Role of clustered Protocadherins in retinal ganglion cell axon morphology

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Clustered protocadherins (cPcdhs, comprised of the α, β, and γ-Pcdhs) have garnered significant attention for their isoform diversity giving each neuron a unique identity essential for neural development and circuit formation. Here, we use a mouse model lacking all isoforms except γC4 (*Pcdhg-1R1*) – which has normal neuronal cell number but disrupted starburst amacrine cell (SAC) self-avoidance – to explore the role of cPcdhs in retinal ganglion cell (RGC) axon phenotype independent of cell death. To analyze the combined effects of α- and γ-Pcdhs, we use AAV vectors with shRNA constructs to knock down the *Pcdha* cluster in *Pcdhg-1R1* mutants. In these animals, we observed that axon terminals of RGCs were densely clustered in lateral geniculate nucleus (LGN). To clarify the subtype-specific axon terminal morphology, we focus on a particular type of RGC using the synthetic promoter ProD1. ProD1-mediated expression is limited to a subset of ON-OFF direction-selective ganglion cells (ooDSGCs), bistratified ganglion cells whose dendrites align with those of SACs and express the marker CART. To visualize individual neurons, we co-injected AAV vectors encoding ProD1 Cre along with Brainbow vectors (AAV-EF1a-BbChT and AAV-EF1a-BbTagBY), which allow the visualization of 8 distinct colors, into the eyes of *Pcdhg-1R1* and C57 mice. All the axon terminals of ProD1-driven RGCs in the LGN were found to colocalize with vesicular glutamate transporter 2 (VGLUT2), a presynaptic marker for RGCs. In *Pcdhg-1R1* mice, we observed clusters of 6-7 boutons in the dLGN. With the additional knockdown of the *Pcdha* cluster, we noticed defects in the dendrite arborization of RGCs in the retina and more severe clustering of axon terminals in the dLGN. Ongoing work aims to define how impaired function in RGCs affect their synaptic connectivity from the retina to the thalamus using WGA (wheatgerm agglutinin). This work will shed light on the mechanisms underlying visual processing abnormalities associated with RGC dysfunction.