The inhibitory effect of simvastatin on growth in malignant gliomas--with special reference to its local application with fibrin glue spray in vivo.

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Abstract:

Simvastatin is one of the competitive inhibitors of HMG-CoA reductase. During clinical trials, it has shown the ability to lower serum cholesterol. We investigated the effect of simvastatin on the growth of malignant gliomas in vitro, semi-in vivo, and in vivo. An in-vitro MTT assay revealed that human malignant glioma cell lines: U-251MG, U-373MG, and U-87MG, and rat malignant glioma cell line C6 were well inhibited in growth in a dose-dependent fashion. An anchorage-independent growth assay showed that the number of colonies (more than 100 microM in size) of human (U-373MG) and rat malignant gliomas (C6) was markedly reduced in a dose-dependent fashion. A flow cytometry analysis revealed that simvastatin treatment led U-251MG cells to accumulate in sub G0-G1. Immunostaining by TUNEL method showed that most glioma cells treated by 10 microM simvastatin had nuclear immunostaining, suggesting apoptotic changes of the treated cells. The human umbilical vein endothelial cells and human lung fibroblasts were inhibited in growth by no more than 20% of controls even with a high dose (10 microM) of simvastatin. In the semi-in vivo model, using newborn rat brain slice cultures, the rhodamine-labeled glioma cells were abolished after 7 days of local simvastatin treatment with fibrin glue probably suggesting that simvastatin led the cells to apoptosis. In rat models using subcutaneously inoculated C6, the local application of simvastatin combined with fibrin glue (spray method) was quite effective in inhibiting the growth of the tumor. These data suggest that simvastatin may be a novel anti-glioma drug, and the local application of simvastatin combined with fibrin glue (by spray method) may be a crucial new clinical strategy

against glioma growth.