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RESEARCH NEWS

Gap junctions and hemichannels keep the RPE connected

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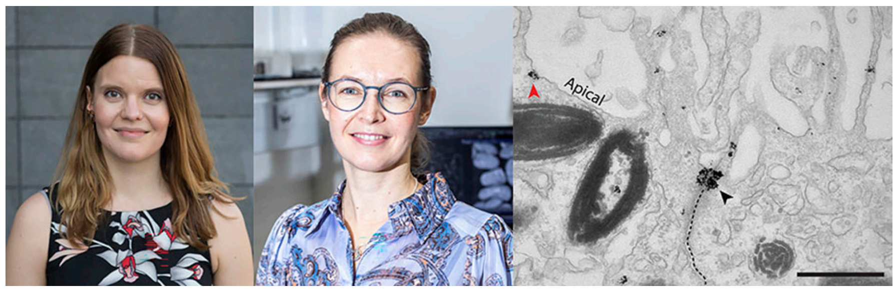
***JGP* study shows that the electrical properties of the retinal pigment epithelium are influenced by connexin-based gap junctions and hemichannels.**

The retinal pigment epithelium (RPE) is a layer of densely pigmented cells that underlies the retina and supports the function of photoreceptors. Some of these support functions—such as the secretion of growth factors and the renewal of photoreceptor membranes via phagocytosis of their outer segments—are regulated by voltage-gated ion channels (1, 2), suggesting that the electrical properties of the RPE are important for retinal health and disease. In this issue of *JGP*, Fadjukov et al. reveal that these electrical properties are regulated by both gap junctions and connexin hemichannels in the RPE (3).



Julia Fadjukov (left), Soile Nymark (center), and colleagues reveal that gap junctions and connexin hemichannels influence the electrical properties of the mammalian retinal pigment epithelium. Immuno-EM of human embryonic stem cell–derived RPE (right) shows the presence of connexin 43 in both gap junctions (black arrowhead) and apical hemichannels (red arrowhead). Credit: Author photos by Miika Fadjukov, Fadjukov Photoshooting and Jonne Renvall, Tampere University.

Gap junctions are composed of connexin proteins, which form hexameric hemichannels in the membranes of many cell types. Hemichannels in neighboring cells can align to create a gap junction that allows small molecules and ions to pass between cells, but individual hemichannels can have gap junction–independent functions as well.

Gap junctions are particularly prominent in the RPE, where they could facilitate electrical coupling between cells and potentially help synchronize the RPE's functions across the epithelial monolayer. Studies in amphibians revealed that RPE cells are, indeed, highly electrically coupled to each other (4); however, the connectivity of the mammalian RPE, and the contribution of gap junctions to the tissue's electrical properties, are largely unknown. Soile Nymark and colleagues at Tampere University, Finland, recently developed the ability to perform patch clamp recordings of single RPE cells in intact monolayers (1). "So, we wanted to look more closely at the electrical characteristics of the mammalian RPE," Nymark says.

Electrical conductance through gap junctions is likely to lower a cell's input resistance, thereby reducing its electrical excitability. Nymark and colleagues, including first author Julia Fadjukov, measured the input resistance of RPE cells in monolayer cultures derived from human embryonic stem cells and also in intact RPE isolated from mouse eyes (3). In both cases, treating cells with the gap junction blocking agent meclofenamic acid (MFA) dramatically increased input resistance, and this effect was reversed when the drug was washed out.

The researchers then switched to a dual patch clamp configuration to measure the extent of electrical coupling between cells. Neighboring RPE cells were, indeed, highly coupled, and this connectivity was abolished by the addition of MFA. Coupling between non-adjacent cells was significantly smaller, however, suggesting that, at least under baseline conditions, the connectivity of mammalian RPE monolayers is relatively low. "However, we think this can be dynamically regulated to allow fast spreading of ions and other signaling molecules across the epithelium," Nymark says.

Based on their measurements, Nymark and colleagues worked with Sophia Wienbar and Gregory Schwartz at Northwestern University to construct a computational model of an RPE cell network. The model revealed that inhibiting gap junctions cannot be the only mechanism by which MFA increases input resistance. Indeed, MFA also blocks individual hemichannels, and Fadjukov et al. determined that there are functional hemichannels in the apical membrane of RPE cells.

To test whether these hemichannels contribute to input resistance, the researchers

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used TAT-Gap19, a specific inhibitor of hemichannels formed by connexin 43, the most prominent connexin in RPE cells. Sure enough, TAT-Gap19 treatment increased input resistance, indicating that hemichannels, as well as gap junctions, influence the electrical properties of the RPE.

Nymark and colleagues now want to investigate whether the connectivity provided by gap junctions helps the physiological processes in the RPE that require precise synchronization, as well as the intriguing possibility that the apical hemichannels facilitate signaling between the RPE and the retina.

References

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