Picking cancer stem cells out of the crowd

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(Medical Xpress) -- Stem cells receive a vast amount of research attention due to their abilities to differentiate, heal, and divide in perpetuity, properties that yield promise for regenerative medicine. In cancer stem cells, however, those same properties pose a dangerous threat. Both healthy and cancer stem cells share a number of features, so targeting the bad while sparing the good has often been a difficult proposition. New research by a Howard Hughes Medical Institute investigator pinpoints differences between cancer stem cells in squamous cell cancer and normal stem cells in the skin, which could be exploited to create powerful new anti-cancer therapeutics.

Eliminating a patient's tumors is not always enough to cure their disease. Not infrequently, a small number of cancer cells escape the therapy and go on to seed new populations of cancerous tumors throughout the body. These are the cells that researchers refer to as cancer stem cells, and HHMI investigator Elaine Fuchs has uncovered key traits of skin cancer stem cells that could be used to single them out for a targeted attack.

Squamous cell cancers are the most common type of cancer worldwide, and can affect a large number of organs. They are most common in the skin, but can also be cancers of the head, neck, lungs, esophagus and more. "We've identified and characterized the individual cancer stem cell which acts like a seed to cause squamous cell cancer, one of the most prevalent and life-threatening types of cancers worldwide," says Fuchs, who heads the Laboratory of Mammalian Cell Biology and Development at The Rockefeller University in New York. "And we've identified differences between cancer stem cells and normal stem cells

of the skin, opening up new doors for the development of improved drugs."

Fuchs and postdoctoral fellow Markus Schober isolated the squamous cell cancer stem cells by using an approach the lab has developed to find the normal stem cells in the skin, which give rise to both epidermis and hair. "We systematically fractionated the cancer into different pools of cells, always testing each fraction to identify the ones that gave rise to cancer when we transferred them to a normal, healthy mouse," Fuchs says. Ultimately, they isolated a group of cells from the original tumor that were potent enough to generate cancer in a healthy mouse with the introduction of just one cell. "When a single cell can give rise to a cancer, you know you have a cancer stem cell."

In results published online the week of June 13, 2011, in the *Proceedings of the National Academy of Sciences*, the researchers characterized those cancer stem cells in detail. By studying cancer stem cells in mice that are either very prone or quite resistant to developing squamous cell cancer, Fuchs and Schober discovered that two signaling pathways are critical to regulating proliferative rates of cancer stem cells, and thereby the aggressiveness of the cancer. The most aggressive, rapidly proliferating cancer stem cells are resistant to the growth-inhibiting signal from tumor growth factor (TGF)-beta, and are very active in integrin signaling. Together, these pathways fuel the proliferation of squamous cell cancer stem cells. "In the very aggressive squamous cell carcinomas, there are many more cancer stem cells," Fuchs says. "It's as if they're not seeing the messages that the surrounding tissue is giving them to say, 'stop making tissue.'"

Fuchs' results could lead to far more precise drug targets and, in turn, more hard-hitting therapies than those currently available. Knowing the characteristics of cancer stem cells can help researchers design therapies that hit only those cells and leave normal stem cells alone. "With

conventional therapies and even new therapies, drug treatments rarely kill off all the cancer cells within the body, so cancers often recur and become even more aggressive. One possible reason for that is that current drugs target the bulk of the tumor without hitting all the cancer stem cells," she says. "By understanding and identifying the tumor-initiating cells and how they differ from the rest of the body as well as from the rest of the cancer, companies can design drugs that are more effective at getting at the roots of the disease."

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