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Cell Suicide Prevented by Survival

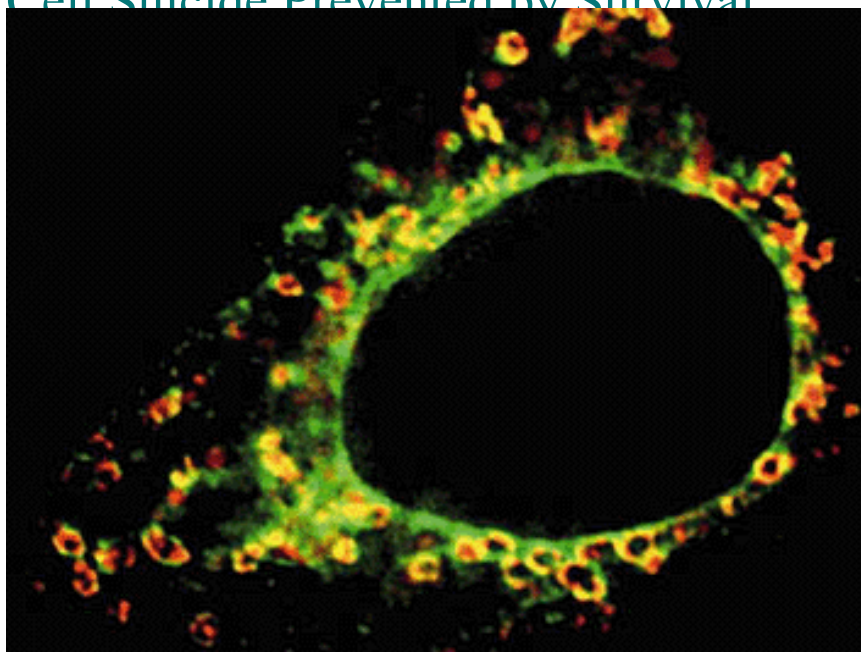


Image Title: The *Drosophila* cell death protein Hid (in green) localizes to mitochondria (in red) in human HeLa cells. High levels of Hid protein induce programmed cell death in many different cell types, but the killing activity of Hid can be blocked by the Ras/MAP-kinase pathway. - Nicolas Haining and Hermann Steller/HHMI at MIT

As most cells age or become damaged, a genetic program triggers their self-destruction. This "programmed" cell death performs a critical housekeeping function that prevents damaged, malfunctioning or misplaced cells from causing future harm.

In some instances, however, the death sentence is commuted and certain cells cheat death. How this happens is still largely a mystery, but recent findings from the laboratory of Hermann Steller, an HHMI investigator at the Massachusetts Institute of Technology, may offer new insight. In the October 30, 1998, issue of the journal *Cell*, Steller's team defines a precise molecular target that allows cells from the fruit fly *Drosophila* to survive in the presence of death-inducing stimuli.

For the last several years, influential researchers such as Martin Raff of the Medical Research Council Laboratory for Molecular Cell Biology at University College in London, have advanced the idea that the survival of all cells is governed by "social controls" that exert their effects via extracellular signals. An extreme view of social control, noted by Raff in a 1992 *Nature* review article, is the notion that "just as a cell seems to need signals from other cells in order to proliferate, so it needs signals from other cells in order to survive."

"It seems that cell survival and cell death are subject to the same kinds of social controls that operate on cell proliferation; yet compared with the control of cell proliferation, relatively little is known about the control of cell survival," writes Raff in *Nature*.

Cancer cells provide one of the best examples of this theory in action, says Steller. "At some point during tumorigenesis, every cancer cell achieves some independence from extracellular survival factors, that is, it escapes the 'social controls' of cell death and survival," he says. Certain neurodegenerative disorders may arise when brain cells may trigger cell death too easily. Again, Steller notes, the cause may be traced to inappropriate social control over cell survival or cell death.

Steller's team entered this burgeoning field a few years ago when they canvassed the *Drosophila* genome in search of genes that execute programmed cell death, otherwise known as apoptosis. They found three closely linked genes that are required for programmed cell death during *Drosophila* development. Any of these genes could trigger cell death by itself when present at a high concentration. Two genes, *reaper* and *grim*, are specifically expressed in cells that are doomed to die. The third gene, *hid*, (head involution defective), is also expressed in cells that continue to live, indicating that the killing activity of the Hid protein must be kept in check by other mechanisms.

In the *Cell* article, Steller's team now reports that Hid is the target of survival signals, such as growth factors, received from the extracellular environment. Steller suspects that Hid protein is an enforcer of social controls. During development, Hid is expressed at various times in many different regions where cells make critical decisions between life and death. It appears that cells that express Hid are sensitive to death-inducing signals. These cells "have one foot in the grave," Steller says, and will die unless supported by survival signals. "This suggests that competition for growth factors mediated through the Hid protein may indeed play a role in the programmed cell death that sculpts tissues during development," says Steller.

Furthermore, the *Drosophila* studies showed that the activity of the Ras protein already known to be crucial for cell growth and differentiation and to play a role in almost one-third of human cancers is instrumental in determining whether Hid triggers cell death.

Ras attaches to the inner surface of the cell membrane, where it relays signals from outside the cell. Ras is activated through a chain of events that begins

when an extracellular signal binds to a specific receptor embedded in the cell surface. Once activated, Ras drives biochemical responses inside the cell through several "effector" pathways. In one of those pathways, Ras turns on the enzyme MAP-kinase, which adds a phosphate group to specific proteins, including Hid.

"Hid is harmless as long as it is phosphorylated, but if survival signaling drops or disappears, unphosphorylated Hid accumulates and that leads to apoptosis," Steller says.

He notes that the *hid* gene has not been identified in mammals yet. Based on studies in which the *Drosophila* gene is inserted into mammalian cells grown in culture, Steller is confident that at least one mammalian version of *hid* will be discovered.

"The Hid protein is a powerful inducer of apoptosis in mammalian cells, where it remains subject to similar controls by regulators of apoptosis," says Steller. "It is likely that a similar mechanism operates for the control of cell survival by survival factors in mammals."

The mammalian version of Hid could be an attractive target for therapy of neurodegenerative diseases, spinal cord injury or stroke. Researchers hypothesize that stroke reduces brain cells' access to survival signals and gradually causes apoptosis in millions of additional cells that survive the initial insult. "It may be that the Hid pathway operates for the social control of cell survival by neurotrophins, for example," Steller states.

Steller is also enthusiastic about prospects for treating cancer cells that have freed themselves of external survival signals. "The role of Ras in cancer has been recognized for a long time," says Steller, "but most efforts have historically focused on its contribution in driving cancer cells to proliferate. Only recently has it become clear that Ras also promotes cell survival, and I believe that our results may eventually provide the basis for the design of new cancer drugs. The MAP kinase-Hid interaction is very strong and might be interrupted by drugs."