



The impact of cholesterol deficiency on retinal development, structure and function

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Cholesterol is an essential molecule for the development and viability of higher eukaryotic organisms. Much attention has been paid to conditions where the over-abundance of cholesterol results in pathology (e.g., atherosclerosis). However, there is a family of human hereditary disorders that involve the inability to synthesize cholesterol, resulting in cholesterol deficiency and associated multiple phenotypic anomalies, failure to thrive, and profound neurological defects. One of these, Smith-Lemli-Opitz syndrome (SLOS), is caused by mutations in the gene that encodes in the last enzyme in cholesterol biosynthesis (DHCR7, 3 β -hydroxysterol- Δ 7-reductase; EC 1.3.1.21), resulting typically in excessive accumulation of 7-dehydrocholesterol and grossly diminished cholesterol levels in all bodily tissues.

Using a pharmacologically-induced rat model of SLOS, we have demonstrated a progressive retinal degeneration that impacts both rod- and cone-mediated vision, correlating well with clinical findings.

Ongoing studies with this model are probing the molecular and cellular processes underlying this retinal degeneration, as well evaluating potential therapeutic interventions to prevent or attenuate the disease severity. The results of these studies suggest that SLOS involves dysregulation of multiple genes and global involvement of other metabolic pathways beyond the initial defect in cholesterol biosynthesis, as well as oxidative modification of both lipids and proteins. We propose that antioxidant supplementation as an adjunct to the current standard of care (cholesterol supplementation) may provide substantial improvement to the therapeutic efficacy of managing SLOS and related cholesterol deficiency syndromes.