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Researchers find key step in programmed cell death

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Investigators at St. Jude Children's Research Hospital have discovered a dance of proteins that protects certain cells from undergoing apoptosis, also known as programmed cell death. Understanding the fine points of apoptosis is important to researchers seeking ways to control this process.

In a series of experiments, St. Jude researchers found that if any one of three molecules is missing, certain cells lose the ability to protect themselves from apoptosis. A report on this work appears in the advance online publication of *Nature.*

"This is probably the first description of what is happening mechanistically that contributes to the ability of cells to delay apoptosis," said James Ihle, Ph.D., the paper's senior author and chair of the St. Jude Department of Biochemistry. "It provides incredible insights into how three proteins work and how they can control apoptosis."

The molecular interactions that St. Jude researchers describe in *Nature* play out in nerve cells and blood cells that develop from hematopoietic (blood-forming) stem cells.

A research team elsewhere recently reported that Kostmann's syndrome, a potentially fatal inherited deficiency of granulocytes in children, caused by excessive apoptosis of granulocytes, results from a deficiency in one of the three proteins, called Hax1.

“This suggests that the protein is playing basically the same role in humans as we described in mice,” Ihle said.

Apoptosis rids the body of faulty or unneeded cells. However, molecular malfunctions that trigger apoptosis may cause some diseases, including Parkinson’s disease. Understanding the biochemical interactions that control the extent of programmed cell death could lead to new treatments.

St. Jude biochemists have long studied how cytokines—small proteins used by neurons and blood-borne cells to communicate messages—contribute to keeping cells alive. For example, they demonstrated earlier that most cytokines controlling hematopoietic cells require an enzyme called Jak2, or Jak3 in lymphocytes, at the receptors where cytokines attached to the cell.

In screening for components that are regulated by the Jak enzymes, the St. Jude team found the Hax1 protein.

“That was intriguing because several studies suggested that Hax1 was controlled by cytokine signaling,” Ihle said. “Also, studies have suggested that if you overexpressed Hax1 in cells, the cells were protected from undergoing apoptosis.”

To pursue this lead, the researchers genetically engineered mice that lacked the gene for Hax1. The results showed that apoptosis in the animals’ brain caused extensive nerve cell degeneration that killed the mice within 10 to 12 weeks. Second, apoptosis in immune-system lymphocytes occurred in the altered mice eight hours sooner than in those with the Hax1 gene, when limited amounts of cytokines were available.

“That additional window of survival is extremely important because in

the body, cytokines are limiting." Ihle said. "The key observation was that Hax1 was important in helping cells to survive. Importantly, what happened to the mice we generated was remarkably similar to what happens if you remove the mitochondrial enzymes called HtrA2 or Parl."

Exploring the similarities, the investigators found that Hax1 and Parl pair up in the inner membrane of the mitochondria—tiny chemical packets that serve as the main energy source for cells. HtrA2 is made in the cell's cytoplasm and is transported into the mitochondria, where the enzyme must have a region removed for it to be active. This requires snipping away 133 amino acids, the building blocks of proteins. The St. Jude researchers demonstrated that it is the Hax1/Parl pair that positions HtrA2 to allow the precise snipping that is required. Without Hax1, the snipping does not occur and HtrA2 remains inert.

In lymphocytes, members of the Bcl-2 family of proteins both protect and initiate apoptosis. For this reason, Ihle and the researchers explored this family of proteins to understand why lymphocytes needed an active HtrA2 mitochondrial enzyme. This led them to discover that if active HtrA2 were present, the incorporation of a protein called Bax into the mitochondrial outer membrane did not occur. This was significant since accumulation of Bax in the outer mitochondrial membrane allows the release of proteins that set off a chain of biochemical reactions, including the activation of enzymes that are responsible for cell death.

Source: St. Jude Children's Research Hospital