

Cone Viability Factors: Molecular and Functional Studies

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In retinitis pigmentosa, a majority of causative mutations affects genes solely expressed in rods but cone degeneration follows the rod cell loss. Following transplantation and in vitro we demonstrated the role of photoreceptor cell paracrine interactions and identified a Rod-derived-Cone Viability Factor ,RdCVF, which increased cone survival in the rd1 mouse retina.

The characterization of the function of this gene (nucleoredoxin like1) and its ortholog RdCVF2 (nucleoredoxin like 2) points towards a dual function i.e. cell signaling and redox control. The genes Nxn1 and Nxn2 encode for both a short protein isoform corresponding to the trophic factors and an additional longer isoform with extend homology to the family of thioredoxins, which are involved in the defense against oxidative stress.

Analysis the RdCVF signaling and the phenotype of the mice with inactivation of the Nxn1 or Nxn2 genes establishes a rationale for an integrated signaling coupling retinal insults to neuroprotective response. The study of the two mutants shows that the phenotype, i.e. the progressive loss of cone function and density, is exacerbated by the induction of oxidative stress (e.g. light damage) and that the two genes are involved in different patterns of response to oxidative stress, thus excluding genetic redundancy.

We investigated whether RdCVF administration could not only induce cone cell rescue but also preserve cone function using the P23H rat retina. In this animal model of autosomal dominant retinitis pigmentosa, RdCVF injections provided a preservation of the electroretinogram amplitude to a higher extent than cone cell density. Effects on the morphology of cone outer segments account for this higher functional effect and might be related to the demonstration of a strong and specific interaction of RdCVF with the microtubule associated protein Tau.

These results indicate that RdCVF can not only rescue partially cones but also preserve significantly their functional activity, demonstrating thereby the potential of RdCVF for preserving vision in patients.