Lovastatin induces apoptosis of anaplastic thyroid cancer cells via inhibition of protein geranylgeranylation and de novo protein synthesis.

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Abstract

Lovastatin has been used to treat hypercholesterolemia through blocking the mevalonate biosynthesis pathway. Inhibition of mevalonate synthesis may result in antiproliferation and cell apoptosis. The aim of the present study was to examine the apoptotic effect of lovastatin in human ARO cells and delineate its underlying molecular mechanism. Our results showed that lovastatin dose- and time-dependently induced apoptosis in ARO cells. Pretreatment with cycloheximide dose-dependently suppressed lovastatin-induced apoptosis, suggesting that de novo protein synthesis is required for lovastatin effect on the induction of apoptosis in ARO cells. Treatment of the cells with 50 microM lovastatin induced cytochrome c translocation from mitochondria to cytosol; increases in caspase-2, -3, and -9 activity; and poly (ADP-ribose) polymerase degradation in a time-dependent manner. However, administration of mevalonate or geranylgeraniol, but not farnesol, dose-dependently prevented lovastatin-induced poly (ADP-ribose) polymerase degradation and the occurrence of apoptosis, but treatment with geranylgeranyl transferase inhibitor, GGTI-298, which blocks the geranylgeranylation, induced an increase in the percentage of the apoptotic cells. These data suggest that geranylgeranylation is required for survival of the lovastatin-treated ARO cells. To support this notion, we demonstrate that lovastatin dose-dependently decreased the translocation of RhoA and Rac1, but not Ras, from cytosol to membrane fraction. Moreover, the lovastatin-induced translocation inhibitions in RhoA and Rac1 were prevented by mevalonate and geranylgeraniol but not farnesol. In conclusion, our data suggest that lovastatin induced apoptosis in ARO cells by inhibiting protein geranylgeranylation of the Rho family but not farnesylation of the Ras family.