Penn researchers identify major genetic factor that keeps moles in non-cancerous, no-growth state

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Moles are benign tumors found on the skin of almost every adult. Scientists have known for years that a mutation in the BRAF gene makes them start growing, but until now haven't understood why they stop. Now, researchers from the Perelman School of Medicine at the University of Pennsylvania have identified a major genetic factor that keeps moles in their usual non-cancerous, no-growth state. The study was published online first this summer in the journal Cancer Discovery.

"The BRAF mutation that stimulates the initial growth of moles also stimulates the production of a tumor suppressor protein, p15, which ultimately acts as a powerful brake on further cell division," said senior author **Todd W. Ridky MD, PhD**, an assistant professor of Dermatology at Penn. "It's this cell division that ultimately allows the transition from a normal mole into melanoma. When mole cells lose the p15 brake, cells can start dividing again and can progress into cancer."

For their study, Ridky and his colleagues developed a new model of human melanoma, using tissue engineering to make skin grafts containing human mole cells in which p15 was removed. When combined with other mutations known to be important for the development of melanoma, and transplanted into mice, the p15 depleted cells progressed into melanoma.

"The model tissues are medically relevant because they used the naturally occurring human mole cells in the 3-dimensional environment of living skin, which allows detailed functional studies - the field hasn't had an experimental system like this before," said lead author Andrew McNeal, a research specialist in Ridky's lab.

How Moles are Born

Both moles and melanomas originate from melanin-producing cells (melanocytes) within the skin. Scientists have known for more than a decade that one particular mutation is responsible for the abnormal melanocyte growth that creates the majority of both benign moles and cancerous melanomas. The mutation, in a cell-growth gene called BRAF, causes BRAF to be in an "always on" state, continuously promoting cell division.

In moles, however, cell proliferation typically stops after the cluster of melanocytes has reached the few millimeters (or roughly the size of a pencil eraser). "Why moles stop growing, despite all that BRAF activity, has been a long-standing question in the field," Ridky said. ¬To answer that question, Ridky and colleagues studied mole cells isolated directly from normal benign moles removed from patients, and compared them to melanocytes isolated from normal (non-mole) skin. The mole melanocytes had 140 times more p15 than the normal skin melanocytes.

Comparing cells from patient melanomas that had originated from previously benign moles, the researchers found generally high p15 levels in the mole tissue, and very low or undetectable p15 in the melanomas. This suggested that p15 is important for holding regular moles in a benign state, and that any subsequent loss of p15 would promote the transition to melanoma. Ridky and his team showed that the BRAF over-activation that drives the mole growth also causes the mole cells to secrete a signaling molecule called TGF-β, which in turn, signals back to the mole cells to make p15. These findings hinted at a possible explanation for the curious fact that most moles have to reach a diameter of at least a few millimeters before they stop growing - TGFB has to build up to a sufficient level first, and small collections of mole cells don't lead to enough local TGFB production in the mole to stop cell division.

An Overlooked Factor

The importance of p15 has been largely underappreciated up to now, said Ridky, because many researchers have assumed that a different, but related, tumor suppressor protein, p16, does the main work of growth-inhibition in moles. The gene for p16 is physically close to p15 in the nuclear DNA, is present in moles, and is also lost in melanomas and many other cancers. While the two tumor suppressors normally work together to keep the brakes on cell proliferation in moles, Ridky and his team found evidence suggesting that p15 has unique functions. For example, inserting p15 into normal cells was enough to halt proliferation completely, whereas inserting p16 only slowed proliferation.

"Clearly p15 is doing things that p16 doesn't, and that's something that the field has mostly overlooked," Ridky said.

Modeling Melanoma, and Beyond

Ridky now plans to experiment extensively with the model to provide insights into how melanoma develops, and how it might be targeted with new therapies.

He and his colleagues also will study p15's possible roles in other cancers. "That deletion that simultaneously takes out both p16 and p15 is among the most common DNA deletions in human cancers," Ridky said. "Cancer biologists have generally assumed that p16 is the more important of the two, but I think that we're going to find important and unique roles for p15 even beyond the context of moles and melanoma."

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