Level of cellular stress determines longevity of retinal cells

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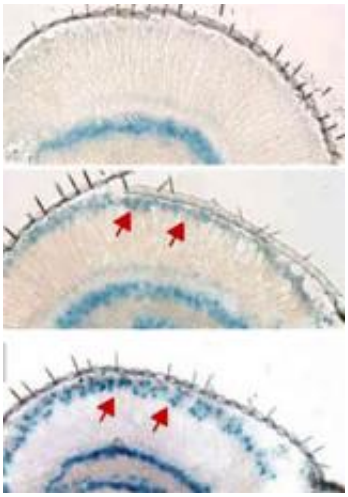

Knocked out. Compared to normal fruit fly retinas (top), those that lack one copy of NinaA (middle) or both (bottom) increase the expression of proteins (blue) that protect retinal cells from free radicals. This response is thought to add protection against the onset of neurodegeneration.

(PhysOrg.com) -- Stress can be adaptive. It can make you sharper, help you focus and it can even improve your performance. But too much of it can tax cells to the point where they can no longer cope and slowly self-destruct. Scientists at Rockefeller University now show that when the protein-making factory of the cell is exposed to moderate stress, neurons in the fruit fly retina and other cells not only resist death but also shore up their defenses against damaging free radicals and ultraviolet radiation.

The finding sheds light on the molecular mechanism by which cells compute their fate, and may point to therapeutic targets that protect against or delay the onset of neurodegeneration.

In their work, Hermann Steller, head of the Strang Laboratory of Apoptosis and Cancer Biology, and César Mendes, a former graduate student in the lab, genetically turned on three known cell death signals in fruit fly retinal cells, each of which directs the cell to undergo a process of controlled suicide. But when they knocked out a gene called NinaA, they saw that the cells halt their descent toward death. “The loss of NinaA tosses the cell a lifeline,” says Steller, who is also a Howard Hughes Medical Institute investigator and Strang Professor at Rockefeller. “It can send a pro-life signal that tells the neuron, ‘give repair a chance.’”

NinaA encodes for a protein that folds rhodopsin, the light-absorbing molecule that allows us to see color, into its proper shape. In cells that lack NinaA, rhodopsin doesn’t fold properly and starts to accumulate in the endoplasmic reticulum (ER), the cellular factory where proteins are modified, packaged and shipped to their proper destinations. In response to this accumulation, called ER stress, the cells activate a repair pathway to fix the problem, either derailing or halting the cell’s death cascade.

“Unlike other studies that use pharmacology and overexpression systems that quickly overwhelm cells and drive them to death, we managed to induce a more physiological and nonlethal level of ER stress by removing one or both copies of the NinaA gene,” says Mendes, who is now a postdoc at Columbia University. “This is one of the beauties of Drosophila as a model system — the capability to finely tune genetic dosage.”

The team, including Bertrand Mollereau, who is now a professor at the École Normale Supérieure de Lyon in France, believes that a mechanism

underlying this protection may involve antioxidant genes that protect retinal neurons from ultraviolet radiation and free radicals. When these neurons are exposed to mild ER stress, the team showed that they upregulate genes that shield them from the substances' harmful effects. "As in neurodegenerative diseases, when photoreceptor neurons die, they may never be replaced," explains graduate student Alexis Gambis, who also worked on the project. "The antioxidant upregulation is one way neurons have evolved to protect themselves from exogenous stress and it's especially important in the eye, which receives damaging UV energy from the sun."

But while the loss of NinaA delays the cell death cascade, this protection is lost when rhodopsin is absent from retinal cells, suggesting that it's actually the loss of NinaA and the resulting ER stress, and not the loss of rhodopsin's function, that makes the cells live longer. The finding further disentangles the molecular decision points at which cells choose between life and death under ER stress, which has been linked to a host of human diseases, including Alzheimer's, diabetes and cancer. "Cells don't make these decisions lightly," says Steller. "They have had millions of years to figure how to direct their fate."

More information: The EMBO Journal online: April 2, 2009. ER stress protects from retinal degeneration, César S. Mendes, Clémence Levet, Gilles Chatelain, Pierre Dourlen, Antoine Fouillet, Marie-Laure Dichtel-Danjoy, Alexis Gambis, Hyung Don Ryoo, Hermann Steller and Bertrand Mollereau

Provided by Rockefeller University (news : web)