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RESEARCH NEWS

FAT3 provides a flicker of light

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JGP study (Avilés et al. https://doi.org/10.1085/jgp.202413642) reveals that visual perception of high-frequency flickers requires signaling by the tissue polarity protein FAT3 in retinal bipolar cells.

The retina contains >80 types of interneurons, whose cell bodies and synaptic connections are organized into a series of stereotypical layers within the eye. This laminar organization depends, in large part, on the activity of the membrane protein FAT3 in retinal amacrine cells. In this issue of *JGP*, however, Avilés et al. reveal that FAT3 is specifically required for the retina to respond to high-frequency flickers of light, and that this appears to be due to a distinct function of FAT3 at the dendritic synapses of retinal bipolar cells (1).

Light signals are detected by rod and cone photoreceptors in the outer nuclear layer of the retina and are transmitted to bipolar cells via synapses located in the outer plexiform layer. The bipolar cells are found in the inner nuclear layer alongside amacrine cells, and these interneurons all synapse with each other in the inner plexiform layer, where they also connect to the retinal ganglion cell layer that mediates output from the retina. In *Fat3* mutant retinas, amacrine cell bodies migrate to ectopic locations and form synapses in new places (2) because the FAT3 protein recruits cytoskeletal effectors required for cell migration and neurite retraction (3).

"However, the functional outcome of these cellular and structural manifestations [in *Fat3* mutant retinas] was a mystery," explains Evelyn Avilés, now an assistant professor at Pontificia Universidad Católica de Chile. "In this study, we aimed to determine the impact of FAT3 loss and lamination defects on retinal physiology and vision."

Yunlu Xue and colleagues, including first author Avilés and co-corresponding authors Lisa Goodrich and Constance Cepko of Harvard Medical School, used electroretinography (ERG) to compare the retinal responses of *Fat3*-mutant mice and control littermates (1). Remarkably, the researchers found that, despite the lamination defects, *Fat3*-mutant mice were able to detect basic dim and bright stimuli just as well as control animals.

"We decided to test these mice with some additional ERG protocols, namely the flicker ERG and step ERG," says Xue, an Investigator & Team Leader at Lingang Laboratory in Shanghai. Both of these ERG protocols measure retinal responses that are thought to be mediated by OFF-cone bipolar cells (OFF-CBCs), a type of bipolar cell that synapses with cone photoreceptors (4, 5) and expresses FAT3 (6).

The flicker ERG measures the response to high-frequency flickers, and Avilés et al. found that this response was greatly reduced in *Fat3*-mutant mice. Similarly, the step ERG protocol, which measures retinal activity when a long step of light is turned off, revealed a significantly reduced response in *Fat3* mutants.

Using a vision-cued fear conditioning assay, Avilés et al. confirmed that many *Fat3*-mutant mice are unable to perceive flickering light. Notably, deleting *Fat3* specifically from amacrine cells had no effect on the flicker ERG response while still causing lamination defects, supporting the idea of a distinct function for FAT3 in OFF-CBCs.

This function appears to involve FAT3's intracellular domain because mice expressing a version of FAT3 lacking this domain also showed defects in their flicker and step ERG responses. Avilés et al. determined that FAT3's intracellular domain binds to several proteins implicated in synaptic function and development, including the receptor-type protein tyrosine phosphatase PTPσ. PTPσ is expressed in OFF-CBCs and colocalizes to postsynaptic dendrites with the glutamate receptor subunit GRIK1. Synaptic levels of both PTPσ and GRIK1 were reduced in *Fat3*-mutant mice.

Evelyn Avilés and Yunlu Xue.

"Our observations support a model in which FAT3 locates to the dendrites of bipolar cells, where its intracellular domain interacts with PTPσ, GRIK1, and/or other, unidentified proteins, that are critical to fast synaptic transmission from cone photoreceptors to support the retina's response to high-frequency flickers," says Avilés.

"Much more needs to be done to fully understand the molecular mechanisms underlying the synaptic communication between cone photoreceptors and a dozen subtypes of bipolar cells," Xue says. "We would also like to investigate how the loss of FAT3 impacts the physiology of retinal ganglion cells, the output neurons of the retina."

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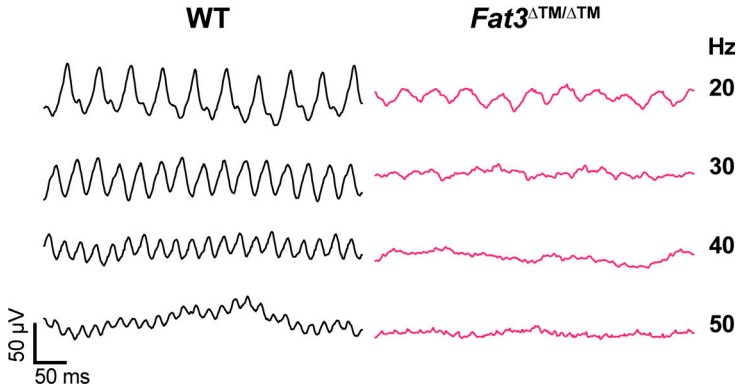

ERG recordings show that compared with control mice (left), the retinal response to high-frequency flickers is reduced in *Fat3*-mutant mice (right). Avilés et al. suggest that this is due to the role of FAT3's intracellular domain in localizing postsynaptic proteins to the synapses between cone photoreceptors and the OFF-CBC subtype of retinal bipolar cells.

References

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