MedicalXpress

Cancer biologists identify major player in cell growth

February 6 2007

When cells go about the business of dividing, they can get sidelined. Maybe there aren't enough nutrients. Maybe there aren't the right signals to resume multiplying. Either way, cells go quiet.

What can restart cell division -- the process that drives the development of embryos, the renewal of hair, skin and blood, and the creation of cancer -- is a single transcription factor called GABP, according to new research from The Warren Alpert Medical School of Brown University and Rhode Island Hospital.

The work, published online in *Nature Cell Biology*, introduces a new pathway that can be manipulated to control cell growth. Since cell growth is a fundamental biological process, the research may shed light on everything from miscarriages to muscular dystrophy. The main application, however, is cancer. Since a key characteristic of cancer cells is unchecked growth, the research identifies potential targets for new treatments.

"As a scientist and a physician, I am tremendously excited," said Alan Rosmarin, M.D., an associate professor in the Department of Medicine and the Department of Molecular Biology, Cell Biology and Biochemistry at Brown and director of clinical oncology research for Lifespan, Rhode Island's largest health care system. "This discovery not only adds to our basic understanding of cell division, it could lead to better cancer drugs. And they're needed. Cancer touches everyone."

During the cell cycle, the four-phase process of cell division, there is a period when the biochemical brakes are put on and cells become inactive. Then the process is kick-started and cells move into the so-called S phase, when DNA is duplicated. This is a critical juncture. If genes are missing or broken, these alterations are passed on to the new cell -- and could result in disability or in diseases such as cancer.

So biologists are keenly interested in identifying the accelerators that rev-up cell division. Ets transcription factors, a family of gene-regulating proteins that are major players in embryonic and cancer development, seemed obvious culprits. Rosmarin, a hematologist-oncologist, studies one member of the Ets family called GABP. This transcription factor helps make a variety of cells, including white blood cells. If those cells develop abnormally, leukemia results.

But the exact function of GABP in the cell cycle wasn't known. Rosmarin wanted to find out. So he and members of his laboratory created mice that carried a mutation -- tiny DNA sequences were inserted into their GABP-making gene. These DNA bits would serve as a time bomb of sorts, deleting a critical piece of the gene when given a chemical signal.

From these mice, Rosmarin and his team grew fibroblasts -- common connective tissue cells -- in a Petri dish with nutrient-rich serum and watched them grow. When they detonated their time bomb, GABP was disrupted, and the fibroblasts' ability to divide was dramatically reduced. At the same time, other genes known to restart cell division were unchanged.

The team confirmed GABP's critical role in cell growth another way. Simply forcing dormant cells to make GABP, they found, was enough to rouse cells from their slumber and get them to grow again.

"So we've found a new pathway to control cell growth," Rosmarin said. "Now that we know a way to disrupt GABP and stop division, there is the possibility that a drug can be made to do the same thing in cancer cells."

Source: Brown University

Citation: Cancer biologists identify major player in cell growth (2007, February 6) retrieved 20 September 2024 from https://medicalxpress.com/news/2007-02-cancer-biologists-major-player-cell.html

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