# Simvastatin reverses high glucose-induced apoptosis of mesangial cells via modulation of Wnt signaling pathway.

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## Abstract

BACKGROUND/AIMS: Disruption of Wnt/beta-catenin signaling in mesangial cells is a pathogenic consequence of diabetic nephropathy. We examined the role of simvastatin (SIM) in modulation of Wnt/beta-catenin signaling in the apoptosis of high glucose (HG)-stressed mesangial cells in vitro and in vivo. METHODS: For in vitro studies, we cultured mesangial cells, with or without SIM pretreatment, in 35 mM glucose and then assayed Wnt activity and apoptosis. For in vivo studies, we administered SIM to streptozocin-induced diabetic rats for 28 days and then dissected renal tissues for immunohistological assessment of Wnt signal expression and apoptosis of glomerular cells. RESULTS: SIM reduced the promotional effect of HG on caspase-3 expression, PARP activation, and cell apoptosis. HG significantly reduced Wnt4 and Wnt5a mRNA expression and SIM restored Wnt4 and Wnt5a mRNA expression to the level of controls. SIM also suppressed HG-mediated activation of GSK-3b and restored nuclear beta-catenin levels and phospho-Akt expression. This suggests that SIM alters the stability of beta-catenin, a critical element of mesangial cell survival. Exogenous SIM treatment blocked DNA fragmentation, increased the Wnt/beta-catenin immunoreactivities of cells adjacent to renal glomeruli, and attenuated urinary protein secretion in diabetic rats. CONCLUSIONS: SIM reduces the detrimental effects of HG on diabetic renal glomeruli in vitro and in vivo. SIM prevents HG-induced downregulation of Wnt/beta-catenin signaling and thereby blocks mesangial cell apoptosis. 2007 S. Karger AG, Basel