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Scientists identify molecule that inhibits stem cell differentiation

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(PhysOrg.com) -- Scientists have now identified a molecule that helps stem cells know whether to self-renew to create more stem cells, or to differentiate into specialized, non-dividing adult skin cells.

Like as not, the recent holidays probably included some reminiscing about family history. There may even have been some remonstrations and recommendations from well-meaning elders to younger kin about their lives' paths. It turns out stem cells have a similar need for long-term memory to help them know who they are and what they should become. Scientists at the Stanford University School of Medicine have now identified a molecule involved in keeping skin stem cells on the straight and narrow.

"We're starting to understand the molecular mechanism of cellular memory," said Paul Khavari, MD, PhD, professor of dermatology. "How a stem cell remembers what it is, and why it might go astray."

The molecule, called DNMT1, helps the stem cells know whether to self-renew to create more stem cells, or to differentiate into specialized, non-dividing adult skin cells. It's important because too much self-renewal can lead to cancer, and too little can inhibit wound healing.

Khavari is the senior author of the research, published online Jan. 17 in *Nature*. He is also a member of Stanford's Cancer Center and Bio-X and the clinical chief of the dermatology service at the Veterans Affairs Palo Alto Health Care System. Postdoctoral scholar George Sen, PhD, is the

lead author of the work.

Much ado is made over pluripotent cells — such as embryonic stem cells and their laboratory doppelgangers, induced pluripotent stem cells — which have the potential to differentiate into any of the body's different cell types. But adult stem cells, while more limited in their ability to create new types of cells, still have important roles in the body. They're particularly vital in skin, blood and other tissues that must constantly regenerate new cells.

Skin stem cells, for instance, must know when to self-renew — by dividing to create new daughter stem cells — and when to differentiate into one of the many specialized, but mostly non-dividing cells that migrate upward to form the surface layers of your skin. A misstep in either direction can have dire consequences. Unnecessary differentiation can exhaust the pool of available stem cells and leave the skin unable to maintain itself or heal wounds. Uncontrollable self-renewal of undifferentiated stem cells, however, is the cause of many cancers.

Khavari and Sen found that DNMT1 helps by keeping stem cell differentiation in check. It works by duplicating in newly formed daughter stem cells the parent cell's patterns of DNA modifications, called methyl groups. These methyl groups turn off genes that are important in differentiation and ensure that the daughter cells remain reliable, steady members of the stem cell society.

This isn't the first time DNMT1 has been identified as an important regulatory molecule. In fact, it's so critical to development that certain laboratory mice, engineered so they can't express the gene, die before birth. This lack of an appropriate animal model has made it difficult to study DNMT1's function in adult tissues. But Khavari and Sen suspected that it had a role in adult stem cells — in part because it's been shown to be expressed at high levels in certain human cancers.

“It seems that in these cancers, DNMT1 may be signaling the stem cells to keep dividing and to avoid differentiation,” said Sen.

Khavari and Sen studied human skin cells in a laboratory dish to discover that the expression of the protein is curtailed when the cells begin to differentiate and migrate to the skin’s surface. When they blocked DNMT1 expression in human skin grafted on to laboratory mice, only about one-third of the grafts lasted three weeks or more.

“It’s as if we’re seeing a kind of cellular amnesia in the stem cells without DNMT1 expression,” said Khavari. “Without the proper patterns of methylation, these cells can’t remember they’re supposed to be stem cells, and instead begin differentiating and migrating to the skin’s surface.” In contrast, all of the grafts with unaltered DNMT1 expression remained healthy — most likely because they had an ample pool of stem cells with which to maintain themselves.

Further study showed that the effects of DNMT1 and another protein important in methylation, UHRF1, may be countered in differentiating cells by a family of proteins called GADD45 that removes methyl groups from DNA. This yin and yang activity helps the cells navigate the tricky waters of differentiation and migration.

“Our ability to control the cells’ differentiation state is going to be very important for our future attempts at regenerative medicine,” said Khavari, referring to scientists’ hope of being able to use stem cells to repair injuries or to create entirely new organs. “We have to be able to strike the right balance between methylation and demethylation. There are a lot of other actors to track down.”

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