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Simvastatin targets pancreatic cancer stem-like cells and sensitizes PDA cells to chemotherapeutic drugs via sonic hedgehog signaling

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Pancreatic ductal adenocarcinoma (PDA) is a disease with an exceptionally poor prognosis, high therapy resistance and poor effective therapeutic options. Advances in therapeutic treatments are urgently required. Cancer stem-like cells (CSCs), capable of unlimited self-renewal, have been proposed as a mechanism for cancer growth, therapy resistance and metastasis, involving PDA. Besides a function in normal tissue development, Sonic hedgehog (Shh) is highly expressed at all stages of human PDA. Recent data demonstrate that the expression of Shh is highly upregulated in CSCs and regulates them. Simvastatin, which is widely prescribed as cholesterol-lowering drug, was shown to inhibit tumor growth, metastasis and cancer-specific mortality in some studies, but the available data are not consistent. Most importantly, the hypothesis of my thesis, namely that simvastatin attacks pancreatic CSCs by inhibition of Sonic hedgehog signaling was never examined before. In my thesis, I evaluated the effect of simvastatin on 3 established and 1 primary PDA cell lines, as wells as non-malignant pancreas cells and mesenchymal stromal cells from human bone marrow. Results from cell viability assays show that simvastatin significantly reduces viability even at low concentration in CSC-enriched cell lines. I observed synergetic effects on pancreatic cancer cells upon combination of simvastatin with gemcitabine in vitro. Colony and spheroid assays indicated that simvastatin inhibits self-renewal, with an even stronger effect upon combination with gemcitabine. In addition, simvastatin significantly induced the differentiation potential. My results obtained with pancreatic cancer xenografts transplanted on the CAM of fertilized chicken eggs show that simvastatin inhibits tumor growth and metastasis in vivo. Importantly，no pronounced toxic side effects of simvastatin to non-malignant cells or chick embryos occurred. My further experiments suggest that the underlying mechanism of simvastatin is

associated with inhibition of cholesterol biosynthesis, which is essential for post-translational modification and thereby Sonic hedgehog activation. Simvastatin alone or combined with gemcitabine diminished the expression of Shh and related proteins Smo, Gli1 and activated the expression of the Gli-inhibitor Sufu. Likewise, the siRNA-mediated inhibition of Shh expression mimicked the simvastatin effect, whereas it´s overexpression prevented it. I confirmed these in vitro and in vivo findings in tissue of patients who did (n=34) or did not (n=34) receive simvastatin prior to surgery. Thus, the expression of Shh, its downstream signaling protein Gli1, along with the levels of progression markers Vimentin, CXCR4 and c-Met were lower in PDA tissues from patients with statin medication. Therefore, I conclude that simvastatin, as a robust, cost-effective and well-tolerated drug for prevention of hypercholesterolemia, may also be suited to prevent PDA and to improve the efficacy of standard therapy in patients suffering from PDA.