Human cells secrete cancer-killing protein

23 July 2009

Human cells are able to secrete a cancer-killing protein, scientists at the University of Kentucky's Markey Cancer Center have found.

Researchers led by Vivek Rangnekar, UK professor of radiation medicine, have determined that the tumor-suppressor protein Par-4, initially thought to be active only within cells expressing the Par-4 gene, is in fact secreted by most human and rodent cells and can target large numbers of cancer cells by binding to receptors on the cell surface.

This discovery, published today in the leading journal *Cell*, makes Par-4 a very attractive molecule for future research aimed at developing new cancer treatments.

"It was a pleasant surprise, when we noticed that Par-4 protein is secreted by cells," Rangnekar said. "This new finding means it is not necessary to make genetic modifications, or to employ recombinant viruses, to deliver the Par-4 gene to cancer cells, and it significantly expands the potential applications of Par-4 to selectively kill cancer cells."

Funded by several grants from the National Institutes of Health, Rangnekar's study found that when the Par-4 molecule binds to its receptor GRP78 on the surface of a tumor cell, it triggers a biological process called apoptosis or "cell suicide." Consistent with previous research by Rangnekar's laboratory with intracellular Par-4, the newly discovered secreted Par-4 acts selectively against cancer cells, leaving healthy cells unharmed. Few other molecules are known to exhibit such selectivity.

One molecule, known as TRAIL, also exerts cancer-cell-specific effects. However, Rangnekar's most recent study discovered that apoptosis inducible by TRAIL is dependent upon extracellular Par-4 signaling via cell surface GRP78. Thus, the researchers conclude, Par-4 activates a novel pathway involving cell surface GRP78 receptor for induction of apoptosis. In other words, without Par-4, TRAIL lacks the ability to cause "cell suicide."

Rangnekar first discovered the Par-4 gene in 1993. In 2007, Rangnekar's team introduced the gene into a mouse embryo, creating a cancer-resistant "supermouse" that did not develop tumors. In fact, the mice possessing Par-4 actually live a few months longer than lab mice without the gene, indicating that Par-4 mice have no toxic side effects.

While Par-4 is not necessarily a "magic bullet" — it does not target every type of cancer cell — Rangnekar says it could play a major role in developing new combination treatment modalities for cancer patients. His hope is that the next generation of treatments will be even more effective than conventional treatments available today, with fewer and less severe side effects.

"I look at this research from the standpoint of how it can be developed to benefit the cancer patient, and that's what keeps us focused," Rangnekar said, discussing the potential of Par-4 in 2007. "The pain that cancer patients go through — not just from the disease, but also from the treatment — is excruciating. If you can treat the cancer and not harm the patient, that's a major breakthrough."

Rangnekar holds the Alfred Cohen, M.D., Endowed Chair in Oncology Research at the UK College of Medicine.

Source: University of Kentucky

APA citation: Human cells secrete cancer-killing protein (2009, July 23) retrieved 18 June 2021 from https://medicalxpress.com/news/2009-07-human-cells-secrete-cancer-killing-protein.html

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