3885 - B0165

Mitochondrial transfer between inner retinal neurons

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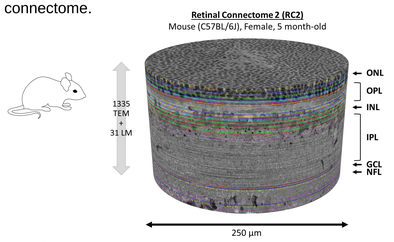
Purpose

Intercellular mitochondrial transfer has been reported across a variety of cells and tissues under both physiological and pathological conditions. Such transfer has shown broad therapeutic potential. The effectiveness of this therapy, however, is limited by a lack of understanding of the cellular and molecular mechanisms. Here, the ultrastructural features of mitochondrial transfer between inner retinal neurons discovered through retinal connectomics analysis is shown.

Methods

Retinal Connectome 2 (RC2) was built by automated transmission electron microscopy at ultrastructural (2nm/pixel) resolution. RC2 is a 0.25mm diameter volume of retina obtained from a 5-month-old female C57BL/6J mouse. The Viking application was used to visualize and annotate inter- and intracellular features of interest in the connectome.



Conclusion

These findings demonstrate active mitochondrial transfer between different classes of endogenous inner retinal neurons and suggests it may represent an important component of tissue homeostasis in the retina. Features of this transfer differ from previously reported mitochondrial transfer between photoreceptors upon transplantation, which may indicate cell type- or context-dependent differences in the cellular or molecular mechanisms. Our findings demonstrate active mitochondrial transfer between different classes of endogenous inner retinal neurons and suggest it may represent an important component of tissue homeostasis in the retina. Features of this transfer differ from previous reports by the Wallace and Pearson groups of material transfer between photoreceptors upon transplantation through tunneling nanotubes (Ortin-Martinez *et al*., 2021; Kalargyrou *et al*., 2021), which may indicate cell type- or context-dependent differences in the cellular or molecular mechanisms. Understanding these mechanisms could serve as a catalyst for development of novel therapeutics for disease in the retina and beyond.

Related Presentations

"Structural motifs of excitatory synapses in the mammalian retina" Taylor Otterness: Poster 1641 - B0347, Monday, April 24, 11:30 am - 1:30 pm & 5:15 - 6:15 pm

"Species-specific connectivity in the Aii connectome" Crystal Sigulinsky: Minisymposium: Advances in retinal connectomics: Tuesday, April 25, 8:45 am

"Müller cell connectomics in health and disease" Rebecca Pfeiffer: Minisymposium: Advances in retinal connectomics: Tuesday, April 25, 9:05 am

Support

This work was supported by National Institutes of Health [RO1 EY015128(BWJ), RO1 EY028927(BWJ), T32 EY024234(CLS), P30 EY014800(Core)]; the National Science Foundation NN2 2014862), an unrestricted grant from Gabe Newell (BWJ), and an Unrestricted Grant from Research to Prevent Blindness to the Department of Ophthalmology and Visual Sciences. Funding for the JEOL JEM-1400 TEMs generously provided by the late Martha Ann Healy and the Bloomberg Family.

Literature Cited:

-Ortin-Martinez A, Yan NE, Tsai ELS, Comanita L, Gurdita A, Tachibana N, Liu ZC, Lu S, Dolati P, Pokrajac NT, El-Sehemy A, Nickerson PEB, Schuurmans C, Bremner R, Wallace VA. 2021. Photoreceptor nanotubes mediate the in vivo exchange of intracellular material. *EMBO J*. 40(22):e107264. PMID: 34494680

-Kalargyrou AA, Basche M, Hare A, West EL, Smith AJ, Ali RR, Pearson RA. 2021. Nanotube-like processes facilitate material transfer between photoreceptors. *EMBO Rep*. 22(11):e53732. PMID: 34494703

-**RenderApp** (RRID: SCR_017350): Patterson, S.S., Kuchenbecker, J.A., Anderson, J.R. et al. An S-cone circuit for edge detection in the primate retina. Sci Rep 9, 11913 (2019).

Commercial Disclosures: SW, CLS, JRA, BWJ: None

Results

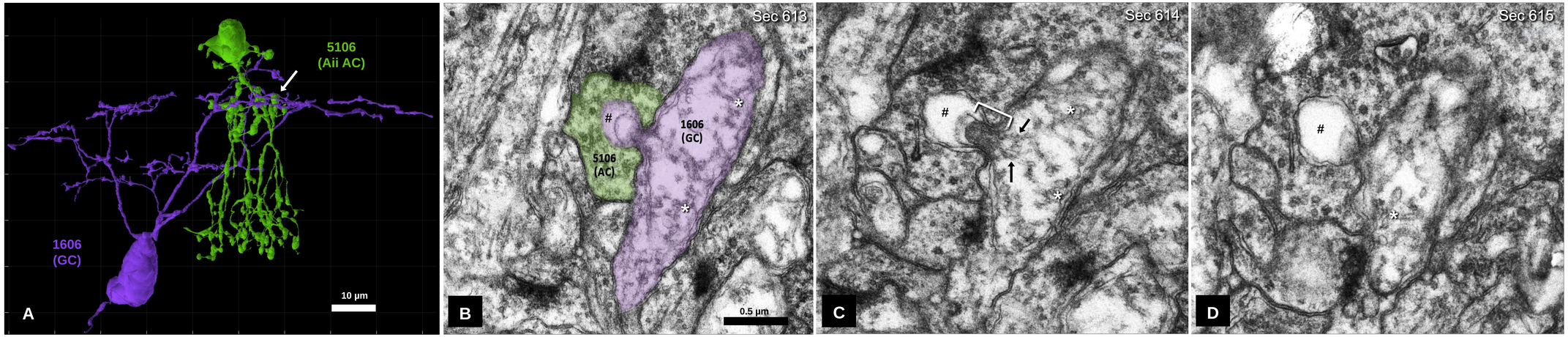
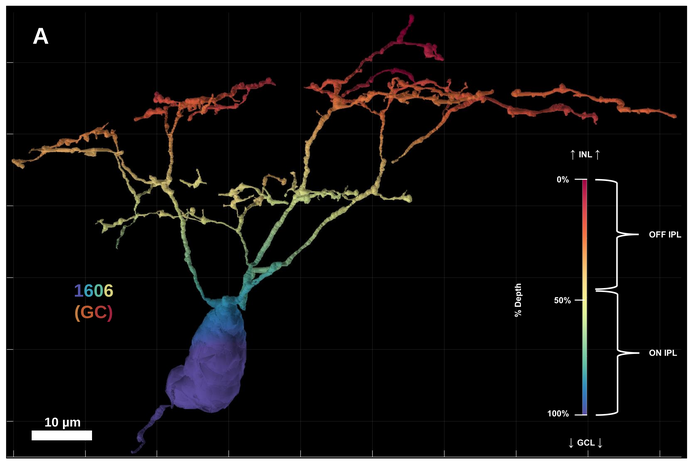
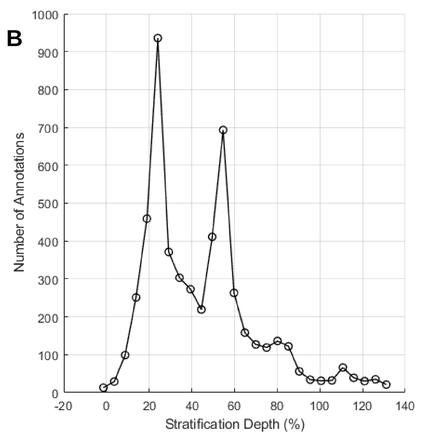


Figure 1. Mitochondrial transfer between a bistratified ganglion cell and Aii amacrine cell. (A) 3D rendering (RenderApp, Patterson *et al.*, 2019) illustrating the site of material transfer observed in the mouse inner plexiform layer between a bistratified ganglion cell (GC) and Aii amacrine cell (AC), as designated by the white arrow. (B-D) Transmission electron micrographs of material transfer in adjacent serial sections. The transferred material can be defined as a mitochondrion, confirmed by the presence of cristae (*). At the transfer site, a short, electron-dense 140-nm diameter tube with a curved cap (bracket in C) is tightly associated with the inner mitochondrial membrane of one neurite and extends into a vacuole (#) within the apposing neurite formed by the plasma membranes of the two cells. Thin cytoskeletal components consistent with actin microfilaments extend into the mitochondrion (black arrows in C). Abbreviations: Ganglion Cell (GC), Amacrine Cell (AC).





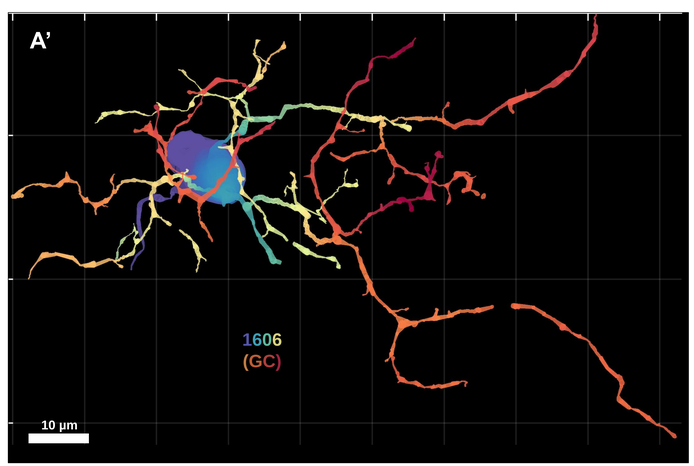


Figure 2. Stratification analysis supports a bistratified GC. (A) Side view of 3D rendering of GC 1606 colorized according to stratification depth using RenderApp (Patterson *et al.*, 2019) reveals arborization in both the ON and OFF IPL. Color bar denotes depth stratification within the inner plexiform layer. (A') Top-down view of 2D rendering of GC 1606 stratification depth using RenderApp as in A. (B) Corresponding histogram plot of GC 1606 stratification. Morphology consistent with GC Type 2 (Helmstaedter *et al.*, *Nature* 2013). Abbreviations: Ganglion Cell (GC), Ganglion Cell Layer (GCL), Inner Nuclear Layer (INL), Inner Plexiform Layer (IPL).

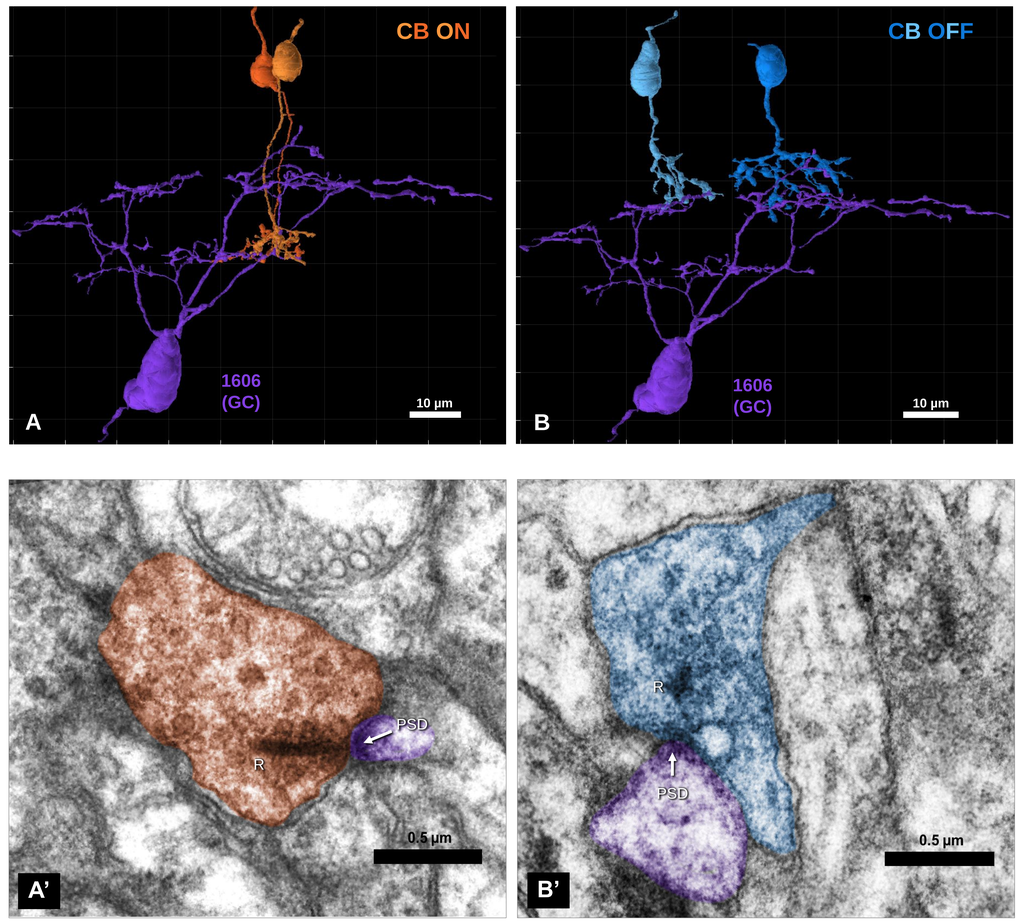


Figure 3. Synaptic confirmation of ON/OFF GC 1606. (A) 3D rendering (RenderApp, Patterson *et al.*, 2019) of two CB ON cells (orange) providing ribbon input to GC 1606 (purple). (A') Transmission electron micrograph of ribbon synapse between CB ON and GC 1606. (B) 3D rendering of two CB OFF cells (blue) providing ribbon input to GC 1606 (purple). (B') Transmission election micrograph of GC receiving ribbon input from CB OFF. Abbreviations: Ganglion Cell (GC), CB OFF (OFF Cone Bipolar Cell), CB ON (ON Cone Bipolar Cell), Ribbon (R), Postsynaptic density (PSD).