CIENTISTS & RESEARCH RESEARCH ABSTRACT I FIND SCIENTISTS & RESEARCH MOleccular Mechanisms of Hormone Action in Drosophila I HMI INVESTIGATORS Summary: Carl Thummel's laboratory uses the fruit fly, Drosophila, as a model system to study the molecular mechanisms of hormone signaling. I HMI INVESTIGATORS Summary: Carl Thummel's laboratory uses the fruit fly, Drosophila, as a model system to study the molecular mechanisms of hormone signaling. INTERNATIONAL RESEARCH SCHOLARS Small lipophilic hormones, including steroids, retinoids, and thyroid hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that accur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. Immediate the molecular mechanisms of hormone action in a simple model system—the fruit fly Drosophila melanogaster. Pulses of the steroid hormone edysone act as a critical temporal signal for the insect, triggering the insect grows in size, and metamorphosis—the dramatic transformation of a carawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two objecte larval tissues and Search PubMed	CIENTISTS & RESEARCH RESEARCH ABSTRACT IND SCIENTISTS & RESEARCH MOleccular Mechanisms of Hormone Action in Drosophila I HMI INVESTIGATORS Summary: Carl Thummel's laboratory uses the fruit fly, Drosophila, as a model system to study the molecular mechanisms of hormone signaling. I INTERNATIONAL RESEARCH SCHOLARS Small lipophilic hormone, including steroids, retinoids, and thyroid hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological response during development. I Hormonal Honchman triggers Death (cran. 42 400) Our laboratory is studying the mechanisms of hormone action in a simple model system—the formone signal to direct appropriate biological response act as a critical temporal signal for the insect, triggering the major development transitions in the life cycle. These transitions include molting of the larval cutice as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively activa adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic I Hormonal Lab (utah.edu)		TS & RESEARCH JANELIA FARI	1 GRANTS & FELLOWSHIPS	RESOURCES & PUBLICATION
 a FIND SCIENTISTS & RESEARCH A Action in Drosophila A Action in Drosophila A Action in Drosophila A Action in Drosophila, as a model system to study the molecular mechanisms of hormone signaling. Corrone sig	 A HMU INVESTIGATORS A IHMU INVESTIGATORS A JFAC FELLOWS A INTERNATIONAL RESEARCH SCHOLARS INTERNATIONAL RESEARCH SCHOLARS INTERNATIONAL RESEARCH SCHOLARS Mobile LAUREATES Small lipophilic hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms of hormone- ation in a simple model system—the fruit fly <i>Drosophila</i> as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include moting of the laval cutica as the insect grows in size, and metamorphosis—the dramatic transcripting factors a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and their replacement by developing adult tissues. We are studying the melectular basis of these two hormone- estudying the melectular basis of these two hormone- 	SCIENTISTS & RESEARCH	RESEARCH ABSTRACT		OCTOBER 13, 20
 a FIND SCIENTISTS & RESEARCH A Action in Drosophila A Action in Drosophila A Action in Drosophila, as a model system to study the molecular mechanisms of hormone signaling. Corrone signaling. Corrone signaling. Small lipophilic hormones, including steroids, retinoids, and thyroid hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms of hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms of hormone receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms of hormone action in a simple model system—the fruit fly Drosophila melangaster. Pulses of the steroid hormone action in a simple model system—the fruit fly Drosophila major developmental transting of the insect, triggering the major developmental transting for the insect, triggering the major developmental transting for the insect. Triggering the major developmental transting for hearantic transtormation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the extruction of obsolet Barval tissues and 	 a FIND SCIENTISTS & RESEARCH b FIND INVESTIGATORS c Action in Drosophila c Action in Drosophila, as a model system to study the molecular mechanisms of hormone signaling. c HHMI INVESTIGATORS c INTERNATIONAL RESEARCH SCHOLARS c NOBEL LAUREATES C MOBEL LAUREATES	OVERVIEW			
 HHMI INVESTIGATORS JFRC GROUP LEADERS JFRC FELLOWS LAUREATES INTERNATIONAL RESEARCH SCHOLARS INTERNATIONAL RESEARCH SCHOLARS MOBEL LAUREATES HHMI-NIH Research Scholars Small lipophilic hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclean how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. Our laboratory is studying the mechanisms of hormone and ourse of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the melanogaster. Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the missect grows in size, and metamorphosis—the dramatic transformation of a crawing larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and 	 HHMI INVESTIGATORS JFRC GROUP LEADERS JFRC FELLOWS HHMI PROFESSORS INTERNATIONAL RESEARCH SCHOLARS INTERNATIONAL RESEARCH SCHOLARS MOBEL LAUREATES Small lipophilic hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cent. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear neoptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila</i> melanogaster. Pulses of the steroid hormone edysone act as a critical temporal signal for the insect, triggering the maction in a simple model system—the fruit fly <i>Drosophila</i> melanogaster. Pulses of the steroid hormone edysone act as a critical temporal signal for the insect, triggering the misect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the edysone activation of two divergent genetic programs: the destruction of two divergent genetic programs: the destruction of obsolete larval tissues and their replacement by developing adult tissues is achieved by the edysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and their replacement by developing stores two hormone- studying the molecular basis of these two hormone- 				
 FIRC GROUP LEADERS FIRC FELLOWS FIRC FELLOWS Summary: Carl Thummel's laboratory uses the fruit fly, <i>Drosophila</i>, as a model system to study the molecular mechanisms of hormone signaling. MHMI PROFESSORS INTERNATIONAL RESEARCH SCHOLARS INTERNATIONAL RESEARCH SCHOLARS MOBEL LAUREATES Small lipophilic hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila melanogaster</i>. Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of wo divergent genetic programs: the destruction of obsolete larval tissues and 	 FIRC GROUP LEADERS Summary: Carl Thummel's laboratory uses the fruit fly, <i>Drosophila</i>, as a model system to study the molecular mechanisms of hormone signaling. HHMI PROFESSORS INTERNATIONAL RESEARCH SCHOLARS MOBEL LAUREATES HHMI-NIH Research Scholars Program, also known as the Cloister Program. More * Janelia Farm Research Campus location in a simple model system—the fruit fly <i>Drosophila</i> melanogaster. Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the maging developmental transitions in the life cycle. These transformation of a crawing larva into a highly mobile and reproductively active adult fly. Metamorphosis = -the dramatic transformation of a crawing larva into a highly mobile and reproductively active adult fly. Metamorphosis achieved by the edysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and their replacement by developing adult tissues and their replacement by developing adult tissues and their replacement by developing adult tissues of these two hormone- 	HHMI INVESTIGATORS			Thummel
 hormone signaling. hormone signaling. RELATED LINKS international research Scholars NOBEL LAUREATES Small lipophilic hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila melanogaster</i>. Pulses of the steroid hormone edysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis—the dramatic transformation of two divergent genetic programs: the destruction of bosolete larval tissues and 	 hormone signaling. hormone signaling. INTERNATIONAL RESEARCH SCHOLARS INTERNATIONAL RESEARCH SCHOLARS INTERNATIONAL RESEARCH SCHOLARS Small lipophilic hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal asignal to direct appropriate biological responses during development. Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila melanogaster</i>. Pulses of the steroid hormone activate as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cuticle as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and their replacement by developing adult tissues. We are studying the molecular basis of these two hormone- 	JFRC GROUP LEADERS	the fruit fly, Drosophil		
 INTERNATIONAL RESEARCH SCHOLARS Small lipophilic hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur Program. More • Danelia Farm Research Campus Learn about the new HIMI research campus located in Virginia. More • Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila melanogaster</i>. Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cuticle as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis sa chieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and 	 * INTERNATIONAL RESEARCH SCHOLARS * INDELLAUREATES Small lipophilic hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent ranscription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila</i> melanogaster. Pulses of the steroid hormone eactived transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and their replacement by developing adult tissues. We are studying the molecular basis of these two hormone- 	• • • • •	3	mechanisms of	RELATED LINKS
RESEARCH SCHOLARS Sinial hipoprinic hormones, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. ■ Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila melanogaster</i> . Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cutice as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and ● Search PubMed	RESEARCH SCHOLARS Shiftain lipophilic hormone, play a central role in the development and physiology of higher organisms. These signals are transduced by members of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. Image: Search Compusition of the control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. Image: Search PubMed Janelia Farm Research Campus Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila melanogaster</i> . Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cuicle as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larval into a highly mobile and their replacement by developing adult tissues. We are studying the molecular basis of these two hormone- Search PubMed				AT HHMI
 * NOBEL LAUREATES * NOBEL LAUREATES * NOBEL LAUREATES * HORDOWNED AND PROVIDED OF THE INJUST OF THE INDUCTION OF THE 	 ■ NOBELLAUREATES ■ Homostic and providing of the nuclear receptor superfamily that act as hormone-dependent transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila melanogaster</i>. Pulses of the steroid hormone edysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cutice as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and their replacement by developing adult tissues. We are studying the molecular basis of these two hormone- 	RESEARCH SCHOLARS	and thyroid hormone, play a	central role in the	Maturation Discovered
HHMI-NIH Research Scholarstranscription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development.Image: Hormonal Henchmar Triggers Death (03.24.00)Janelia Farm Research Campus Learn about the new HHMI research campus located in Virginia. More ◆Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila</i> melanogaster. Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cuticle as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues andSearch PubMed	HHMI-NIH Research Scholars transcription factors, reprogramming gene expression within a target cell. Extensive studies in vertebrate systems have defined the molecular mechanisms by which nuclear receptors control promoter activity. In contrast, much less is known about the events that occur downstream from the receptor. It remains unclear how hormone-regulated target genes propagate the hormonal signal to direct appropriate biological responses during development. ●N THE WEB Janelia Farm Research Campus Learn about the new HHMI research campus located in Virginia. More ◆ Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila</i> <i>melanogaster</i> . Pulses of the steroid hormone ecdysone act as a critical temporal signal for the larval cuticle as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of two divergent genetic programs: the destruction of two divergent genetic programs: the destruction of two divergent genetic ● Search PubMed	NOBEL LAUREATES	signals are transduced by me	embers of the nuclear	(06.03.05)
Janelia Farm Research Campus Learn about the new HHMI research campus located in Virginia. More → Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila</i> <i>melanogaster</i> . Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cuticle as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and Source is a contine web the fourth of the store of	 Janelia Farm Research Campus Learn about the new HHMI research campus located in Virginia. More • Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila</i> <i>melanogaster</i>. Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cuticle as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and their replacement by developing adult tissues. We are studying the molecular basis of these two hormone- 	Scholars Learn about the HHMI-NIH Research Scholars Program, also known as the Cloister	transcription factors, reprogr within a target cell. Extensive systems have defined the me nuclear receptors control pro- much less is known about th	Triggers Death	
Campus Learn about the new HHMI research campus located in Virginia. More → Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila</i> <i>melanogaster</i> . Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cuticle as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and	Campus Learn about the new HHMI research campus located in Virginia. More • Search PubMed Our laboratory is studying the mechanisms of hormone action in a simple model system—the fruit fly <i>Drosophila</i> <i>melanogaster</i> . Pulses of the steroid hormone ecdysone act as a critical temporal signal for the insect, triggering the major developmental transitions in the life cycle. These transitions include molting of the larval cuticle as the insect grows in size, and metamorphosis—the dramatic transformation of a crawling larva into a highly mobile and reproductively active adult fly. Metamorphosis is achieved by the ecdysone activation of two divergent genetic programs: the destruction of obsolete larval tissues and their replacement by developing adult tissues. We are studying the molecular basis of these two hormone-		hormone-regulated target ge signal to direct appropriate b	The Thummel Lab	
studying the molecular basis of these two hormone-		Campus Learn about the new HHMI research campus located in	action in a simple model syst melanogaster. Pulses of the as a critical temporal signal f major developmental transit transitions include molting of insect grows in size, and me transformation of a crawling reproductively active adult fl by the ecdysone activation of programs: the destruction of their replacement by develop studying the molecular basis	Search PubMed	

The entire adult fly is carried within the larva in the form of small clusters of diploid adult progenitor cells. These cells are dispensable for larval growth and viability but are called into action at the onset of metamorphosis when sequential pulses of ecdysone trigger their morphogenesis and differentiation to form an adult animal. We have conducted several genetic screens for genes involved in formation of the adult leg as a model system for understanding how the hormone directs terminal differentiation. To date, 17 regions on the autosomes as well as mutations in 16 specific loci have been identified that are required for this response, defining a central role for the Rho1 small GTPase in controlling cell shape changes through effects on the actin cytoskeleton. A longterm goal in these studies is to identify the link between the ecdysone signal and Rho1 activation, providing insights into the molecular mechanisms by which a hormonal signal can drive tissue morphogenesis.

Unexpectedly, we have discovered that a parallel morphogenetic program occurs in response to ecdysone at an earlier stage in development—during embryogenesis. Ecdysone signaling at this stage is required for coordinated changes in cell shape that drive major morphogenetic movements, establishing the body plan of the first instar larva. Some of the mutations recovered in our genetic screens for adult leg development also affect these embryonic morphogenetic events, suggesting that the hormone acts through a common pathway to drive morphogenesis at different stages in the life cycle.

As the adult tissues grow and develop during metamorphosis, they replace larval tissues that are rapidly destroyed. We have shown that the destruction of the larval midgut and salivary glands occurs as a steroidtriggered programmed cell death response. Ecdysone coordinately induces two death-activator genes, reaper and hid, immediately before the onset of larval tissue cell death. Our functional studies indicate that these genes act together, in a partially redundant manner, to direct the death of larval tissues, and that premature activation of this pathway is prevented by the DIAP1 death inhibitor. In addition, we have shown that the ecdysone-receptor complex directly induces reaper transcription, providing a link between the steroid hormone and a programmed cell death response. We have also identified several key ecdysone-inducible transcription factors that direct appropriate *reaper* and *hid* expression in doomed salivary glands, defining a genetic cascade that leads to the destruction of this tissue. These studies provide insight into how the larval tissues are destroyed during metamorphosis, as well as a framework for understanding how steroid hormones control programmed cell death in other organisms.

Past studies of metamorphosis have required dissection or sectioning of animals to follow events that occur underneath the opaque pupal cuticle. We have circumvented this problem by expressing green fluorescent protein (GFP) in specific tissues and following, in time-lapse movies, the development of these tissues in living animals. This method has provided a foundation for open-ended genetic screens to dissect the molecular mechanisms of steroid-triggered programmed cell death. We are screening for mutants that show normal responses to ecdysone during development but retain persistent salivary glands that express GFP. A pilot screen identified eight genes in this pathway, including several transcription factors and signaling molecules. We are characterizing several of these loci in more detail, as well as conducting an open-ended EMS screen to saturate the third chromosome for genes in this pathway. This approach uses the animal for perhaps its greatest strength, as a genetic tool to unravel complex biological pathways that are likely to be conserved in other organisms—in this case, providing a foundation for understanding the molecular basis of steroid-triggered programmed cell death.

The Drosophila genome encodes 18 canonical members of the nuclear receptor superfamily, of which only one (EcR) has a known ligand that binds to its ligand-binding domain (LBD) and activates target gene transcription. This observation raises the question of whether the remaining orphan receptors have ligands and, if so, how these novel hormones and their receptors contribute to growth and development. We are taking a genomic approach toward defining the regulation and function of the nuclear receptor gene family in Drosophila. To date, we have characterized the temporal expression patterns of all detectable nuclear receptors throughout the major ecdysone-triggered transitions in the life cycle. We are also performing genetic studies of cofactors that modulate receptor activity, as well as generating mutations in receptor genes as a step toward understanding their functions. Current efforts are focused on DHR4, DHR96, the Drosophila ortholog of vertebrate estrogen-related receptor, and the Drosophila ortholog of vertebrate HNF4. In addition, we are using transgenic animals that express a fusion of the yeast GAL4 DNA-binding domain with a nuclear receptor LBD, in combination with a GAL4dependent reporter gene, to follow receptor activation during development. In collaboration with Henry Krause's lab (University of Toronto), we have characterized the activation patterns of GAL4-LBD constructs for all 18 Drosophila nuclear receptors during embryogenesis and the onset of metamorphosis. Our long-term goal in this study is to identify novel compounds that can activate these receptors, using the animal as a tool for ligand discovery. This method provides a new direction for defining the mechanisms of hormone action during development, as well as a means of determining how nuclear receptors can exert their multiple roles in the context of an intact developing animal.

This research is supported in part by a grant from the National Institutes of Health.

Last updated: January 18, 2006

Back to Top 🔺

HHMI

Home | About HHMI | Press Room | Employment | Contact

© 2006 Howard Hughes Medical Institute. A philanthropy serving society through biomedical research and science education. 4000 Jones Bridge Road, Chevy Chase, MD 20815-6789 | (301) 215-8500 | e-mail: webmaster@hhmi.org