St. Jude identifies the specific cell that causes eye cancer, disproving long-held theory

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Investigators at St. Jude Children's Research Hospital have identified the cell that gives rise to the eye cancer retinoblastoma, disproving a long-standing principle of nerve growth and development. The finding suggests for the first time that it may one day be possible for scientists to induce fully developed neurons to multiply and coax the injured brain to repair itself.

A report of this work appears in the Oct. 19 issue of the journal “Cell.” Michael Dyer, Ph.D., an associate member in the St. Jude Department of Developmental Neurobiology, is the report’s senior author.

Retinoblastoma arises in the retina—the multi-layered, membrane lining the back of the eye that responds to light by generating nerve impulses that are carried into the brain by the optic nerve.

The immediate importance of the St. Jude finding is that it unexpectedly showed that retinoblastoma can arise from fully matured nerves in the retina called horizontal interneurons. This disproves the scientific principle that fully formed, mature nerves cannot multiply like young, immature cells, Dyer said. Human neurodegenerative disorders such as Alzheimer’s disease can occur when differentiated nerves in the brain try to multiply, and in the process, trigger a self-destruct program called apoptosis. Differentiation is the process by which cells lose their primitive, stem-cell-like properties that include the ability to grow and multiply, and instead develop specialized shapes and functions.

“For the past 100 years, it’s been ingrained among scientists that differentiated mature nerves are so elaborate that they can’t divide, and if they try to divide, they undergo apoptosis,” Dyer said. “There was no exception to this rule until now. This is the first time that anyone has shown that under certain conditions, a fully mature and differentiated nerve can undergo cell division and multiply.”

The discovery that fully differentiated horizontal interneurons can multiply to form retinoblastoma also challenges the established scientific belief that cancer cells are most aggressive when they are undifferentiated, Dyer said. For example, the leukemic cells of chronic myelogeneous leukemia (CML) are much less aggressive when they are differentiated; and it is generally not aggressive until the tumor cells sustain mutations that block differentiation.

“On the contrary, we showed that when certain genes are inactivated in the retina, horizontal neurons that are already differentiated and fully integrated into the brain can start multiplying rapidly and produce a very aggressive cancer,” Dyer said. “This opens an exciting new chapter in the study of neurons and brain tumors.”

An important implication of this finding is that if researchers were able to alter the activity of certain genes in fully developed neurons, they might be able to trigger them to multiply temporarily and replace the neighboring neurons that were lost as a result of neurodegenerative diseases such as Alzheimer’s, Dyer said. “Having nerves duplicate themselves might be more efficient than trying to stimulate nerve replacement by inserting stem cells into the brain, since the existing nerves would already be in the right place to restore missing brain cells,” he said. “However, there is still a lot of research required to determine if it is possible to control gene activity to make this approach practical.”

Dyer’s group made their discovery by developing different populations

of mice whose retinas lacked one or more members of the Rb family of genes that include Rb, p107 and p130. This family of related genes is critical to the ability of an immature cell to stop dividing and begin to differentiate so it acquires certain specific characteristics required to do its job in the body.

The St. Jude researchers showed that when the mouse retina had reduced Rb family function, fully differentiated horizontal neurons could multiply while retaining all of the differentiated features of normal horizontal neurons.

As part of the study, the St. Jude team conducted microscopic and biochemical studies to prove that the multiplying cells were horizontal interneurons. Using such techniques, the researchers showed that as the horizontal interneurons multiplied their numbers up to 50-fold, they maintained their normal position in the retina as well as their normal connections to other cells.

If the horizontal interneuron cell division was allowed to proceed unchecked, highly differentiated tumors formed that resembled normal horizontal neurons. Unexpectedly, these tumors were aggressive and spread rapidly.

The investigators concluded that the Rb family's only task is to prevent mature horizontal interneurons from multiplying as they did when they were immature cells.

Source: St. Jude Children's Research Hospital

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