# The metabolic response of Müller glial cells to photoreceptor degeneration

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Müller glia can alter their metabolic support during late phases of degeneration. Thus our long-term goal is to enhance neuronal survival by prolonging the ability of Müller glia to support metabolism. Our first aim is to visualize and quantify the metabolic states of activated glia during early degeneration stages.



Metabolic neuron-glia interactions. Adapted from Antonetti et al., *Diabetes*, 2006
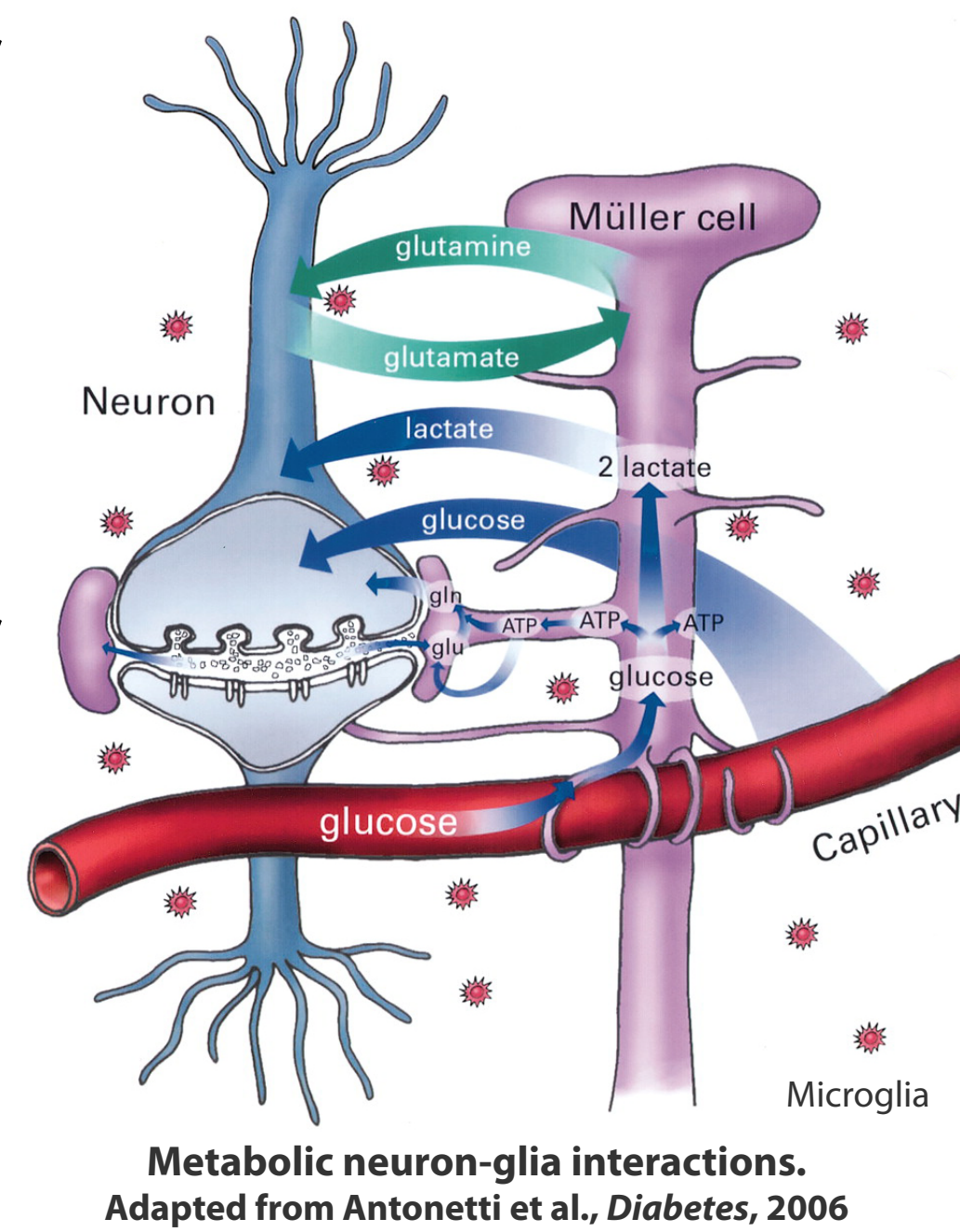
## Light-induced degeneration increases Müller cell density, intermediate filament expression and possibly vacuolization near dying cells.
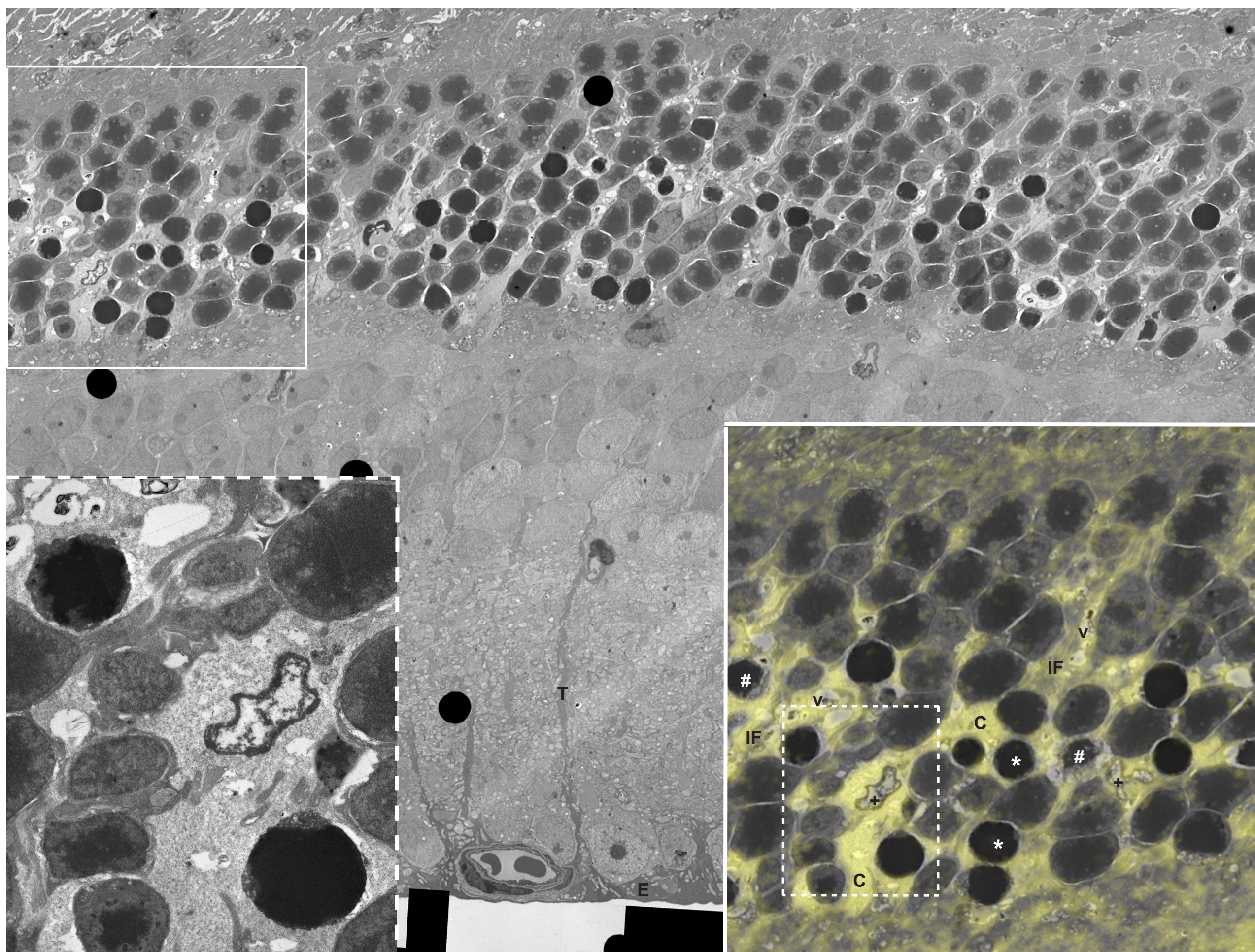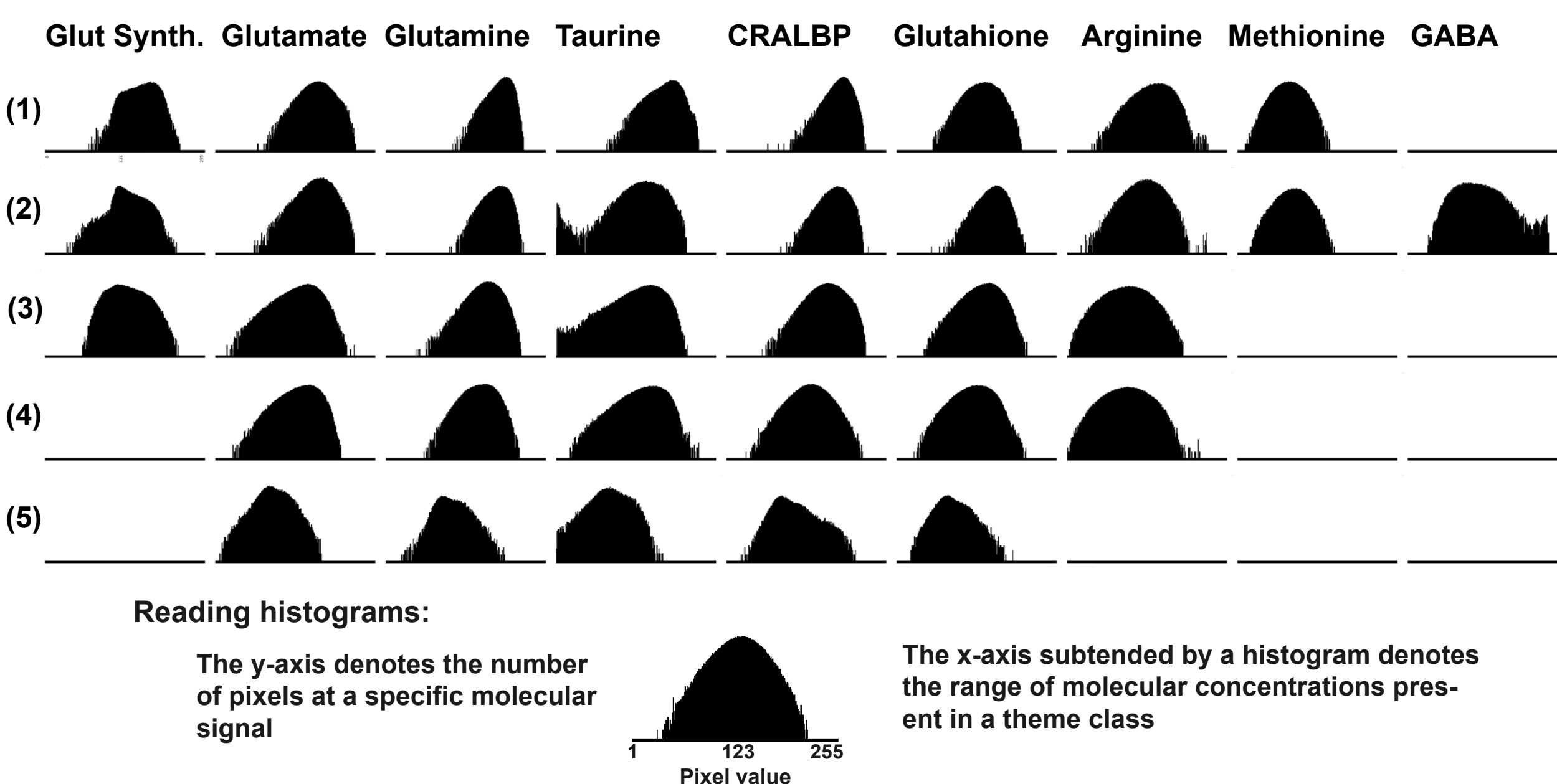


Electron microscopy of albino BALB/c mouse retina exposed to 12 hours light damage (~2k LUX; peak wave length ~470 nm). EM mosaic represents over 500 tiles. In areas of photoreceptor degeneration, Müller glia display high ribosome density at the trunk (T) and endfeet (E). In the enlarged region of ONL, the glutamine synthetase (GS) signal, in yellow, highlights Müller cell cytoplasm (C), intermediate filaments (IF) and vacuoles (v) with debris. The GS signal is particularly strong around photoreceptors with condensed chromatin and condensed cytoplasm (*), condensed chromatin and swollen cytoplasm (#), or evaginating nuclei (+).

## Photoreceptors and Müller glia in degenerating zones displayed diverse metabolic profiles within their populations and compartments
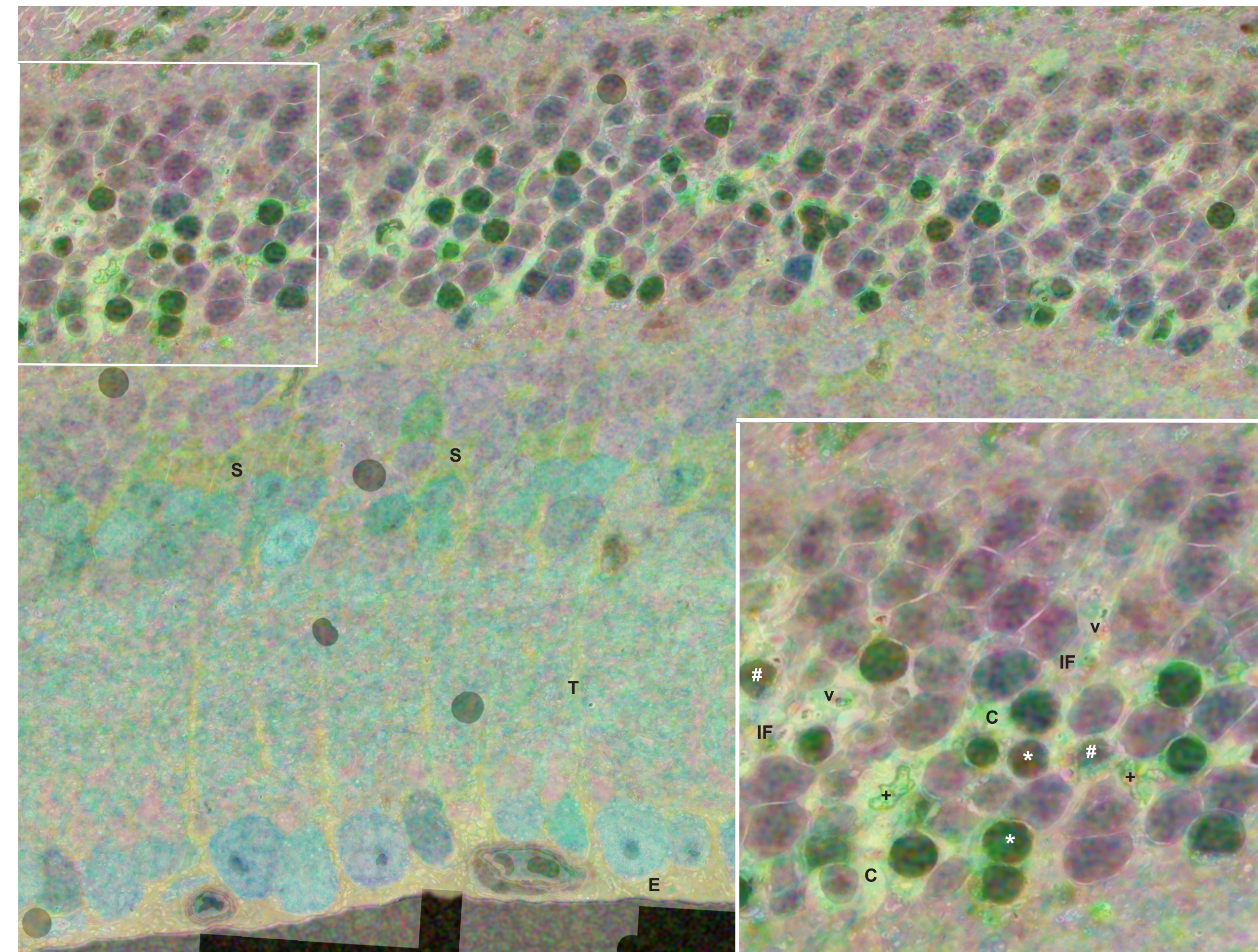


Taurine (red).glutamine (green).glutamate (blue) composite overlaid on electron microscopy. RGB has an opacity of 60%. The various yellow hues in Müller glia represent distinct taurine-glutamine mixtures at the endfeet (E), trunks (T) and soma (S). While the various blue hues at the photoreceptor layer represent stressed cells rich in taurine and glutamate.

## Müller glia displayed enhanced metabolic signals for glutamate metabolism, osmoregulation, retinoid metabolism, anti-oxidation, and protein synthesis



Reading histograms:

The y-axis denotes the number of pixels at a specific molecular signal

The x-axis subtended by a histogram denotes the range of molecular concentrations present in a theme class

Molecular signatures in Müller glia. Müller glia were classified using the glutamine synthetase and glutamate signal. Cell classes were derived from computational molecular phenotyping (CMP) utilizing the k-means algorithm. Each class can produce a histogram for their respective metabolite or proteomic signal. Signals not statistically different from background were omitted, including rhodpsin (1D4), LWS opsin and glycine.

## Müller glial compartments displayed distinct molecular profiles according to metabolic demands and degree of degeneration
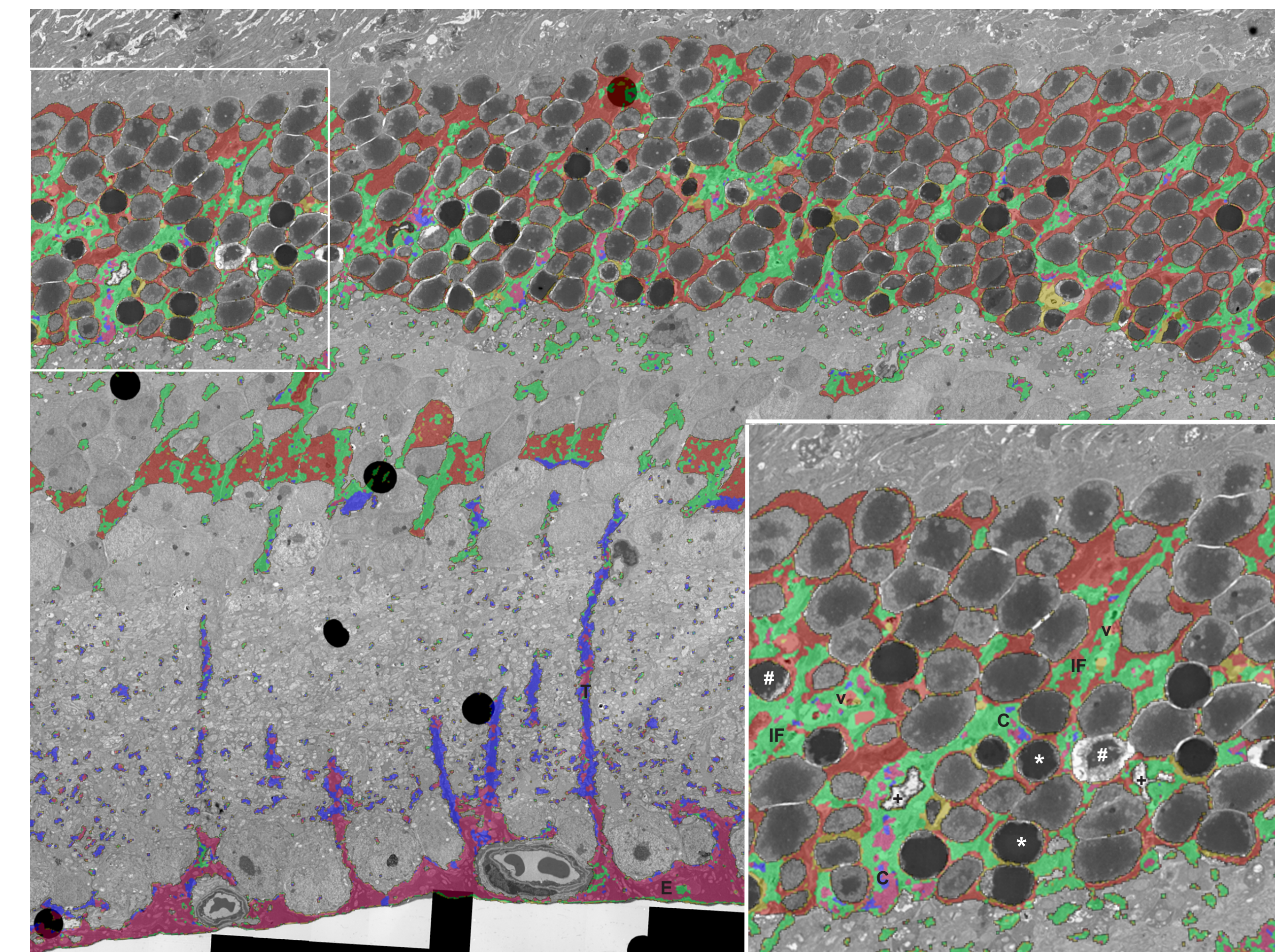


Metabolic theme map of Müller glia in degenerating zones. The theme map displays the results from the clustering to extract all distinct molecular phenotypes. Pink areas represent rich levels of GS, glutamate, glutamine, taurine and CRALBP; moderate levels of glutathione and arginine; and low levels of methionine. Green areas displayed similar marker distribution but at lower levels. Blue areas have high glutathione and low GABA content. Red areas have low GS levels. Brown areas appear to be photoreceptor cytoplasm

## Müller glia are highly sensitive to neuronal stress and compartmentalize their metabolic response

| Theme class | Compartments | ultrastructure feature | Metabolic signature |
|---|---|---|---|
| (1) pink | Endfeet<br>Near engulfed material | Ribosomes<br>Intermediate filament<br>vacuoles | High: GS, E, Q, TT, CRALBP<br>Moderate: J, R<br>Low: M |
| (2) blue | IPL Trunk | Ribosomes<br>Intermediate filament | High: J, E, Q, CRALBP<br>Moderate: GS, TT, R<br>Low: M, GABA, |
| (3) green | near dying cells<br>around MG nuclei | cytoplasm + vacuoles<br>Intermediate filament | High: Q, CRALBP<br>Moderate: GS, E, TT, J<br>Low: R |
| (4) red | around stressed cells<br>nucleus | Thick interm. filament bundles<br>Chromatin | High: Q<br>Moderate: E, TT, J, CRALBP<br>Low: GS, R |

(5) Brown areas appear to be swollen photoreceptor cytoplasm