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By amplifying cell death signals, scientists make precancerous cells self-destruct

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When a cell begins to multiply in a dangerously abnormal way, a series of death signals trigger it to self-destruct before it turns cancerous. Now, in research to appear in the August 15 issue of *Genes & Development,* Rockefeller University scientists have figured out a way in mice to amplify the signals that tell these precancerous cells to die. The trick: Inactivating a protein that normally helps cells to avoid self-destruction.

The work, led by Hermann Steller, Strang Professor and head of the Laboratory of Apoptosis and Cancer Biology, is the first to reveal the mechanism by which a class of proteins called IAPs regulates cell death. By exposing the mechanism in a living animal, the finding also marks a breakthrough in the field and opens the door for developing a new class of drugs that could aid in cancer therapy and prevention.

"In a way, these mice are guiding clinical trials," says Steller, who is also a Howard Hughes Medical Institute investigator. "We now can study how IAPs contribute to the development of cancer in a living animal and develop drugs to prevent or thwart the disease."

IAP stands for "inhibitor of apoptosis protein," and these proteins do exactly what their name implies. By inhibiting apoptosis, or programmed cell death, they keep cells alive by directly binding to executioner enzymes called caspases. But until now, precisely how IAPs save cells from death has remained unclear.

With graduate student Andrew Schile and postdoc Maria Garcia-

Fernandez, Steller studied the X-linked inhibitor of apoptosis protein, or XIAP, and the role of its largely ignored RING domain, which has been implicated in promoting cell death as well as survival. Steller, Schile and Garcia-Fernandez found that genetically targeting and removing RING affected only some cell types in healthy mice. And even though the mice without the RING had more cell death than the mice with the RING, both lived normal lives under normal laboratory conditions.

But when the scientists compared mice that were genetically predisposed to developing cancer, they found that those without the RING lived twice as long as those with it.

"Cancer cells thrive by disabling the molecular machinery that tells sick cells to die," says Steller. "By removing the RING, we wanted to see whether we would trick the machinery to turn back on. And that's what happened. Cells die more readily, making it much more difficult for cancer to be established."

Steller and his team specifically showed that the RING transfers molecular tags on caspases that label these enzymes for destruction. The more tags, the stronger the signal to save the cell from death. However, when the RING is removed, fewer molecular tags are transferred to caspases and often, the signal to save the cell from death is not strong enough. So, more cells die.

The game is not over. Several distinct IAP genes are known to exist, but which ones are important in the development of cancer has also stymied researchers. "We need to use genetics to sort out which individual IAPs contribute to tumors and which IAPS we need to target in order to cure cancer," says Steller. "This was a very big step in understanding what role IAPs play in cancer, but it isn't the last."

Source: Rockefeller University