MedicalXpress

Death, division or cancer? Newly discovered checkpoint process holds the line in cell division

July 1 2008

Each day, a staggering number of cells perform a feat that still amazes researchers with its complexity: they divide to produce perfect replicas of each other. The process is called mitosis, and an inability to control it is one of the hallmarks of cancer.

Little is known about the biochemical processes that control mitosis, but now researchers from Fox Chase Cancer Center and Technion-Israel Institute of Technology in Haifa, Israel, have discovered a novel activity, called the mitotic checkpoint factor 2 (MCF2). This appears to be integral in preventing cells that are unable to equally separate their chromosomes from dividing. The identities of the proteins involved in MCF2 remain to be determined, however, their findings offer insight into a fundamental question of biology, which may also help to increase the efficiency of cancer drugs that disrupt DNA replication, like gemcitabine, or drugs that prevent mitosis, like paclitaxel.

They publish their findings today online in the Early Edition of the *Proceedings of the National Academy of Sciences*.

"At any given moment, 250 million cells in your body are undergoing mitosis in order to replenish cells that die as a result of normal turnover," says Tim J. Yen, Ph.D., senior member at Fox Chase. "The mitotic checkpoint is a complex series of quality control systems, just like in a factory assembly line, that ensures that each new cell gets their proper

share of DNA."

"Cancer cells tend to bypass quality control, such as the mitotic checkpoint, so as to allow them to shuffle their deck of chromosomes to select for traits that promote drug resistance and the ability to divide uncontrollably," says Yen.

Yen, along with visiting researcher Avram Hershko, Ph.D., of Technion, discovered the ability of MCF2 to block mitosis by shutting down an ubiquitin ligase enzyme known as the anaphase-promoting complex/cyclosome (APC/C). Hershko was awarded the 2004 Nobel Prize for Chemistry along with former Fox Chase researcher Irwin Rose, Ph.D., for the discovery of ubiquitin-mediated protein degradation at Fox Chase.

Their findings show that MCF2 joins a previously known group of proteins – the mitotic checkpoint complex – to inhibit the pro-division APC/C protein complex. According to Yen, MCC and MCF2 team up to prevent the activation of APC/C by a signaling molecule called Cdc20. "The mitotic checkpoint is a molecular failsafe system, an intricate clockwork mechanism to ensure that everything is working properly before it allows a cell to divide," Yen says.

When sells divide, one of the first steps is to replicate DNA, which are in the familiar X- and Y-shaped structures called chromosomes. Before the cell can split, the mitotic checkpoint proteins monitor the mechanical connection between microtubule fibers (which act like rope to pull apart replicated pairs of chromosomes) and the chromosomes. If everything is in place, the checkpoint proteins release APC/C and allow division to continue. If not, the cell self-destructs before it can divide.

If the checkpoint proteins themselves are faulty, however, mitosis results in aneuploidy, the loss or gain of chromosomes in the daughter cells.

This increases the risk of cancer, and promotes the resistance of cancer cells to chemotherapies.

Certain cancer drugs, such as paclitaxel and gemcitabine, exploit the mechanisms of mitosis to kill cancer cells. Although they act through very different mechanisms, both paclitaxel and gemcitabine sabotage the events monitored by the checkpoint proteins, which then leads to cell death. According to Yen, a deeper understanding of the mechanisms of mitosis will make these drugs, and others like them, more effective and more enduring.

While the researchers characterize the discovery as an important step in understanding mitosis, the existence of MCF2 raises more questions than it does answers. "We still have a lot to understand in how all the components of the mitotic checkpoint fit together and even more to understand in how the chromosomes are aligned and separated so exactingly," Yen says.

Source: Fox Chase Cancer Center