MedicalXpress

# 'Destruct' triggers may be jammed in tumor cells, UF geneticists say

April 30 2008

Tumor cells living in the cross hairs of radiation or chemotherapy may be able to escape death because their self-destruct mechanisms are jammed, say University of Florida scientists writing in a recent issue of *Developmental Cell*.

Scientists studying fruit fly cells discovered that slight changes in the protein scaffolds that support the genes “reaper” and “hid” — aptly named for their roles in triggering cell death — cause the cells to become naturally resistant to X-rays during early development.

“It turns out that a piece of DNA that is required for mediating this process of cell death is blocked,” said Lei Zhou, Ph.D., an associate professor of molecular genetics and microbiology in the UF College of Medicine. “When it is blocked, the cells just don’t die, even when subjected to heavy doses of radiation. This may be what is happening in some resistant cancer cells. The pro-apoptotic genes cannot be induced to cause cell death.”

The study may be the first to link apoptosis, the gene-driven process that leads to the necessary destruction of old, damaged, or infected cells, with epigenetics — the study of how gene function changes even when the genes themselves don’t change.

Scientists believe that defects in cell death regulation may be responsible for tumor formation and the spread of cancer, because the cells escape the safeguards that normally clean up malignant cells.

In their experiments, UF researchers found the location of the DNA sequences known to trigger reaper, hid and other genes related to cell death in fruit flies. Similar genes exist in humans.

By monitoring gene activity levels and changes in chromatin — the protein spools that the genes wrap around — researchers were able to detect factors that made the cells resistant to radiation.

Scientists first noticed drastic changes in sensitivity to radiation in developing fruit fly cells in the mid-1970s. Similarly, a sensitive-to-resistant transformation takes place in people during the development of brain cells, which are extremely sensitive to radiation in their formative stages but more durable once they grow into adult neurons.

However, the underlying cellular and molecular causes of the transformations were undetected. The latest findings suggest that like the fruit fly cells, tumor cells may have a degree of epigenetic protection from radiotherapy or chemotherapy.

“We are talking about a piece of DNA that is very sensitive when open, but modification of its supporting structure has caused it to condense,” said Zhou, who is affiliated with the UF Shands Cancer Center and the UF Genetics Institute. “If we reverse this and open the DNA supporting structure, we can conceivably make the cells sensitive to radiation once more. Controlling the blocking-unblocking mechanism to make the cells sensitive could potentially lead to better cancer therapy.”

Conceivably, certain drugs that open “enhancer” regions of cell-death genes in tumor cells could improve the effectiveness of cancer treatments.

“The scientists took a different approach to look at the regions of the genome important for DNA-damage induced cell death,” said Kristin

White, Ph.D., an associate professor of dermatology at Harvard Medical School and Massachusetts General Hospital, who did not participate in the research. “One of the most interesting aspects of this work is the finding that changes in chromatin structure regulate the expression of genes that are important in this death, and that this regulation can extend over long distances in the genome.

“The research shows there is still a lot to learn about DNA damage-induced cell death,” she said. “We need to understand all aspects of this if we want to improve cancer therapy. This work suggests that we need to look harder at chromatin-modifying enzymes as new targets to alter the response of cancer cells to radiation.”

Source: University of Florida

Citation: 'Destruct' triggers may be jammed in tumor cells, UF geneticists say (2008, April 30) retrieved 20 April 2024 from https://medicalxpress.com/news/2008-04-destruct-triggers-tumor-cells-uf.html

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