Abstract 777 B750

# Complex Rewiring in Retinal Remodeling

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**Purpose**: Our goal was to explore the nature and scope of anomalous rewiring in microneuromas formed during retinal remodeling in late-stage retinal degenerations.

**Methods**: Serial section ultrastructural computational molecular phenotyping (Jones et al. 2003 J Comp Neurol 464: 116) in the RCS (*mertk*) rat model of inherited retinal degeneration was performed on retinal microneuromas in PND 200-900 animals. Ultrastructural data were acquired from high resolution film-imaging of 90 nm sections and GABA, glycine, taurine and glutamate signals acquired from flanking 40 nm optical sections. Datasets were visualized as rgb and theme maps of classified cell types, and the emergent circuits modeled.

**Results**: Thousands of small synaptic aggregates (microneuromas) are formed *de novo* in the remnant inner nuclear layer of the remodeling rodent retina. Serially reconstructed microneuromas reveal important key features. (1) All types of neurons can contribute terminal processes to a microneuroma. One microneuroma contained 36 separate processes, including BCs, GCs, glycinergic ACs and GABAergic ACs, most of which made synapses and terminated in the microneuroma. (2) A new process can be both pre- and post-synaptic. Panel C shows partial circuitry of a reconstructed microneuroma. BC1 sends processes into both the microneuroma and the IPL, engaging in numerous presynaptic and postsynaptic assemblies. Included in this array is the anomalous chain of BC0 → BC1 → BC15 → AC6 → BC1. Modeling of such circuits shows high instability and resonant activity. (3) Microneuromas are also connected to the inner plexiform layer (IPL). BCs with extensive IPL connections also send single processes into microneuromas where they form and receive synapses.

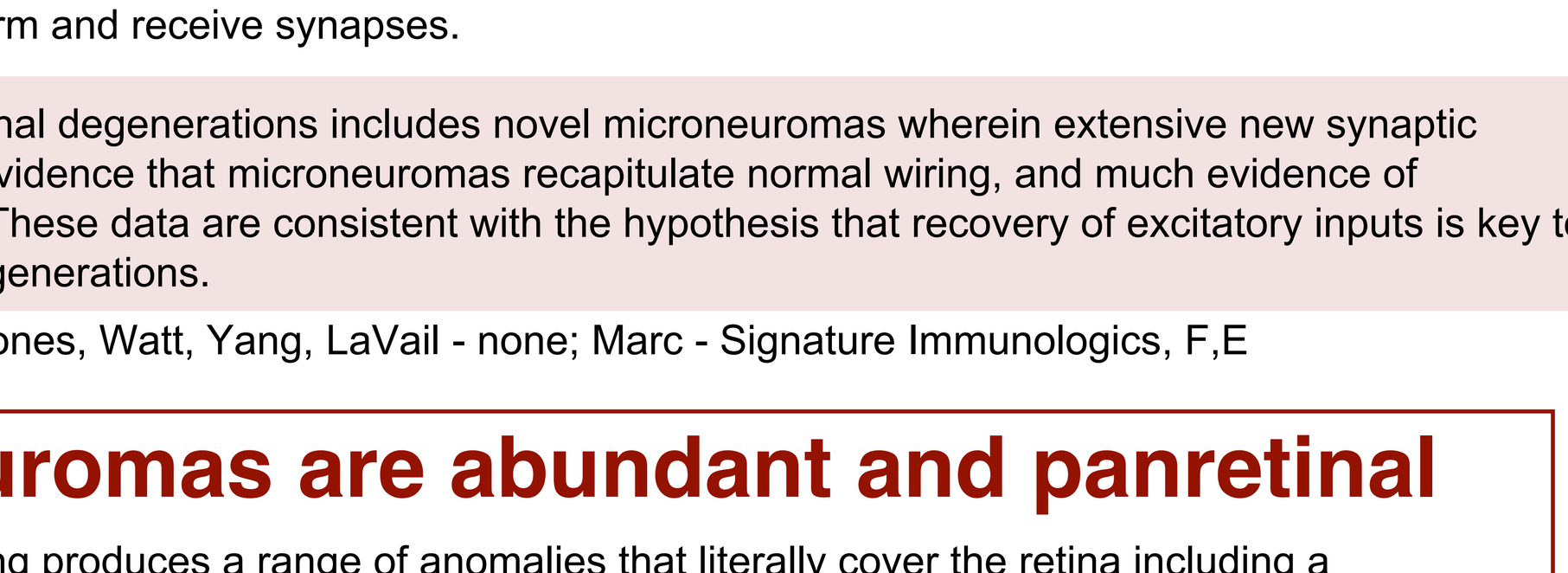
**Conclusions**: Rewiring in retinal degenerations includes novel microneuromas wherein extensive new synaptic forms emerge. There is little evidence that microneuromas recapitulate normal wiring, and much evidence of anomalous corruptive wiring. These data are consistent with the hypothesis that recovery of excitatory inputs is key to neuronal survival in retinal degenerations.

**Commercial Relationship**: Jones, Watt, Yang, LaVail - none; Marc - Signature Immunologics, F,E

## A. Microneuromas are abundant and panretinal

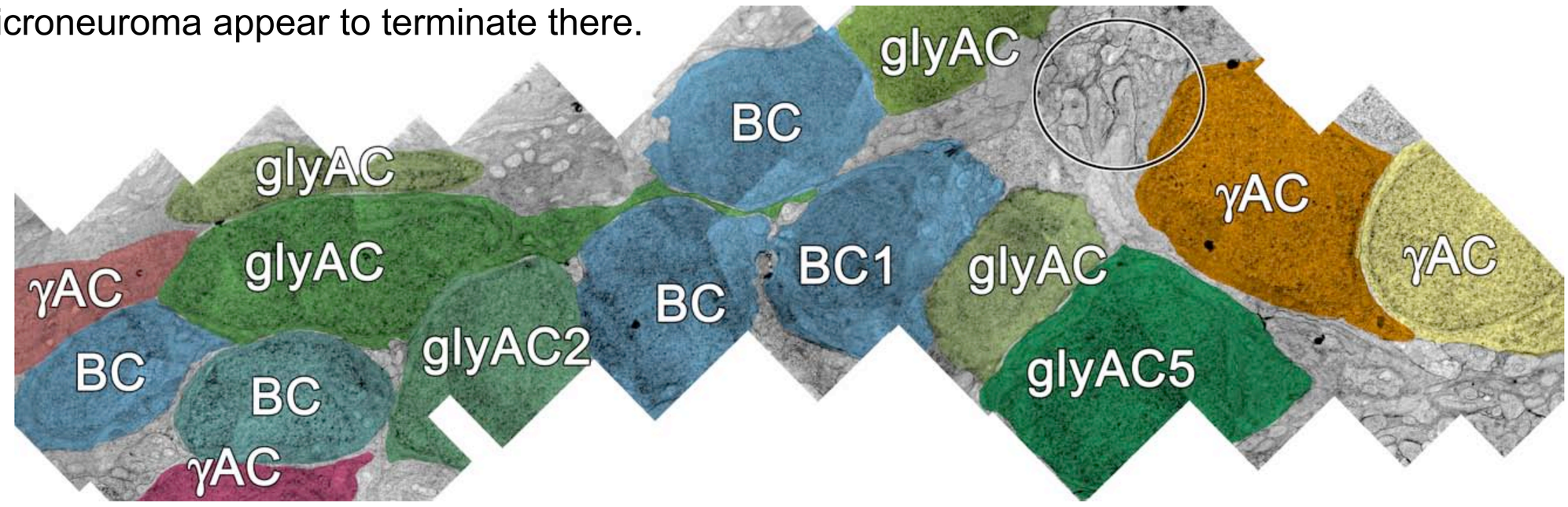
Advanced phase 3 remodeling produces a range of anomalies that literally cover the retina including a confluent glial seal, topological disruptions due to glial hypertrophy and sparse vascular invasion, formation of new fluid channels and widespread formation of **new neurite tracts and focal synaptic microneuromas.**

This RCS rat retina shows panretinal defects at a density of about 790 major defects / $mm^2$, equivalent to 40,000 / eye, a quarter of which are microneuromas that include bipolar, amacrine and ganglion cell processes. These defects are mapped (at right) in a 250 nm thin-section GABA signal from a pnd 900 RCS rat over a 4.29 mm retinal arcs.

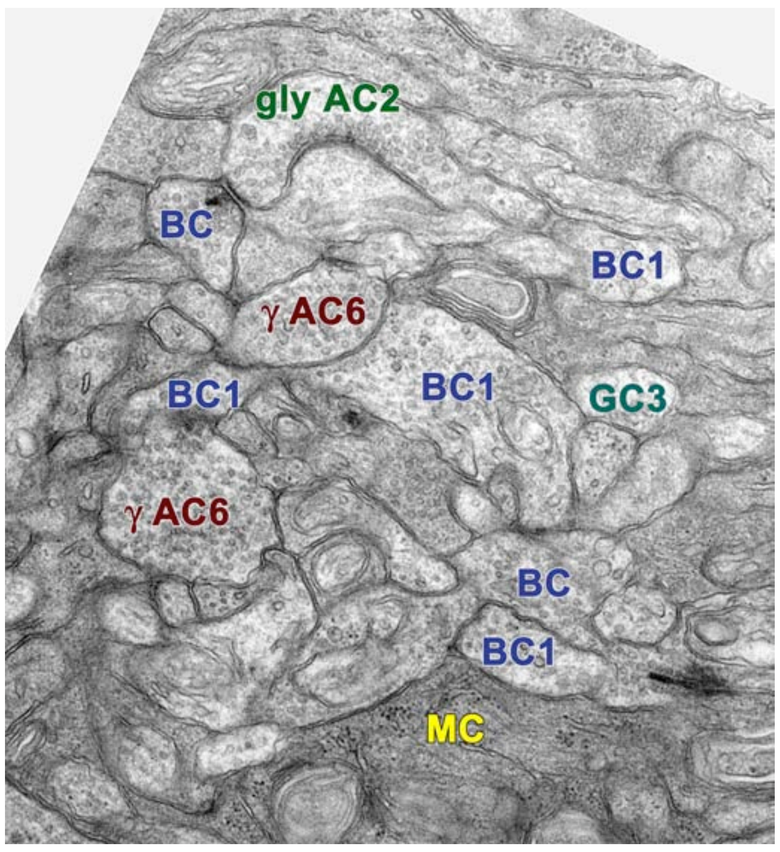


# B. Small clusters of neurons form new circuits

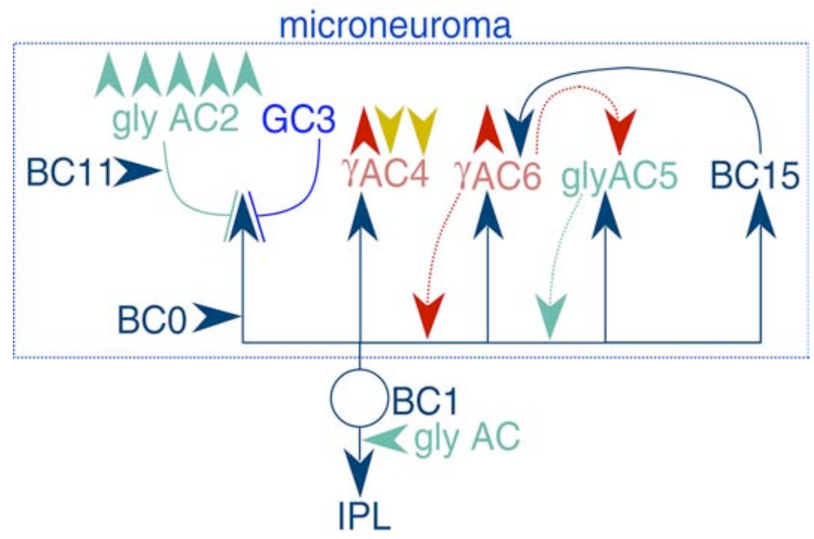
Microneuromas and the cells that form them can be tracked via serial section ultrastructural reconstruction combined with Computational Molecular Phenotyping (CMP) to classify every cell and process. This classified field of cells lies directly under the glial seal and flanks a microneuroma (circled). Several cells contribute processes to it, especially bipolar cell 1 (BC1). Most of the processes entering the microneuroma appear to terminate there.




# C. New circuitry is complex and abnormal

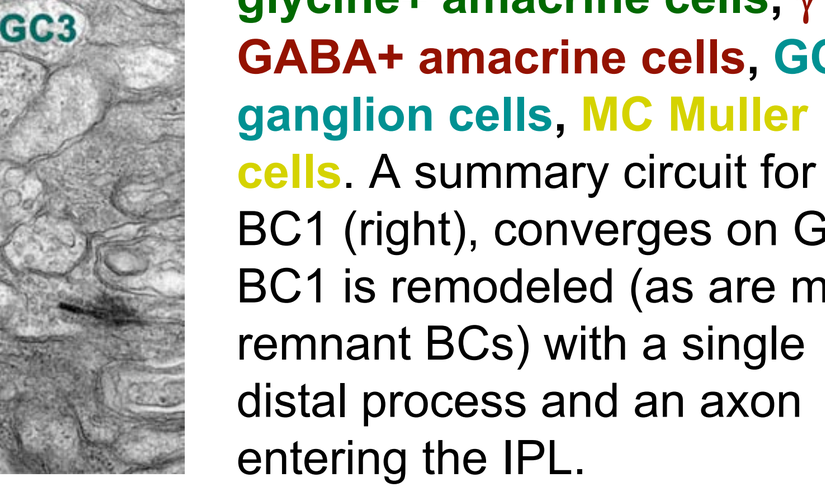


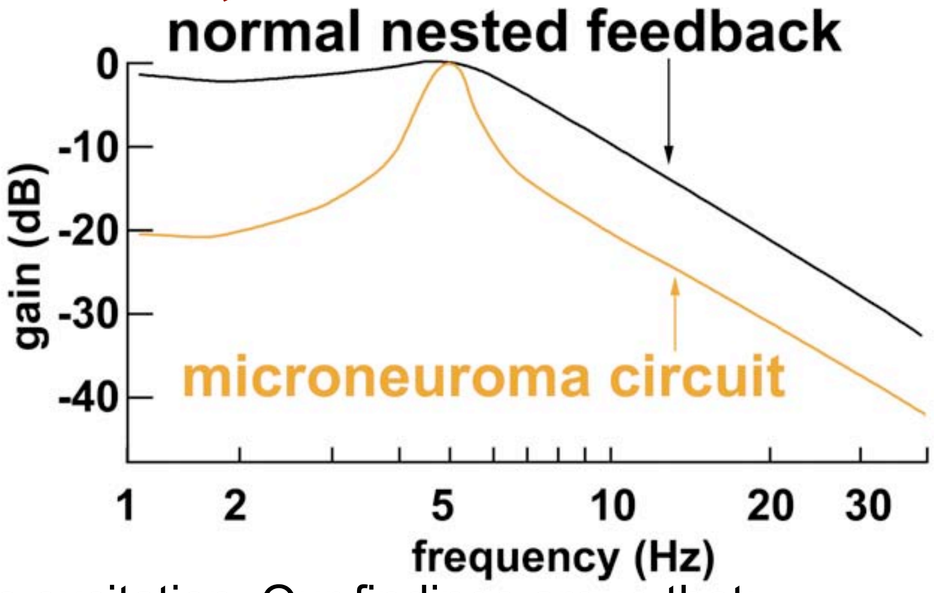

Individual microneuromas show abundant connections and it is not possible to infer whether they are "correct" from single or unclassified images. Combining CMP and serial section reconstruction enables comprehensive wiring summaries for elements in the microneuroma. At left is a single frame from a microneuroma with key processes labeled: **BC bipolar cells**, **gly AC glycine+ amacrine cells**, **γ AC GABA+ amacrine cells**, **GC ganglion cells**, **MC Muller cells**. A summary circuit for BC1 (right), converges on GC3. BC1 is remodeled (as are most remnant BCs) with a single distal process and an axon entering the IPL.




# D. Rewiring serves cell survival, not vision

We cannot record from microneuromas, but we can model them (Marc & Liu, JCN, 2000). Rewired circuits show poor fidelity and underdamped impulse responses (left) whose power spectra (right) reveal their resonant proclivities. Many studies of CNS development and degeneration show that neuronal survival requires excitation. Our findings argue that:




- **In retinal degenerations, survivor neurons build new circuits to optimize and prolong excitation**
- **In retinal degenerations, survivor neurons do not intrinsically know how to build visual circuits**
- **In retinal degenerations, neurons that fail to rewire into resonant circuits will die**
- **In retinal degenerations, there is a "mystery" source of intrinsic excitation**