A new cellular pathway linked to cancer is identified

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In the life of a cell, the response to DNA damage determines whether the cell is fated to pause and repair itself, commit suicide, or grow uncontrollably, a route leading to cancer. In a new study, published in the July 25th issue of *Cell*, scientists at NYU Langone Medical Center have identified a way that cells respond to DNA damage through a process that targets proteins for disposal. The finding points to a new pathway for the development of cancer and suggests a new way of sensitizing cancer cells to treatment.

"One of the major messages of this study is that we have a new pathway that responds to DNA damage," says Michele Pagano, M.D., the May Ellen and Gerald Jay Ritter Professor of Oncology and Professor of Pathology at NYU School of Medicine, who was recently appointed a Howard Hughes Medical Institute Investigator. "It is already known that the three major protein players in this pathway are deregulated in human cancers, so deregulation of this pathway is probably going to contribute to tumorigenesis (the development of cancer)."

DNA damage can be caused by carcinogens in the environment, errors in DNA replication, or glitches in the cellular machinery caused by aging, among other factors. If a cell detects DNA damage when it is about to divide, it activates the so-called G2 checkpoint, a pause button that allows the cell time to correct the problem before cell division, the process whereby a cell makes two copies of itself. The cell maintains a paused state based on a series of proteins, a pathway, that work together like gears in a machine. Some are switched on and others are turned off

(often by degradation) to maintain the checkpoint.

In addition to the new pathway's association with cancer, it suggests a potentially new way to sensitize cells to chemotherapy, says Dr. Pagano. Tumor cells already have a less efficient checkpoint because of defects in other regulatory pathways. Up to 60% of cancers, for example, have mutations in p53, a tumor suppressor gene and G2 checkpoint regulator that operates in a separate pathway.

Inhibiting this new pathway with a drug could make cancer cells especially vulnerable to DNA damage, causing cancerous cells to die rather than pausing to correct the problem, Dr. Pagano says. Unlike cancer cells, which already have a less efficient checkpoint, normal cells have a fully functioning G2 checkpoint and divide less frequently, sparing them from drug-induced cell death.

The central player in this pathway is the protein complex called APC/C, which is involved in multiple aspects of cell regulation through a trash disposal system that shreds proteins. In response to DNA damage, the cell targets Cdc14B, an enzyme that rips phosphate groups off of other proteins, to APC/C, an action which turns on the shredder.
Once APC/C is turned on, it tags its target, Plk1, for disposal. If Plk1 remains active, the cell will continue to divide. Unlike the G2 checkpoint pathways that have been previously described, the researchers believe this one is "ancient" because it is evolutionarily conserved in organisms from yeast to humans.

According to the study, the deregulation of these three pathway components (Cdc14B, APC/C, and Plk1) in cancer cells correlates with lower survival rates in patients. Researchers will need to perform further studies to determine how these proteins are altered in cancer. Some of the effect might be due to changes in the levels of proteins expressed, but it is currently unknown whether mutations to these proteins might

also play a role.

Source: New York University School of Medicine