How 'IAP antagonist' chemicals kill tumors

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Chemical compounds specially designed to neutralize proteins that would otherwise allow tumor cells to cheat death have been recognized for some time by scientists as a promising new avenue for cancer therapy. Now, two studies in the November 16, 2007 issue of the journal *Cell*, a publication of Cell Press, provide insight into just how these antagonists of the anti-death—so-called Inhibitor-of-Apoptosis (IAP)—proteins work to fight tumors.

The researchers reveal that the compounds hit specific IAP proteins known as cIAPs. That came as a surprise, they said, because the chemicals had originally been designed to target another of the anti-death proteins. The studies further show that the small molecule inhibitors not only block the death-defying proteins, but they also actively engage other players that lead to the death of tumor cells. Meanwhile, the chemicals seem to have little effect on healthy cells.

“There has been an effort for several years to look for IAP antagonists, which seem to be very good in causing cell death in cancer,” said Domagoj Vucic of Genentech, Inc. in South San Francisco, who led one of the two studies. “It was thought they might be used in combination with other drugs. But now, we show that these chemicals are capable of inducing apoptosis all on their own.”

“It appears that when you remove cIAP1 in sensitive cancer cells, it opens the tap and everything just goes [toward cell death],” added John Silke of La Trobe University in Australia, who led the other study. “cIAP1 seems to be critical in deciding the life-or-death balance.”

Apoptosis or programmed cell death is a cell suicide mechanism with a major role in development and homeostasis in all animals, Vucic explained. It is now accepted that apoptosis is also an extremely important defense against tumors, Silke added.

Scientists initially discovered the IAP proteins capable of blocking cell death in, of all things, a caterpillar virus, Silke said. The IAP proteins were later found in other organisms, from flies to mammals. The proteins were also shown to rise in human cancer, making them attractive targets for the development of novel cancer therapeutics. Scientists have therefore sought to design molecules that could antagonize IAPs, taking the lead from natural IAP antagonists.

Vucic's group now shows that an IAP antagonist leads cIAPs to be marked for degradation by cellular components known as proteosomes. "This is an amazingly rapid occurrence, happening within two minutes in cells in culture after exposure to the compound," said Vishva Dixit, who is also from Genentech.

They found that treatment with the IAP antagonist led to the activation of a "NF-"B pathway" that produces another protein, called tumor necrosis factor (TNFa). "TNFa comes back and binds its receptor, triggering unimpeded apoptosis and killing cancer cells," Vucic said.

Likewise, Silke's team showed that "synthetic and naturally occurring IAP antagonists kill susceptible tumor cells through their action on cIAP1, resulting in NF-"B activation, which drives TNFa production and initiates tumor cell death." Silke noted that the congruence between the findings of the two studies is a "really good sign."

"These studies show the potential for these drugs, although there is a long road to go," Silke added. "It also demonstrates an important principle: If you can understand how something works through basic

scientific discoveries, then you can really start to make targeted tumor therapies. We can begin to understand how tumors live and how to make them die."

Vucic said that a phase I clinical trial designed to test the safety of one of their IAP antagonist compounds in human patients is already underway.

Source: Cell Press