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Researchers Discover Cell Death Switch

There are times when a cell's "decision" to die is a good idea. During viral infection, for example, cell death can deprive an invading virus of the infrastructure it needs to replicate and infect other cells. Scientists have learned a great deal about this orderly, programmed cell death which is known to scientists as apoptosis but the mechanisms that turn on the process have remained largely hidden from researchers.

Researchers at the Howard Hughes Medical Institute (HHMI) at Duke University in collaboration with scientists at the Dana-Farber Cancer Institute have now found that nitric oxide (NO), a well-studied molecule implicated in a host of communication pathways in and between cells, is also a switch that controls whether cells live or die.

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- Jonathan S. Stamler

The discovery, which is reported in the April 23, 1999, issue of the journal *Science*, reveals a potential therapeutic target for a host of ailments, including cancer, liver failure and diseases of the immune system, heart and brain.

"Nitric oxide is among the most pervasive signaling molecules in biology," said Jonathan S. Stamler, an HHMI investigator at Duke University. "It binds to proteins and regulates their activity, and there is increasing evidence that it regulates cell growth, cell differentiation and now the death program of cells."

Stamler and his colleagues found that NO molecules occupy a critical site on the enzyme caspase, a molecular "executioner" within human cells. When occupying this site, NO effectively plugs a communication pathway that activates caspase and triggers cell death.

"We showed that nitric oxide sits on the site and keeps the enzyme inactive," said Stamler. "Conversely, the nitric oxide is removed in cells programmed to die. Simply put, if you block nitric oxide production within the cell, you make the cell more susceptible to cell death. And if you add it back, you prevent cell death."

Apoptosis can be triggered through a biochemical chain of events known as the Fas pathway. When activated, the Fas pathway initiates a cascade of signals within the cell that ultimately turns on caspase. When NO occupies the site on caspase, however, the death message is blocked. Fas somehow manages to pop the nitric oxide off the cells that are programmed to die.

The discovery of the NO switch, said Stamler, reinforces research in animals that shows that it may be possible to reverse heart failure, liver damage or arteriosclerosis by interfering with apoptosis. It may be possible, for example, to construct synthetic molecules that can act within cells to block or inhibit the cell death that occurs in heart and liver disease. "We'd like to think modulation of the nitric oxide system can be used for therapeutic gain," he said.

Similarly, says Stamler, the NO switch could be used to prevent tumor formation or progression. "In cancer cells, where nitric oxide is overproduced, for example, we should be able to take out nitric oxide and promote cell death." One catch, Stamler added, is that scientists do not yet know how to remove NO from its position on the caspase enzyme.

It may be possible to identify chemicals that knock nitric oxide off its caspase perch, he said. "There must be things that remove the nitric oxide molecule, but we don't yet know what they are."