MedicalXpress

Genome-wide survey nets key melanoma gene

February 7 2008

One might call it a tale of two melanocytes. Given the same genetic mutation, why does one melanocyte shut down growth and become a relatively benign mole, while another rages out of control and develops into deadly melanoma?

In trying to tease out the answer to this simple question, Howard Hughes Medical Institute (HHMI) researchers have uncovered a protein that stops the growth of melanoma, a cancer that develops from pigment-producing cells in the skin called melanocytes. HHMI investigator Michael Green and colleagues at the University of Massachusetts Medical School reported their identification of the genetic underpinnings of a new way to thwart one of the deadliest forms of cancer in the February 8, 2008, issue of the journal *Cell*.

Green and his colleagues began by designing experiments that would help them determine what separates melanomas from ordinary moles at the genetic level. Moles, also known as nevi, and melanoma often result from the same genetic mutation, and the biological pathway that differentiates the two had been a mystery. The new study uncovers a relatively unknown protein that regulates the melanocyte's "decision" to ward off cancer by either entering a programmed hibernation or committing suicide.

According to the American Cancer Society, 60,000 people in the United States developed melanoma in 2007, and more than 8,000 died of the disease. Melanoma is caused by the uncontrolled proliferation of melanocytes, whose pigment, melanin, protects the skin against the sun's

ultraviolet rays. Nevi, which are benign, are also caused by abnormal growth and differentiation of melanocytes.

While nevi are, by definition, non-cancerous, more than half the time the same mutation is at fault in melanoma and nevi: a single amino acid change in a protein called BRAF. BRAF is part of a signaling system that is important for cell growth and proliferation. The BRAF mutation found in nevi and melanoma increases the activity of the BRAF protein, prompting cells to multiply abnormally. In some melanocytes with this mutation, the proliferation cannot be stopped, and cancer develops.

But sometimes when the mutated BRAF gene is expressed in melanocytes, those cells go into a state of permanent hibernation via a process known as senescence. These cells form nevi, not melanoma. This, according to Green, indicates that the genetic checks and balances within those cells are working correctly. “The cell has sensed this oncogenic influence—activated BRAF—and that induces an anti-cancer mechanism to throw the cell into this frozen state,” he said. Green added that sometimes cells simply commit suicide instead of senescing.

Cancer results when something blocks this failsafe mechanism, said Green. “While this phenomenon was known, the components and the pathways involved were not,” he said.

Green, his postdoctoral fellow Narendra Wajapeyee, and their colleagues did a genome-wide search for the proteins involved. They used engineered retroviruses to insert short bits of RNA to selectively turn off individual genes in a series of melanocytes. Some of the cells progressed to cancer, while others did not. After testing thousands of genes, they found 17 that were required for activated BRAF to induce either senescence or suicide. Together, Green said, the proteins made by these genes make up the body’s melanoma defense pathway.

Green's group found that three of those proteins are required for both the senescence and programmed cell death pathways. The identity of one of those proteins, insulin-like growth factor binding protein 7 (IGFBP7), surprised the researchers. Not much was known about IGFBP7, except that it was secreted, said Green. A secreted protein does not stay inside the cell that produces it, but instead is released from the cell and moves through the blood to other cells. Green said that a secreted protein's role in the pathway caught them off guard, because "we would have thought this process would be purely intracellular."

Green and his colleagues focused their attention on IGFBP7 because its presence suggested something intriguing: If one otherwise healthy melanocyte begins expressing BRAF, the IGFBP7 it produces can enter cells around it, prompting lots of melanocytes to "switch off," rather than risking a tumor.

In the experiments reported in *Cell*, the researchers exposed human melanoma cells in culture to recombinant IGFBP7. The protein had the same genetic code as the human version, but was produced using genetically modified insect cells. The melanoma cells that were treated with IGFBP7 committed suicide-- just as though their anti-cancer mechanism was working correctly.

The researchers also injected the protein into the bloodstream of mice on to which human melanoma tumors had been grafted. IGFBP7 entered the tumor cells and stopped their growth in the mice. "Melanoma cells [caused by BRAF mutations] shut off expression of this key regulator," said Green. "Because of that, the cells escape from senescence and form a tumor."

According to Green, the research also answers another controversy in the field: Are nevi dead-ends or are they precursors to melanoma" "If you go in and see a dermatologist, if they see a mole, they will generally… cut it

off," he said. "They don't want to take the chance that it could be a precursor."

However, Green thinks his results point in the other direction. Because IGFBP7 is a secreted protein, even if one activated BRAF-containing -- but otherwise healthy -- cell in the nevi stopped producing IGFBP7 and threatened to form a tumor, the IGFBP7 being secreted from the cells around it would kill it. "It's an extremely powerful anti-cancer mechanism," said Green.

The team's findings are important not only from a research standpoint, but also for future clinical treatments, Green noted. Melanoma can be surgically removed if caught early, but in advanced cases there is really no treatment for it. Green said IGFBP7's ability to target melanoma tumors throughout the body may make it a powerful tool for cancer therapy. "We're really very excited about the prospects of trying to advance this as a melanoma treatment," he said.

Source: Howard Hughes Medical Institute