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Study of dark-skinned mice leads to protein linked to bone marrow failure in humans

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The study of dark-skinned mice has led to a surprising finding about a common protein involved in tumor suppression, report researchers at the Stanford University School of Medicine. The results may lead to new treatments for bone marrow failure in humans.

The protein, called p53, has been dubbed the "guardian of the genome" for its ability to recognize DNA damage and halt the division of potentially cancerous cells. However, in a new twist, it appears that p53 also responds to disruptions in the cell's protein factories, leading to changes in skin color and causing anemia in mice.

"This may be just the tip of an iceberg," said Gregory Barsh, MD, PhD, professor of genetics and of pediatrics. "When we think of p53, we think in extremes: high levels cause cell death, low levels cause cancer. This research shows that even moderate changes can have very important consequences. It also suggests that the activation of p53 may be involved in more pathways than we previously anticipated."

Barsh is the senior author of the study, which will be published online in *Nature Genetics* on July 20. Kelly McGowan, MD, PhD, a dermatologist and postdoctoral scholar in Barsh's laboratory, is the first author.

The researchers studied mutations that darken the feet, tails and ears of normally light-skinned mice. Alterations in pigmentation are not only easy to identify, but also often involve a variety of biologically important pathways that control more than just hair or skin color.

McGowan homed in on two skin-darkening mutations, which she found affected specific protein components of the cell's ribosomes. Ribosomes act as cellular protein factories, translating the instructions encoded by RNA molecules into new proteins to do the cell's work.

The discovery was interesting because mutations affecting one of the same ribosomal proteins in humans are associated with Diamond-Blackfan syndrome, a condition that causes a type of anemia specific to red blood cells. When the scientists examined the dark-skinned mice more closely, they found that these mice exhibited similar abnormalities in red blood cell formation.

"Diamond-Blackfan itself is fairly rare," said McGowan, "but the bone marrow failure that sometimes occurs in these individuals happens quite often in many other disorders, including acute myelogenous leukemia and multiple myeloma."

People with bone marrow failure are unable to produce enough red blood cells, white blood cells and/or platelets. They are susceptible to uncontrolled bleeding, infection and fatigue. Understanding the disorder in mice may help scientists and physicians develop new treatment for other, similar conditions.

Interestingly, people with mutations in the same ribosomal protein can exhibit a range of very different symptoms. Such variation suggests that, although the mutations occur in the all-important ribosomes, the problem isn't the result of ham-handedly interfering with all protein production in the cell.

McGowan, Barsh, and their colleagues found that skin from the feet of the mutant mice exhibited elevated levels of p53. This elevation, or "activation," of p53 stimulated the production of a protein called Kit ligand that stimulates the growth of pigment cells, which turned the

mice's skin darker than normal. In contrast, mutant mice unable to express p53 had normal levels of Kit ligand. They also had light-colored feet and unaffected numbers of red blood cells.

"The involvement of p53 in this pathway suggests that the variability seen in human disease may be due to a varying extent to which p53 is activated, or expressed," said McGowan. "The mild anemia seen in these mice and in some humans with Diamond-Blackfan syndrome may be due to mild activation of p53. More severe anemia or bone marrow failure may be the result of very high levels of p53 activation."

The researchers hypothesize that increased activation of p53 affects different types of cells in the body in different ways. In skin cells, it increases the amount of Kit ligand and causes darker skin, whereas in bone marrow cells it causes anemia by causing the death of red blood cell precursors. These results suggest that moderating the levels of p53 may be one way to treat a variety of bone marrow failures in humans.

In the future, McGowan and Barsh will focus on using what they've learned to develop a better mouse model of bone marrow failure in which to try new drugs and therapies. They will also search for additional skin-darkening mutations that affect this and other previously unknown p53 pathways.

"This illustrates the potential benefits that come from basic science research," said Barsh. "Although you don't always know where you're going to end up, many advances in human health would not have been discovered any other way."

Source: Stanford University