

# Statins synergize with hedgehog pathway inhibitors for treatment of medulloblastoma

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## Abstract

© 2018 American Association for Cancer Research. Purpose: The role of cholesterol biosynthesis in hedgehog pathway activity and progression of hedgehog pathway medulloblastoma (Hh-MB) were examined in vivo. Statins, commonly used cholesterol-lowering agents, were utilized to validate cholesterol biosynthesis as a therapeutic target for Hh-MB. Experimental Design: Bioinformatic analysis was performed to evaluate the association between cholesterol biosynthesis with hedgehog group medulloblastoma in human biospecimens. Alterations in hedgehog signaling were evaluated in medulloblastoma cells after inhibition of cholesterol biosynthesis. The progression of endogenous medulloblastoma in mice was examined after genetic blockage of cholesterol biosynthesis in tumor cells. Statins alone, or in combination with vismodegib (an FDA-approved Smoothed antagonist), were utilized to inhibit medulloblastoma growth in vivo. Results: Cholesterol biosynthesis was markedly enhanced in Hh-MB from both humans and mice. Inhibition of cholesterol biosynthesis dramatically decreased Hh pathway activity and reduced proliferation of medulloblastoma cells. Statins effectively inhibited medulloblastoma growth in vivo and functioned synergistically in combination with vismodegib. Conclusions: Cholesterol biosynthesis is required for Smoothed activity in the hedgehog pathway, and it is indispensable for the growth of Hh-MB. Targeting cholesterol biosynthesis represents a promising strategy for treatment of Hh-MB.

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