TARGETING THE MEVALONATE PATHWAY INHIBITS THE FUNCTION OF THE EPIDERMAL GROWTH FACTOR RECEPTOR: SYNERGISTIC CYTOTOXICITY INDUCED BY LOVASTATIN AND GEFITINIB

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INTRODUCTION. The EGFR is a key regulator of growth, differentiation and survival of epithelial cancers (1). In a small subset of tumors, the presence of activating mutations within the ATP binding site infers increased susceptibility to gefitinib, a potent tyrosine kinase inhibitor of EGFR (2). Agents that can inhibit EGFR function through different mechanisms may enhance gefitinib activity in patients lacking these mutations. Mevalonate metabolites play significant roles in the function of the EGFR (3), therefore, mevalonate pathway inhibitors may potentiate EGFR targeted therapies.

METHOD. In this study, we evaluated the effect of lovastatin on EGFR function and on gefitinib activity. Effects on EGFR function were analyzed by Western blot analysis using phospho-specific antibodies to EGFR, AKT and ERK. Cytotoxic effects of lovastatin and/or gefitinib were evaluated by MTT assay and flow cytometry.

RESULTS. Lovastatin treatment inhibited EGF induced EGFR autophosphorylation by 24hrs that was reversed by the co-administration of mevalonate. Combining lovastatin and gefitinib treatments demonstrated enhanced inhibition of AKT activation by EGF in SCC9 cells. The combination of 10µM lovastatin and 10µM gefitinib treatments showed co-operative cytotoxicity in all 8 squamous cell carcinomas, 4/4 NSCLC and 4/4 colon carcinoma cell lines tested. Isobologram and flow cytometric analyses of three representative cell lines with wild-type EGFR ATP binding sites confirmed that this combination was synergistic inducing a potent apoptotic response.
Figure 1. Western blot analysis of EGFR and activated phosphorylated EGFR in the SCC9 HNSCC derived cell line following addition of 50ng/ml of EGF for 15min. Activation of EGFR was inhibited with 10μM lovastatin treatment. Co-administration with 100μM mevalonate reversed this effect.

Figure 2. Isobologram analysis of the combination of lovastatin and gefitinib show synergistic cytotoxic effects in a variety of tumor derived cell lines.

**DISCUSSION.** Taken together, these results demonstrate that targeting the mevalonate pathway can inhibit EGFR function. They also suggest the potential utility of combining these clinically relevant therapeutic approaches.

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**REFERENCES**