Cougling architecture of the Ai/ON cone bipolar cell network in the degenerate retina

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Purpose: Retinal network hyperactivity within degenerative retinal networks is a component of the disease process with implications for therapeutic interventions for blinding diseases that depend upon the surviving retinal cells. Connexin36-containing gap junctions centered on the Ai amacrines cell network appear to mediate the aberrant signaling observed in mouse models of retinal degeneration. However, it remains unclear whether this hyperactivity reflects changes in the underlying circuitry or dysfunction/dysregulation of the normative circuitry. Mapping retinal circuitry in the ultrastuctural rabbit Retinopathy of RGC-1 (RGC), has revealed normal circuitry and the underlying degenerative junctions. In addition to connexional Ai/To-Ai and Ai/ON cone bipolar cell (CB) coupling, we describe pervasive intra- and cross-class coupling motifs among ON CBs that extend and dramatically exceed the coupled Ai/To CB network topologies. Since virtually every gap junction in the inner plexiform layer contains Connexin36, these circuits likely participate in the aberrant signaling of degenerative retina. This study examined degenerative CBs in the PathoConnectome framework (PCF), an ultrastructural pathoconnectome of a rabbit model of retinal pigmentation.

Approach: RGC-1 is a 2mm resolution volume of retina from a 10 month-old, transgenic P347L rabbit model of autosomal dominant retinitis pigmentosa. In phase 1 retinal remodeling, a time period where cone and rod photoreceptors are still present, albeit going through stress. RSC1 spares the viable to basal outer nuclear layer and extends by autotransplantation of retinal microcyoto and computational assembly. ON CBs, Ai amacrines, and their coupling partners were annotated using the Wikivision application and explored with 3D rendering and graph visualization of connectivity. Gap junctions were validated by 0.20 mm resolution recapitulation with normalized IxI normalization of 10-5. Motifs were compared to those discovered in RGC-1. RGC is a 2 mm resolution, 0.25 mm diameter volume of a light-adapted adult female Dutch Belted rabbit retina spanning the ganglion cell through inner nuclear layers.