**Geranylgeraniol prevents the simvastatin-induced PCSK9 expression: role of the small G protein Rac1**

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Statins are known to increase the plasma levels of proprotein convertase subtilisin kexin type 9 (PCSK9) through the activation of the sterol responsive element binding protein (SREBP) pathway due to the inhibition of cholesterol biosynthesis. In the present study, we explore a possible role of the prenylated proteins on the statin-mediated PCSK9 induction in Caco-2. Simvastatin (40µM) induced both mRNA (14.3 ± 3.9 fold) and protein (2.0 ± 0.07 fold) PCSK9, after 24h incubation. The induction of PCSK9 mRNA was partially, but significantly, prevented by the co-incubation with mevalonate, farnesol and geranylgeraniol, while a complete prevention was observed on secreted PCSK9, evaluated by ELISA assay. Under the same experimental conditions, mevalonate, geranylgeraniol, but not farnesol, prevented the activation of the PCSK9 promoter by simvastatin in a sterol responsive element dependent manner. Simvastatin reduced by -35.7±15.2% the Rac1-GTP levels, while no changes were observed on RhoA- and Cdc42-GTP. This effect was prevented by mevalonate and geranylgeraniol. Rac inhibitor significantly induced PCSK9 levels, and a suppression of Rac1 expression by siRNA, counteract the effect of simvastatin on the induction of PCSK9 mRNA. Finally, simvastatin inhibited the nuclear translocation of STAT3 and its knock-down by siRNA increased significantly the susceptibility of Caco-2 to simvastatin on PCSK9 expression. Taken together, the present study reveal a direct role of Rac1 on simvastatin-mediated PCSK9 expression via the reduction of STAT3 nuclear translocation.