MedicalXpress

Scientists discover source of cancer stem cells' resistance to radiation

February 4 2009

Much to the dismay of patients and physicians, cancer stem cells — tiny powerhouses that generate and maintain tumor growth in many types of cancers — are relatively resistant to the ionizing radiation often used as therapy for these conditions. Part of the reason, say researchers at Stanford University School of Medicine, is the presence of a protective pathway meant to shield normal stem cells from DNA damage. When the researchers blocked this pathway, the cells became more susceptible to radiation.

"Our ultimate goal is to come up with a therapy that knocks out the cancer stem cells," said Robert Cho, MD, a clinical instructor of pediatrics. "If you irradiate a tumor and kill a lot of it but leave the cancer stem cells behind, the tumor has the ability to grow back." As a result, patients can relapse months or years after seemingly successful treatment.

Cho and radiation oncologist and post-doctoral fellow Maximilian Diehn, MD, PhD, are co-first authors of the research, which will be published on Feb. 4 in *Nature*. They collaborated with scientists at Stanford and City of Hope National Medical Center to conduct the research. They studied breast epithelial stem cells from humans and mice to unravel why cancer stem cells are more resistant to radiation than other cancer cells.

"Since cancer stem cells appear to be responsible for driving and maintaining tumor growth in many tumors, it is critical to understand the

mechanisms by which these cells resist commonly used therapies such as chemotherapy and radiotherapy," said Diehn. "Ultimately, we hope to improve patient outcomes by developing therapeutic approaches that directly target cancer stem cells or that overcome their resistance mechanisms."

The origin of cancer stem cells is still under debate. Some may arise from normal adult stem cells gone awry. Others may represent specialized cells from adult tissues that have acquired a stem-cell-like state through a series of mutations. What's clear is that cancer stem cells can reconstitute an entire tumor cell population when transplanted into an immune-deficient animal, and destroying them is likely to be critical in order to stop the growth and spread of the disease.

But unlike most cells in the body, which are relatively expendable, stem cells are not that easy to kill. Among the millions of easily replaceable minions that carryout the everyday drudgery of living, the much more rare and versatile stem cells comprise a veritable ruling class. It makes sense to protect such a valuable asset.

Diehn and Cho found that, in this case, the protection takes the form of the increased expression of proteins that can bind and deactivate reactive oxygen species, or ROS. These highly unstable small molecules bounce around wreaking havoc on a cell's DNA and proteins. Although they occur naturally in dividing cells, they are also important mediators of the therapeutic radiation and some chemotherapies doctors use to fight cancer.

The researchers knew that blood stem cells had previously been found to have lower levels of reactive oxygen species than non-stem cells. They wondered whether the same would be true for breast epithelial stem cells. They found that normal breast stem cells from mice have lower ROS levels than do non-stem cells, and that this characteristic was

shared by cancer stem cells from both humans and mice.

They found out why when they looked at gene expression levels: the human breast cancer stem cells were churning out much higher levels of antioxidant proteins than were non-stem cells. Antioxidants capture and disarm ROS before they can cause much damage. This may explain why cultured mouse breast cancer stem cells were less likely than other cancer cells to experience DNA damage after ionizing radiation.

"The resistance observed in the breast cancer stem cells seems to be a similar if not identical mechanism to that used by normal stem cells," said Michael Clarke, MD, the associate director of the Stanford Institute for Stem Cell and Regenerative Medicine and the Karel H. and Avice N. Beekhuis Professor in Cancer Biology. Clarke, who discovered the first cancer stem cells in a solid tumor, is a member of the Stanford Cancer Center and the senior author of the research.

"Although your body would normally eliminate cells with chromosomal damage, it also needs to spare those cells responsible for regenerating and maintaining the surrounding tissue — the stem cells," Clarke explained. "It's protective."

This protection backfires in the case of cancer, however. The researchers found that, in mice with mammary tumors, cancer stem cells with low ROS levels were about twice as likely as other tumor cells to survive a course of ionizing radiation. Similar results were seen in human head and neck cancers that had been transplanted into mice.

The discovery could lead to a new approach to treating cancer. Blocking the activity of an important antioxidant called glutathione made the cancer stem cells significantly more sensitive to killing by radiation. Figuring out how to do something similar in human tumors could have important therapeutic benefits.

"Basically we need to figure out a way to inactivate that protective mechanism in cancer cells while sparing normal cells," said Clarke. For many patients, it's a life-or-death question.

"It's like battling weeds," said Cho, of the cancer stem cells' ability to come back even stronger than before. "You can go through a big field with a weed whacker, but the weeds are going to come back unless you get the roots."

Source: Stanford University Medical Center