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Rod-derived cone viability factor for treating blindness

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In patients suffering from retinitis pigmentosa (RP), the most common form of inherited retinal degeneration, the vision loss develops in two successive steps: rod photo receptors loss precedes that of cones. This secondary event leads to central vision loss and potentially complete blindness. Because the cones underlie all visual functions in lighted environment, cone rescue was deemed to be a clinically relevant target. We have identified by high content screening a cDNA encoding the first 109 residues protein that was referred as Rod-derived Cone Viability Factor (RdCVF). The bifunctional Nucleoredoxin-like gene Nxnl1 encodes through alternative splicing for RdCVF, a truncated thioredoxin-like protein that is secreted from rods, and RdCVFL, a thioredoxin protein involved in redox signaling and protection against hyperoxia through its interaction with the microtubule-associated protein TAU. We evaluated the protective effects of AAV-mediated expression of these two isoforms in a recessive model of rod-cone dystrophy, the *rd10* mouse. Intravenous injections of AAV-RdCVF engineered vectors slowed the rate of cone loss and increased the amplitude of the photopic electroretinogram. Expression of RdCVFL but not RdCVF reduced biproducts of oxidative stress. We also show that subretinal injection of AAV-RdCVF prevents the secondary loss of function of the cones in a dominant model of RP, the transgenic P23H rat. These results indicate distinct functions in the retina for these two *Nxnl1* gene products, and suggest that RdCVF holds promise for treating retinal degenerative disease almost independently of the causative mutation.

Biography

Thierry Leveillard completed his PhD in molecular biology at the University of Rouen (France) in 1989. He spent three years as a post-doctoral researcher in San Diego (UCSD and the Salk Institute) and moved back to Strasbourg where he worked at the IGBMC for four years. His current project was initiated in 1998 and ultimately continued in Paris where he was promoted 'Directeur de recherche' in 2006. The identification of this novel member of the thioredoxin family was awarded in 2005 by the Foundation Fighting Blindness. He is particularly interested in the therapy of inherited retinal degenerations and in retinal redox signalling.

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