Escape cancer, but age sooner? The dark side of the tumor suppressing process

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Cells shut down and stop dividing when their DNA is damaged, in a process known as cellular senescence, so as to prevent damaged DNA from leading to unregulated cell division and therefore cancer. However, a new study, published in this week's issue of *PLoS Biology*, has found that when these cells shut down they also spew proteins into their surrounding environment. This causes inflammation and sets up conditions that support the development of age-related diseases including, ironically, cancer. The new research includes the first comprehensive molecular description of a paradoxical process that prevents cancer in younger people, but promotes age-related cancers and other maladies later in life.

"We provide for the first time a broad molecular description of how this well known mechanism for cancer prevention drives aging and age-related disease by changing the local tissue environment," said Judith Campisi, PhD, lead author of the study, who is a Faculty Member of the Buck Institute for Age Research and also Senior Scientist at Lawrence Berkeley National Laboratory.

The study shows that the senescent cells secrete inflammatory, growth-stimulating, immunomodulatory, and other proteins that dramatically change the tissue microenvironment, both in cells grown in the lab and in people undergoing chemotherapy, which can cause DNA damage.

The study also showed that normal cells that acquire a highly active, mutant version of a cancer-promoting protein known as Ras secrete

higher levels of the tissue-altering molecules, as do cells that lose functions of the tumor suppressor protein p53. The study therefore explains why the presence of senescent cells can promote the growth and aggressiveness of nearby precancerous or cancer cells, and further defines a new mechanism by which precancerous or cancer cells that have lost the p53 tumor suppressor, or gained an oncogene such as Ras, promote cancer so efficiently.

"This study defines a new paradigm for how oncogenes promote, and how tumor suppressor genes suppress the development of cancer," said Campisi. "The established role for these genes is to control the cell itself. Our findings show that both types of genes also strongly change the tissue microenvironment, and therefore control cancer by mechanisms that depend not only on the response of the affected cells themselves, but also on the response of neighboring cells, or the local tissue environment." Campisi said the findings also help explain why cancer patients feel so sick when they get chemotherapy. "Chemotherapy is brutal -- both normal and cancerous cells are forced into senescence, with resulting secretion of inflammatory factors that can produce flu-like symptoms during treatment," Campisi said.

While Campisi emphasizes that chemotherapy can cure cancer, she says the study provides a cautionary note for younger patients who receive treatments that could promote the development of further cancers later in life. Campisi said the study points out the need for new biologically targeted therapies for cancer that exploit more specific differences between normal and cancer cells. Current DNA damaging chemotherapy focuses on cells that divide rapidly - impacting cancer cells, as well as all dividing cells including cells in the alimentary canal and hair follicles.

The next phase of the ongoing research involves efforts to encourage the body to eliminate senescent cells more rapidly than it normally does. "That's got to be the goal," said Campisi. "Although senescent cells exist

for the good purpose of preventing cancer, we don't want them to hang around – we want the body to be able to get rid of them."

Citation: Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, et al. (2008) Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6(12): e301. doi:10.1371/journal.pbio.0060301
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