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The Double Life of a Death-Dealing Protein

Researchers have found that a well-known cell-death protein may actually lead a dual life masquerading as an integral part of the machinery that converts glucose to energy. The researchers said that their findings hint that the protein might be involved in some familial forms of diabetes.

The research team, led by Howard Hughes Medical Institute investigator Stanley J. Korsmeyer, published its findings in the August 21, 2003, issue of the journal *Nature*. Lead author of the paper was Nika N. Danial, a postdoctoral fellow in Korsmeyer's laboratory at the Dana-Farber Center Institute at Harvard Medical School.

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— Stanley J. Korsmeyer

Apoptosis, also known as programmed cell death, is the mechanism by which unneeded or defective cells are culled. The protein at the center of the new study is called BAD, which was shown several years ago to trigger apoptosis.

Nika Danial launched her study purely as a scientific expedition to search for BAD's home in the mitochondria, the cell's power plants. Nika asked the bold question of whether there is a rationale for the localization of this apoptotic pathway at the surface of organelles like the mitochondria, said Korsmeyer. She focused on BAD, because we knew its apoptotic activity was turned on and off by phosphorylation, and a previous paper from our lab showed that the induced kinase was located at the mitochondrial membrane.

In a technically demanding series of experiments, Danial isolated mitochondria from liver cells. She determined that BAD existed in a complex in the mitochondrial membrane, along with the enzymes that added or removed phosphate groups from the complex.

The researchers were surprised to find that when the *BAD* gene was knocked out in mice, the enzyme complex containing BAD disassembled. I was expecting a slight shift to a smaller complex size in the BAD-deficient mice, but instead the whole complex looks like it just fell apart, he said.

But the big surprise was when Nika discovered the enzyme glucokinase in the complex, said Korsmeyer. Glucokinase is the key enzyme that catalyzes the initial stage of glycolysis—the breakdown of glucose to produce energy-containing molecules that power the cell's metabolism. The researchers also identified in the complex a protein called an A kinase anchoring protein that might play a role in tethering the complex to the cell structure to which it is providing energy.

In further studies, the researchers determined that BAD was necessary for glucokinase to function normally in breaking down glucose. One notable observation from the studies, said Korsmeyer, was that mice that either lacked BAD, or that had BAD that could not be phosphorylated, showed diabetes-like defects in their metabolism of glucose. The scientists also found that in mice that the presence or absence of glucose affected activation of BAD.

Taking all of these findings into consideration, the researchers hypothesized that BAD seems to lead two lives— one as an integral part of the cell's energy-producing machinery, and the other as a sentinel that triggers cell death when that metabolic machinery becomes abnormal.

Prior to this study, we knew that two important things for cells to stay alive were metabolism, which depends heavily on sugar, and regulation of the core apoptotic pathway, said Korsmeyer. And most of the evidence said that those would be separate, dissectable events. What Nika has done is given us the first evidence that there's coordination of the two pathways within this distinct multi-protein complex.

The researchers are now working with HHMI investigator Gerald Shulman at Yale University to explore in mice whether BAD malfunction can cause diabetes. They are also beginning collaborative studies to determine whether defective BAD proteins might play a role in familial diabetes in humans.

Looking at the big picture, Korsmeyer said, it might be possible that, in thinking about therapeutics to promote or inhibit cell death for treating cancer or other diseases, there might be a role in regulating metabolism to alter cell's susceptibility to apoptosis.