Atorvastatin augments temozolomide’s efficacy in glioblastoma via prenylation-dependent inhibition of Ras signaling.

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Abstract
Ras signaling is often dysregulated and plays essential roles for the maintenance of glioblastoma. The proper function of Ras depends largely on the appropriate post-translational modification termed prenylation. Targeting protein prenylation therefore represents an alternative therapeutic strategy in glioblastoma. In this study, we demonstrate that prenylation inhibition by atorvastatin is active against glioblastoma. Atorvastatin alone dose-dependently inhibits growth and survival of multiple glioblastoma cell lines. Its combination with temozolomide significantly enhances temozolomide’s efficacy in in vitro cultured cell system as well as in vivo xenograft glioblastoma tumor model. We further show that this is achieved by the inhibition of Ras prenylation, leading to decreased activation of Ras and its downstream signaling pathways, including Erk, rS6 and eIF4E. Our findings suggest that inhibition of Ras activity by atorvastatin effectively targets the MEK and other signaling pathways. Our study provides a fundamental evidence to repurpose atorvastatin for a potential treatment of glioblastoma.