This Week in The Journal

Midkine's Contribution to Photoreceptor Regeneration

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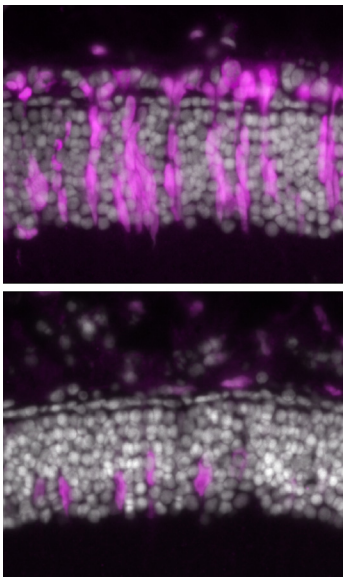
(see pages 1232–1247)

Müller cells, the predominant glia of the retina, carry out many functions typically associated with glia: they take up neurotransmitters, maintain proper ionic balance, and contribute to retinal structure. Furthermore, after retinal injury, Müller glia change shape, secrete neuroprotective molecules, and help form scar tissue. In teleost fish, however, Müller cells have an unusual, additional function: they return to a stem-cell-like state, re-enter the cell cycle, proliferate, and produce multipotent progenitors that can generate any type of retinal neuron. By detailing this process, researchers hope to discover ways to induce similar retinal regeneration in humans.

To understand how zebrafish Müller glia proliferate after retinal injury, Nagashima et al. focused on midkine-a, a growth factor that regulates the cell cycle in embryonic retinal precursor cells and is upregulated after retinal injury in adult fish. Loss-of-function mutations in midkine-a slowed, but did not prevent, retinal development; and light-induced photoreceptor death caused Müller glia to acquire a reactive phenotype, express stem-cell genes, and re-enter the G1 phase of the cell cycle in both wild-type and mutant fish. Expression of *Achl1*, an important driver of reprogramming, was somewhat lower in mutants, however. Moreover, a cyclin protein essential in the S phase of the cell cycle was not upregulated in mutant Müller cells, so the cell cycle stalled. Consequently, regeneration of cone photoreceptors was greatly reduced in mutant fish: whereas newly generated cones fully repopulated the retina by 14 d postlesion (14 dpl) in wild-type fish, few cones were generated in mutants, even by 28 dpl. Additional experiments suggested that midkine-a promotes cell-cycle progression by activating a tyrosine kinase (anaplastic lymphoma kinase), which leads to upregulation of id2a, a protein that inhibits cell-cycle inhibitors. Finally, whereas gliosis was transient in wild-type fish, it persisted through 28 dpl in mutants.

These results suggest that midkine-a regulates the transition from G1 to S phase in dedifferentiated Müller cells in injured zebrafish retina. Notably, the prolonged gliosis that accompanied stalling of the cell cycle is similar to that occurring in injured mammalian retinas. Therefore, increasing midkine levels in mammalian retinas might not only promote photoreceptor regeneration, but also limit the damaging effects of gliosis.



After photoreceptors were killed in wild-type zebrafish retina (top), Müller cells began to proliferate (magenta). Proliferation was greatly reduced in fish lacking functional midkine-a (bottom). See Nagashima et al. for details.

Nucleus Accumbens' Role in Motivation vs Action Selection

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(see pages 1332–1343)

The nucleus accumbens (NAc) integrates information about environmental and internal conditions and, guided by dopaminergic input, promotes behaviors likely to be the most advantageous in the current situation. The precise role of the NAc in such goal-directed behavior is not entirely clear, but the nucleus seems to be most important when an animal must choose which of multiple outcomes to pursue or when rewards are unpredictable or require sustained effort. Dopamine release in the NAc has therefore been hypothesized to motivate animals to undertake an action when outcomes are uncertain. Sicre et al. provide support for this hypothesis.

Rats performed a task in which they were instructed by different sounds to press a response lever (Go) or refrain from pressing the lever (NoGo) to receive a reward. Importantly, rats had to press a different lever to initiate each trial. Thus, the incentive to engage in reward seeking (signaled by pressing the initiation lever) was separable from the ability to select the appropriate action (Go or NoGo). This distinction was manifest as rats became sated during a session: they became less likely to initiate a trial, but the likelihood that they would subsequently respond correctly to the instructive Go/NoGo cue remained unchanged. Importantly, blocking either glutamate or D1 dopamine receptors in the NAc core also reduced the number of trials initiated without affecting the accuracy of Go/NoGo responses.

Electrophysiological recordings showed that many more NAc core neurons responded to the incentive cue (insertion of the initiation lever) than to the instructive cues. Moreover, most neurons that were excited by the incentive stimulus were activated only on trials in which the rat pressed the initiation lever. Notably, however, a small population that included many cholinergic interneurons was more excited when the incentive cue did not result in a lever press.

These data suggest that a major function of D1-receptor-expressing NAc core neurons is to increase the motivation of rats to exert effort, rather than to enable rats to choose the correct action to gain a reward. The results are also consistent with recent work (Collins et al., 2019, Biol Psychiatry 86:388) showing that activation of NAc cholinergic interneurons reduces the ability of reward-associated cues to invigorate actions.

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