Retinal Degeneration and Therapeutic Intervention in an Animal Model of Smith-Lemli-Opitz Syndrome

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The Smith-Lelmi-Opitz Syndrome (SLOS) was the first discovered in a growing family of inborn anabolic defects in cholesterol metabolism, all of which have profound systemic and neurological effects. In SLOS, the last enzyme in the cholesterol pathway, which converts 7-dehydrocholesterol (7DHC) to cholesterol, is defective. Treatment of rats with AY9944, a selective inhibitor of this enzyme, results in deranged sterol metabolism and composition with progressive retinal degeneration and electrophysiological dysfunction, along with hypomyelination of the optic nerve. Feeding a high-cholesterol diet tends to normalize retinal sterol composition and partially rescues retinal function, particularly that of cone photoreceptors, but predictably does not improve myelination. Although there is no concomitant protection against retinal degeneration, photoreceptor cell death is reduced by cholesterol supplementation. The severity of the retinal degeneration correlates with lipid and protein oxidation, although rhodopsin (the major rod photoreceptor protein and visual pigment) remarkably is spared from oxidative damage. Preliminary studies suggest that antioxidants may provide additional protection against retinal degeneration in this model, which may have important consequences to the improved management of SLOS patients. Using genomic (microarrays), proteomic, and lipidomic approaches, we are currently probing the underlying mechanisms of photoreceptor cell death in this SLOS rat model. [Supported by U.S.P.H.S. grant EY007361, the March of Dimes, and Research to Prevent Blindness (RPB).]