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Genetic Switch for Maturation Discovered

Working with fruit flies, researchers have discovered a genetic switch that appears to control an array of intricate processes required for the fly to mature from a slug-like larva to a mobile, sexually active fly. The researchers said their discovery in the fly *Drosophila* could provide insights into how sexual maturation occurs in higher animals, including humans.

The researchers, led by Carl S. Thummel, a Howard Hughes Medical Institute investigator at the University of Utah School of Medicine, published their findings in the June 3, 2005, issue of the journal *Cell*. Thummel and Utah colleagues Kirst King-Jones and Geanette Lam, collaborated on the study with co-author Jean-Philippe Charles from the University of Bourgogne in France.

The genetic maturation switch identified by the researchers, called *DHR4*, is a member of a family of genes that encode proteins called nuclear receptors. These receptors, triggered by hormones, each control a large number of other genes, giving them a critical role in coordinating complex body processes.

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- Carl S. Thummel

Thummel and his colleagues began studying *DHR4* because of its pattern of activity in the developing fly and other insects. "Virtually nothing was known about *DHR4*, but we found it intriguing because it is expressed transiently during the very early stage of metamorphosis," he said. *DHR4* was also intriguing to the scientists because the gene produces a so-called "orphan" nuclear receptor, whose activating hormone was unknown.

To discern the function of *DHR4*, the researchers knocked out the gene in two different ways. Co-author Charles created a mutant form of the fly that completely lacked a functioning gene. And Thummel and his colleagues used a technique called RNA interference that allowed them to selectively inactivate the *DHR4* gene at different stages of the fly's growth.

By analyzing the effects of these two types of gene inactivation, the researchers teased apart two distinct roles of *DHR4* in maturation. They found that one effect of *DHR4* loss was that larvae of the mutant flies stopped eating too early in development, initiating behaviors that led to early pupa formation. These pupae developed into smaller, lighter adult flies. "These mutants eat and grow normally until their last larval stage," said Thummel, "when they stop eating prematurely and go into metamorphosis earlier than they should."

The researchers also found that *DHR4*-deficient flies showed defects in the process of metamorphosis itself. These defects involved the developmental "circuitry" controlled by the key insect steroid hormone ecdysone, known to be a major orchestrator of biological processes throughout a fly's development and a critical regulator of metamorphosis.

"The discovery of *DHR4*'s role in repressing the genetic cascade triggered by ecdysone was very gratifying, because it filled in a piece of an important puzzle," said Thummel. "In flies, the work of many laboratories has produced an elegant, detailed model of the developmental machinery triggered by ecdysone. However, there has been one piece missing, which we have been seeking for many years - how the earliest response to ecdysone is repressed.

"These genes switch on and off really fast," explained Thummel. "We knew that ecdysone turns them on, but we never knew what turned them off. Now we know that *DHR4* is one of the critical components required for shutting down that response, so proper development can proceed."

According to Thummel, understanding the machinery of maturation in fruit flies could lead to important insights into how the process works in higher animals, including humans. "Everyone knows that steroid hormones are required for puberty and adolescence in humans," he said. "But we really don't have a good understanding of the targets of the hormone receptors and how they control the myriad changes that comprise sexual maturation in humans. Part of our goal in studying maturation in *Drosophila* is to use a simple model organism to tackle the major questions of how maturation is regulated and timed.

"As we've studied the details of other signaling pathways in *Drosophila*, we've found they've given us direct clues to what is going on in vertebrate organisms, including humans. So too, we hope that studying these steroid signaling pathways in fly maturation will give us clues as to how steroids control human maturation."

Further studies in his laboratory will concentrate on understanding the molecular trigger for *DHR4*, said Thummel. Also, he said, the researchers will seek to map the regulatory pathways *DHR4* controls and the tissues within which those pathways function.

“This paper provides only a first bare-bones clue to this important process of the timing of maturation,” said Thummel. “Now we want to flesh out this story, to discover the molecular circuitry underlying this critical step in the life cycle.”