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Researchers identify unusual 'altruistic' stem cell behavior with possible link to cancer

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When most groups of mammalian cells are faced with a shortage of nutrients or oxygen, the phrase "every man for himself" is more apt than "all for one, one for all." Unlike colonies of bacteria, which often cooperate to thrive as a group, mammalian cells have never been observed to help one another out. But a new study led by a researcher at the Stanford University School of Medicine has shown that certain human embryonic stem cells, in times of stress, produce molecules that not only benefit themselves, but also help nearby cells survive.

"Altruism has been reported among bacterial populations and among humans and other animals, like monkeys and elephants," said Stanford postdoctoral scholar Bikul Das, MBBS, PhD. "But in mammalian cells — at the cellular level — the idea of altruism has never been described before." Das is the lead author of a paper, to be published online June 11 in *Stem Cells*, documenting altruistic behavior by human embryonic stem cells, or hESCs.

While altruism is generally thought of as a virtue, it can have a downside for hESCs: The altruistic cells appear to be more prone to accumulating mutations, a sign that they could lead to cancers. A better understanding of hESC altruism could provide new insights into cancer therapies, as well as improving scientists' ability to develop safe and effective stem cell treatments for other diseases.

The finding arose from Das' research into how hESCs react to low-oxygen environments, important because many cancerous tumors are low

in oxygen. Embryonic stem cells have the capability to develop into many different cell types through a process called differentiation. Das found that when hESCs were placed for 24 hours in an environment with only one-tenth of a percent of oxygen (the air we breathe, by comparison, is almost 21 percent oxygen), free-radical molecules were generated that began causing internal damage in some cells. Ninety percent of the hESCs differentiated into other cell types or died, with only 10 percent maintaining their so-called "stemness," meaning they retained their ability to develop into any type of cell.

Das wanted to know what set these more hearty cells apart and so began sorting them based on what molecules they contained.

Das and his colleagues discovered that of the embryonic stem cells that had survived the oxygen deprivation, half had high levels of HIF2-alpha (a protein that turns up the production of antioxidant molecules) and low levels of p53 (a protein that normally encourages cells to die when they have too much DNA damage). These levels of HIF2-alpha and p53 are enough, Das showed, to keep the cells from differentiating by turning off cellular pathways typically involved in the process.

But the other half of the stem cells that had kept their "stemness" had relatively normal levels of HIF2-alpha and p53, he and his colleagues report in their paper. There was no clear explanation as to how they would remain undifferentiated without the help of high HIF2-alpha and low p53 — unless the other cells were helping them out.

"When I saw this data, I began to suspect that maybe there was altruism going on," said Das.

To test the theory, Das and his colleagues at the University of Toronto, where he began the work as a graduate student, let the cells with high levels of HIF2-alpha and low levels of p53 soak in a cell culture medium

for 24 hours. Then, he removed the cells and added the other half — those that didn't have high HIF2-alpha and low p53. Sure enough, when the mixture was deprived of oxygen, the cells retained their stemness. Molecules in the liquid had some property that kept them from differentiating. The team discovered that the important molecule in the liquid is an antioxidant called glutathione.

Scientists had previously shown that when embryonic stem cells are under stress, levels of HIF2-alpha and p53 increase and most cells differentiate or die. What makes this study unusual is that Das and colleagues were able to isolate the altruistic cells that exhibit low levels of p53, which helps them to escape death or differentiation.

Most importantly, Das discovered that when hESCs are exposed to stress, the level of p53 fluctuates in a set pattern over time. Depending on the p53 level in the cycle (high or low), stem cells stop their normal cell cycle and follow one of three paths: they differentiate, they die or they repair damage in the cell so they can continue living. While not all the cells cycle at the same time, they all do the same dance.

"We knew these fluctuations occurred but we never understood why," said Das, adding that no other protein involved in cell's internal repair mechanisms is known to fluctuate like p53.

But the new discovery helps explain its importance, he said. Only at one particular point in the fluctuation — affecting around 5 percent of cells at any given time — do hESCs retain their stemness and secrete enough glutathione to help their neighbors do the same. If the p53 level were the same in all the cells at the same time, the entire population of stem cells could differentiate or die at once, leaving no stem cells behind to produce new cells in the future. Thus, the p53 fluctuation enables a few hESCs, which happen to have low levels of it at a given moment, to maintain stemness during stress. It explains why only some of the cells

become altruistic.

The link between the p53 fluctuations and stemness had never been known before. Understanding it could help scientists who are engineering stem cells to use as treatments for diseases; these scientists need stem cells to retain their stemness in the body to be effective.

The disadvantage for stem cells of suppressing p53 is that mutations can accumulate in the cells without causing cell death. And mutation accumulation is a recipe for cancer.

"Evolutionarily, this is why all the cells don't suppress p53 in times of stress," hypothesized Das. "It's too risky in terms of genomic stability."

When Das' team put the hESCs with high HIF2-alpha and low p53 into mice, it took a relatively small number of the altruistic cells to trigger the development of teratomas — tumors made up a mixture of different cell types. It's a leap to assume that this explains how human cancers develop, said Das, but it suggests one theory: A fraction of cells in low-oxygen environments are arrested in a state of high HIF2-alpha/low p53 and start to accumulate mutations, some of which eventually lead to cancer.

Das and his colleagues are now studying whether the altruistic effects that help hESCs survive low oxygen also apply to adult stem cells, which are more differentiated to begin with. While these stem cells don't have the ability to differentiate into any cell in the body, they retain the capability to develop into a few types of cells.

"We want to see whether altruism holds true for mesenchymal and blood stem cells, which are ethically more feasible for future stem cell therapies than embryonic stem cells," he said, adding that it may take years for scientists to fully understand the effects of altruism on stem

cells.

The other Stanford co-author of the paper is Dean Felsher, MD, PhD, associate professor of medicine and of pathology. Other co-authors are at the Hospital for Sick Children in Toronto and at the Tokyo Medical and Dental University.

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