Selective induction of apoptosis by HMG-CoA reductase inhibitors in hepatoma cells and dependence on p53 expression.


Source
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Abstract

HMG-CoA-reductase inhibitors (statins) are widely used drugs to interfere with cholesterol biosynthesis. Besides this usage, evidence is increasing that statins might also be useful in therapy of viral infections or cancer. We investigated the effects of fluva-, simva-, atorva-, rosuva- and lovastatin on the viability of primary mouse and human hepatocytes as well as mouse (Hepa1-6) and human (Huh7, HepG2) hepatoma cell lines. Our results show selective cytotoxic effects of fluva-, simva- and lovastatin on hepatoma cells in comparison to primary hepatocytes. Using human hepatoma cells we found significant reduction of cell viability and induction of apoptosis in HepG2 cells, while statins did not affect Huh7 cells at concentrations not toxic for primary hepatocytes. Stable knockdown of endogenous p53, which is overexpressed in Huh7 cells, was able to restore susceptibility of Huh7 cells towards statin-induced toxicity. The anti-tumor effect of statins did not depend on a lack of cholesterol production, but was restored by supplementation of mevalonate or geranyl-geranyl pyrophosphate, prerequisites for prenylation of small G proteins. In conclusion, statins display a selective apoptotic effect on human hepatoma cells, with fluva-, simva- and lovastatin being both, most selective for tumor cells and most effective in inducing tumor cell apoptosis. Additionally, our results implicate that anti-tumor activity of statins requires cell proliferation and is reduced by p53 overexpression.

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