Blocking DNA repair protein could lead to targeted, safer cancer therapy

EurekAlert

PITTSBURGH, June 1 ? Researchers at the University of Pittsburgh Cancer Institute (UPCI) and the School of Medicine have discovered that inhibiting a key molecule in a DNA repair pathway could provide the means to make cancer cells more sensitive to radiation therapy while protecting healthy cells.

The findings are published in *Science Signaling* and provide new insights into mechanisms of how the body fixes environmentally induced DNA damage and into the deadly neurological disease ataxia-telangiectasia (A-T), said senior author Christopher Bakkenist, Ph.D., assistant professor of radiation oncology, pharmacology and chemical biology at UPCI and the School of Medicine.

"A characteristic symptom of A-T is heightened sensitivity to ionizing radiation, such as X-rays and gamma rays," he said. "If we understand why that happens, then we might be able to reproduce it to make tumor cells vulnerable to radiation treatments while sparing healthy cells, which would make therapy more effective while minimizing side effects."

In A-T, brain areas that control movement progressively degenerate, causing walking and balance problems. Patients carry a gene mutation that stops production of a protein called ATM kinase, which spurs other proteins involved in normal cell division, DNA repair and cell death.

Radiation causes DNA mutations during the process of cell division, when genetic material is copied for a new cell to form. The cell has repair pathways that include checkpoints to look for errors as well as methods to repair them, but if enough mutations accumulate, the cell could become cancerous or self-destruct. A-T patients, who lack the kinase, have a higher risk for developing cancer, Dr. Bakkenist said.

He and his colleagues tested what would happen if they blocked the activity of ATM kinase in cells that make the protein. They had already determined that administering an ATM kinase inhibitor from 15 minutes to 75 minutes after radiation exposure was sufficient to make normal cells more sensitive to the effects of radiation.

To their surprise, they found that inactivation of ATM kinase prevented a type of DNA repair that is essential for proper duplication of genetic material during replication. However, A-T cells did not have this problem despite lacking the kinase; they presumably use another method to check for and correct those errors.

The discovery revealed a new approach to target cancer.

"A characteristic of tumor cells is that they rapidly replicate, possibly because they have mutations that encourage cell division or that thwart repair pathways," Dr. Bakkenist explained. "But ATM kinase remains present in the vast majority of human cancers, so that suggests it is needed by those diseased cells during replication."

Cells that, unlike cancer cells, are not going through what's known as replication stress, would not be affected by an ATM inhibitor and, like A-T cells, likely have another way of repairing certain radiation-induced mutations, he said.

"So that would make cancer cells particularly vulnerable to an ATM inhibitor, while healthy cells should be unaffected," Dr. Bakkenist said.

He and his team are now studying the effects of such inhibitors on pancreatic, lung and breast cancer cells.

SOURCE [1]

Links:
[1] http://www.eurekalert.org/pub_releases/2010-06/uops-bdr060110.php