synthetic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, NK-104, on cultured rat mesangial cell proliferation.

Methods: The cultured rat mesangial cells were stimulated by 10% fetal calf serum or platelet-derived growth factor in the absence or presence of NK-104 and mevalonate metabolites. 5-bromo-2-deoxyuridine incorporation was used to assess DNA synthesis. In other experiments, Ras processing and mitogen-activated protein kinase activation were analyzed by Western blotting.

Results: NK-104 inhibited fetal calf serum- or platelet-derived growth factor-stimulated Ras processing and mitogen-activated protein kinase activation. NK-104 also caused inhibition of fetal calf serum- or platelet-derived growth factor-stimulated 5-bromo-2-deoxyuridine incorporation and cell proliferation. Mevalonic acid, farnesyl pyrophosphate, and geranylgeranyl pyrophosphate significantly prevented these inhibitory effects of NK-104.

Conclusions: The present results suggest that NK-104, by inhibiting the synthesis of isoprenoid metabolites of mevalonate, may modulate Ras-mediated signaling events associated with mesangial cell proliferation. (Hong Kong J Nephrol 2001;3(2):67-73)

Key words: Mesangial cell, Mitogen-activated protein (MAP) kinase, Mevalonate metabolism, NK-104, Ras