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Contact: Jeanne Galatzer-Levy
jgala@uic.edu
312-996-1583
University of Illinois at Chicago

Molecule targets and kills tumor cells, starves blood supply

A man-made chemical compound called ARC causes tumor cells to die but leaves normal cells unharmed, researchers at the University of Illinois at Chicago report in a study highlighted in the March 15 issue of Cancer Research. ARC also proved to have strong anti-angiogenic properties, showing promise as an inhibitor of new blood vessel formation in tumors.

ARC, an acronym for its long chemical name, resembles one of the bases that are the building blocks of DNA. Researchers found it by screening more than 2,000 compounds for their ability to inhibit a key step in the cell cycle. Previous studies had shown that blocking that step spurs apoptosis, or cell suicide, in cancer cells.

When cancer cells (human lung cells that had been transformed by a virus to become cancerous) were treated with ARC, 50 to 70 percent killed themselves within 24 hours. Normal lung cells exposed to two to four times higher concentrations of ARC were unharmed.

"Our results suggest that while ARC induces cell death in tumor cells very efficiently, it only causes a cell-cycle block in normal cells," said Andrei Gartel, assistant professor of molecular genetics at UIC and principal investigator on the study. "This gives ARC an important advantage as a potential anticancer drug, because many of the drugs currently used to fight cancer are also toxic to normal cells."

In other experiments, Gartel said, ARC induced cell suicide in breast, colon, gastric and liver cancer cell lines.

An important aspect of ARC-induced cell suicide, Gartel said, is that it does not rely on p53, a normal protein in cells that is often responsible for initiating cell death after the cell has been treated with cancer drugs. The problem, he said, is that in more than half of all human tumors p53 has been inactivated.

Gartel said while it is not yet known how ARC induces apoptosis in cancer cells, his group has shown that in normal cells the molecule inhibits RNA synthesis, a key step in gene expression.

"One possible reason for ARC's effect on cell death may be that cancer cell lines are more dependent on the protective effect of particular molecules to survive, and when those become less abundant after ARC treatment, the tumor cells undergo apoptosis," he said. "We are continuing our investigation of ARC's mechanism of action."

To test whether ARC could also inhibit blood vessel formation in tumors, scientists at the National Cancer Institute performed three different angiogenesis assays. In all three assays, Gartel said, ARC performed "in the range of effectiveness" of a compound already in clinical trials as an anti-angiogenic agent.

"We think ARC may have potential as an anti-cancer drug," said Gartel. "Here we have a compound that induces cell death in tumors, but not in normal cells, and is highly anti-angiogenic. We have already begun to explore its potential against a range of different types of tumors."

The researchers now must test ARC against other cell lines in the laboratory and perform further preliminary animal experiments before human trials could be planned. Only a tiny fraction of promising candidate drugs enter clinical trials, and few of those are approved.

UIC research specialist Senthil Radhakrishnan is co-author of the study. The study was funded by the UIC Department of Medicine, the Illinois Department of Public Health and the National Institutes of Health.

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