Medical Xpress

The difference between eye cells is... sumo?

March 9 2009

Researchers at the Johns Hopkins University School of Medicine and Washington University School of Medicine have identified a key to eye development — a protein that regulates how the light-sensing nerve cells in the retina form. While still far from the clinic, the latest results, published in the Jan. 29 issue of *Neuron*, could help scientists better understand how nerve cells develop.

"We've found a protein that seems to serve as a general switch for photoreceptor cell development," says Seth Blackshaw, Ph.D., an assistant professor in the Solomon H. Snyder Department of Neuroscience at Johns Hopkins. "This protein coordinates the activity of multiple proteins, acting like a conductor of an orchestra, instructing some factors to be more active and silencing others, and thus contributing to the development of light-sensitive cells of the eye."

Blackshaw's laboratory is trying to understand the steps necessary for developing light-sensitive eye cells to transition into one of two types: rod or cone cells. Any breakdown in the development of either type of cell can lead to impaired eyesight and, says Blackshaw, "the loss of cone cells in particular can lead to irreversible blindness." Rod cells help us see in dim or dark light, and cone cells help us see bright light and color.

The research team was interested in how other genes that are active in the developing retina can act to promote the development of rod cells while suppressing the development of cone cells. So they took a closer look at the candidate protein Pias3, short for protein inhibitor of activated Stat3. Pias3 was known to alter gene control in cells outside of

the eye. In these cells, Pias3 doesn't directly turn genes on and off, but instead adds a chemical tag — through a process called SUMOylation — to other proteins that do switch genes on and off. And, since Pias3 also is found in developing rod and cone and no other cells in the eye, the team hypothesized that it might act to help these cells "decide" which type to become.

To determine whether Pias3 orchestrates rod cell development, the researchers used mice. First, they engineered mice to make more Pias3 than normal in the eye and counted rod and cone cells. Those eyes contained more rod cells than eyes from mice containing a normal amount of Pias3 protein. When they reduced the amount of Pias3 in developing mouse eyes, they found that the cells that might otherwise have been rod cells instead developed into conelike cells. So the team concluded that Pias3 promotes rod cell development and suppresses cone cell development.

Next they wanted to know if Pias3 works the same in eye cells as it does in other cells, through SUMOylation. The team altered the Pias3 protein to disrupt its SUMOylation activity. They found that eyes containing altered Pias3 did not develop the correct number of rod cells, suggesting that Pias3's SUMOylation activity was the key to its ability to promote rod and suppress cone cell development in the eye. The team also found that Pias3 SUMOylates a protein, Nr2e3, already known to influence rod and cone cell development, and showed that SUMOylation is critical for its ability to repress cone development.

Blackshaw hopes that his basic research results will contribute to translational and clinical research to generate more treatment options for blinding conditions such as macular degeneration, which arise from rod and cone cell death. "Future treatments might be designed to pharmacologically manipulate Pias3-dependent SUMOylation and potentially convert photoreceptors to a cone fate, thus providing a

treatment for forms of inherited blindness that selectively result in the death of cone photoreceptors," says Blackshaw.

More information: www.cell.com/neuron/

Source: Johns Hopkins Medical Institutions