

The Smith-Lemli-Opitz Syndrome reveals a novel requirement for cholesterol in Hedgehog signal transduction

Michael K. Cooper^{1,2}, Christopher A. Wassif³, Jussi Taipale¹, Ruoyu Gong¹, Richard I. Kelley⁴, Forbes D. Porter³ and Philip A. Beachy^{1,5}

Departments of ¹Molecular Biology and Genetics and ²Neurology, Howard Hughes Medical Institute and Johns Hopkins University School of Medicine. ³Heritable Disorders Branch, NICHD, NIH. ⁴Kennedy Krieger Institute

The Smith-Lemli-Opitz Syndrome (SLOS) is an inborn error of cholesterol biosynthesis characterized by numerous developmental anomalies, including holoprosencephaly in severe cases. Many of the anomalous structures and organs in patients with SLOS are patterned by the vertebrate Hedgehog family of secreted signaling proteins. We have found that the Hedgehog signal response in cells from a mouse model of SLOS is impaired and that the degree of pathway inhibition correlates with the level of cellular cholesterol depletion. Furthermore, the inhibitory effect of cholesterol depletion appears to operate through the activity of the Smoothed (Smo) protein in Hedgehog signal transduction. These results identify a novel requirement for cholesterol in the Hedgehog signal response and define a mechanism by which both environmental and genetic contributions determine disease severity.