A Potential Role for Statins in Protecting Cells following Myocardial Infarction or Ischemia during CABG, and for Inducing Apoptosis of Malignant Cells

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Background: Protein degradation via the ubiquitin system involves their covalent tagging by ubiquiting following by their proteasome degradation. Hdm2/Mdm2 is a ubiquitin ligase that plays a key role in the regulation of cell growth/death and in malignant transformation. Overexpression of Hdm2/Mdm2 in cardiomyocytes provides protection from death caused by ischemia/reperfusion. Recent studies have shown that 3-hydroxy-3-methyl-glutaryl-CoA(HMG-CoA) reductase inhibitors (statins) induce overexpression of Hdm2/Mdm2. This post-translational effect led us to hypothesize that statins are acting at the level of the degradation/stabilization of Hdm2. In this study we investigated the effect of statins on the Hdm2-p53 pathway in cultured cells.

Methods: Testing the role of a simvastatin in Hdm2-p53 pathway using cell lines [U2OS(p53+/+), HEK-293(p53+/+), H1299(p53-/-) and neonatal-rat ventricular-myocytes (NRVM)], in which the pathway is well established.

Results: We found that incubation of U2OS, NRVM and H1299 cells with simvastatin increases the levels of Hdm2/Mdm2, implying that the effect is p53 independent. On the other hand, simvastatin decreases the levels of Hdm2 in HEK-293 cells, implying that the effect of simvastatin is cell-dependent. In these cells; simvastatin inhibits the degradation of Hdm2.

Conclusions: It is accepted that in many cases**,** Hdm2 supports survival. Our results suggest that simvastatin increases the level of the enzyme in NRVM cells and decreases it in HEK-293 cells. Therefore, statin might be considered a potential drug to cardiomyocytes from death following myocardial infarction or ischemia during CABG. In addition, these findings maybe suggest another potential therapeutic effect for statins induction of death in certain malignant cells.