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## How a Hormonal Henchman Triggers Death

Intricate experiments on fruit fly larval tissues have provided a look at how a hormone triggers the programmed cell death that occurs when immature tissues are pruned away to make room for adult organs.

The experiments, which were designed and carried out by researchers at the Howard Hughes Medical Institute (HHMI) at the University of Utah and Massachusetts Institute of Technology (MIT), show how signals generated by the insect hormone ecdysone orchestrate programmed cell death, a process that takes place in all animals.

The research group included HHMI investigator Carl Thummel and Changan Jiang at the University of Utah, and HHMI investigator Hermann Steller at MIT, and Anne-Francoise Lamblin, who was formerly at MIT and is now at the National Institutes of Health.

In the March 24, 2000, issue of the journal *Molecular Cell*, the scientists report that ecdysone initiates a cascade of biochemical signals that controls genes that destroy salivary gland tissues when the larval fruit fly *Drosophila melanogaster* begins its metamorphosis into an adult.

"Studying the process of programmed cell death during development is nearly impossible in most animals because the cells that are affected are scattered throughout the organism," said Thummel. "As fruit flies develop, however, whole larval organs undergo dramatic mass cell death with incredible speed in order to make room for adult tissues. Using a model system in which cell death is so easily detectable, we are able to see how a hormone triggers this process, which is believed to be similar throughout the animal kingdom."

The researchers studied cell death in *Drosophila* salivary glands because they contain large chromosomes that form easily observable "puffs" when genes are activated. These puffs allow the scientists to link gene activity to biological processes. "We can easily trace the pathway between the hormone trigger and the transcriptional activation of target genes that kill the cells,"

said Thummel.

The experiments revealed key components of a "death cascade" of biochemical signals that is initiated by ecdysone as it plugs into its receptor. Once this receptor is activated, the death-inhibiting gene *diap2* is repressed and the death-activating genes *reaper* and *hid* are turned on.

"We basically filled in the blanks between the ecdysone receptor and the death genes that we had characterized in previous work," said Thummel.

Strangely enough, however, the scientists found that a puzzling burst of protective *diap2* expression occurred right before *reaper* and *hid* were activated.

"This burst of activity does support models that *diap2* normally holds back the death response," said Thummel. "But we still don't know why the salivary gland really cares that it's only got a couple of more hours to live.

"We do know that the ecdysone pulse induces many genes in the gland, and it's possible that the burst of *diap2* activity right before its death preserves an important final function it's trying to hold onto."

One pleasant surprise, said Thummel, was that the pathways seemed relatively simple. "We unexpectedly found that the hormone receptor directly regulates transcription of the *reaper* gene," said Thummel. "It's quite a shallow pathway. We couldn't ask for a simpler circuit."

The researchers still face the far more complicated question of trying to understand why pulses of ecdysone that occur throughout metamorphosis have different effects depending on the developmental stage of the fly.

"Such stage-specificity tells us right away that the process can't be that simple," said Thummel. "There must be other components in this hierarchy that we haven't found yet."

The researchers believe that their findings in fruit flies may lead to a deeper understanding of mammalian cell death programs because inserting either *reaper* or *hid* genes into mammalian cells triggers apoptosis just as if the switch had been thrown by a mammalian apoptosis gene.

"It will likely be very tricky to find the mammalian genes because they have very short regions of homology," said Thummel. "However, so far we do know that many components of the vertebrate cell death pathway have

homologs in flies. And with the publication of the full sequence of the *Drosophila* genome , many other aspects of this critical pathway will soon become clear."