

Key to Treating Cancer May Be Finding its Original Cell

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(PhysOrg.com) -- Cancer biologists are turning their attention to the normal cells that give rise to cancers, to learn more about how tumor growth might be stopped at the earliest opportunity.

"Identifying the specific, normal cells that cancers come from can provide critical insight into how cancers develop," said Robert Wechsler-Reya, an associate professor of Pharmacology and Cancer Biology at Duke University Medical Center. "This may help us develop more rational and effective approaches to treatment."

Every cancer comes from a normal cell. The hard part is finding the cell at the root of each particular subtype of cancer. For the first time, the Duke team has identified two types of cells in the brain that can give rise to the malignant brain tumor medulloblastoma. This dangerous cancer, which occurs most commonly in children, is currently treated with a combination of surgery, chemotherapy and radiation, which have extremely severe side effects, said Wechsler-Reya, who is a member of the Preston Robert Tisch Brain Tumor Center at Duke.

To find the normal cells at the root of medulloblastoma, Wechsler-Reya's laboratory, in collaboration with Brandon Wainwright's laboratory at the University of Queensland in Australia, created mouse models of medulloblastoma by turning off the patched gene, a key regulator of cell growth in the developing brain cerebellum. In particular, they tested the effects of shutting off patched in granule neuron precursors (GNPs), which can only make one particular type of nerve

cell (neuron), or in stem cells, which can make all the different cell types in the cerebellum.

When they deleted *patched* in the neuron precursors, 100 percent of the mice developed medulloblastoma. Deleting *patched* from stem cells initially led to the formation of many more stem cells. However, most of these stem cells went on to form normal cell types within the cerebellum. Only the *patched*-less stem cells that gave rise to GNPs went on to form medulloblastoma tumors.

According to Wechsler-Reya, these studies provide the first definitive proof that medulloblastoma can be triggered in a granule neuron precursor or a stem cell. But even more importantly, they suggest that when it comes to cancer formation, the cell type in which a mutation happens is as important as the mutation itself. Although stem cells that lack *patched* also gave rise to other forms of brain cells, those cells did not form the tumors.

"Simply mutating a gene is not enough to cause cancer," Wechsler-Reya said. "The mutation has to happen in the right cell type at the right time. In the case of *patched*, GNPs provide the critical context for tumor formation."

Wechsler-Reya said that cancer biologists need to learn more about the genes that regulate proliferation (cell division), differentiation, survival, and programmed cell death in normal cells. A mutation in a proliferation gene, for example, can send the cell on a path of exaggerated division of cells -- becoming a fast-growing tumor. Understanding the way these genes are controlled during normal development can shed light on how they go awry in human cancers.

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