Dormant cancer cells rely on cellular self-cannibalization to survive

2 January 2009

A single tumor-suppressing gene is a key to understanding, and perhaps killing, dormant ovarian cancer cells that persist after initial treatment only to reawaken years later, researchers at The University of Texas M. D. Anderson Cancer Center report in the December *Journal of Clinical Investigation*.

The team found that expression of a gene called ARHI acts as a switch for autophagy, or self-cannibalization, in ovarian cancer cells. Often a mechanism for cancer cell death, in this case "self-eating" acts as a survival mechanism for dormant cancer cells.

"Prolonged autophagy is lethal to cancer cells, but a little autophagy can help dormant cancer cells survive, possibly by avoiding starvation," said senior author Robert Bast, M.D., vice president for translational research at M. D. Anderson.

"Dormant cells are a major problem in ovarian cancer, breast cancer and other malignancies," Bast said. "We often see ovarian cancer removed, leaving no remaining sign of disease. After two or three years, the cancer grows back. If any remaining cancer cells had continued to grow normally, the disease should have returned in weeks or months.

"So the assumption is that some cells remain dormant without dividing and without developing a blood supply, but the mechanism for this has not been well understood," Bast said.

Bast and colleagues focused on ARHI, short for aplasia Ras homolog member I, a gene found in normal cells, but that is underexpressed in 60-70 percent of ovarian cancers.

When normal levels of ARHI were restored to ovarian cancer cells in the laboratory, autophagy was induced and cancer cells died within a few days.

When the experiments moved to human ovarian cancer grafts in mice, a different effect was noted. ARHI stopped tumor growth and induced autophagy, but did not kill the cancer cells. When ARHI was turned off at 4 to 6 weeks, the ovarian cancer cells grew rapidly.

"Cancer cells had remained viable during ARHI-induced growth arrest and autophagy, which is consistent with a dormant state," Bast said. "When we blocked autophagy with chloroquine, a drug also used to treat malaria, regrowth of the cancers was inhibited, suggesting that autophagy had helped the cancer cells to survive in the absence of a blood supply."

Autophagy is a cellular survival mechanism that protects cells in a variety of ways. In the case of stress caused by lack of nutrients, autophagy is roughly comparable to a person burning body fat to survive the absence of food.

Several protein survival factors were detected within the microenvironment of the ovarian cancer grafts that could prevent autophagy-induced death of ovarian cancer cells in the laboratory. Blocking these survival factors could provide a novel strategy for eliminating dormant ovarian cancer cells and curing more patients.

Whether cancer cells die an autophagic death, remain dormant or exit dormancy to grow again depends on the balance between ARHI's tumor-suppressing activity and the anti-autophagic and proliferative activity of these environmental survival factors, the authors note.

The ARHI-autophagy pathway also provides an inducible model for tumor dormancy. Lack of a model has hindered understanding of dormant cells and the development of treatments to eliminate them, Bast noted.

Source: University of Texas M. D. Anderson

Cancer Center