# Lovastatin Suppresses Invasiveness of Anaplastic Thyroid Cancer Cells by Inhibiting Rho Geranylgeranylation and RhoA/ROCK Signaling.

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## Abstract

Lovastatin, a competitive inhibitor of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, inhibits the conversion of mevalonate from HMG-CoA. Previously, we have reported that lovastatin treatment induced the occurrence of apoptosis and differentiation in ARO anaplastic thyroid cancer cells. Here, we demonstrated that lovastatin inhibited the ARO cell invasiveness and delineated the underlying molecular mechanism. Lovastatin significantly suppressed the EGF-induced cell adhesion, actin filament reorganization and transmigration. Lovastatin also reduced EGF-induced increases in the levels of phosphorylated p125(FAK) and paxillin. These inhibitory effects mediated by lovastatin can be prevented by pretreatment of the cells with mevalonate or geranylgeraniol (GGOH), but not farnesol (FOH). Accordingly, the consuming and depletion of geranylgeranyl pyrophosphate and consequent suppression of the protein geranylgeranylation, which is essential for activation of Rho GTPases, might account for the lovastatin-induced inhibition of cell motility and invasion. Western blot analysis showed that lovastatin inhibited membrane translocation of Rho (e.g. RhoA and Rac1) through decreasing post-translational geranylgeranyl modification of Rho. In addition, treatment of the cells with specific inhibitors against Rho (Clostridium botulinum C3 transferase) or ROCK (Y-27632) abolished the GGOH-mediated prevention of, and restored the lovastatin-induced decrease of cell invasion. Taken together, our results suggested that lovastatin suppressed EGF-induced ARO cell invasiveness through the reduction of Rho geranylgeranylation, which in turn suppressed the membrane translocation, and subsequent suppression of Rho/ROCK and FAK/paxillin signaling.