Development, characterization, and treatment of a hypomorphic SLOS mouse model

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Introduction: The Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive, multiple malformation syndrome due to mutation of the 7-dehydrocholesterol reductase gene (DHCR7). DHCR7 reduces 7-dehydrocholesterol (7-DHC) to cholesterol. SLOS patients typically have decreased cholesterol and increased 7-DHC levels. Clinical manifestations are facial abnormalities, mental retardation, and limb defects including 2-3 toe syndactyly. The most common missense mutation in DHCR7 is 278C>T (T93M). Dietary cholesterol supplementation has been used to treat SLOS patients and small trials of simvastatin therapy to decrease 7-DHC levels have been reported.

Objective: To investigate therapeutic interventions for SLOS.

Methods: We generated a hypomorphic SLOS mouse model by "knocking-in" a T93M mutation using targeted homologous recombination in embryonic stem cells.

Results: T93M homozygous and T93M/null are viable, fertile, and appear to have normal growth. Phenotypically T93M/T93M and T93M/null mice have mild dilatation of the third and lateral ventricles, and T93M/null mice have 2-3 toe syndactyly. 2-3 toe syndactyly is the most common physical finding in SLOS patients. Sterol profiles analyzed by Gas Chromatography/Mass Spectrometry of brain, liver, and kidney in both one day and six weeks old mice showed elevated 7-DHC. As expected, 7-DHC levels were higher in T93M/null compared to T93M/T93M mice. To experimentally evaluate dietary cholesterol supplementation we compared T93M/null and wild type control mice at 8 weeks of age on a regular versus cholesterol supplemented diet. After 5 months, no survival or pathological differences were found. Sterol analysis of tissues showed biochemical improvement in some peripheral tissues; however, brain sterol levels were not changed. Neuromuscular testing (vertical pole and hanging wire) indicated that cholesterol supplementation may improve neuromuscular status. Treatment of T93M/null mice with simvastatin at doses of 10, 20 or 30 mg/kg/day by subcutaneous injection at 2 to 5 months of age for 3 weeks significantly decreased 7-DHC levels in serum, and in some peripheral tissues. Notably, simvastatin therapy also decreased dehydrocholesterol levels in the brain.

Conclusion: We are describing the development of a viable SLOS mouse model, and have demonstrated a beneficial effect of both cholesterol and simvastatin therapy in this mouse model.