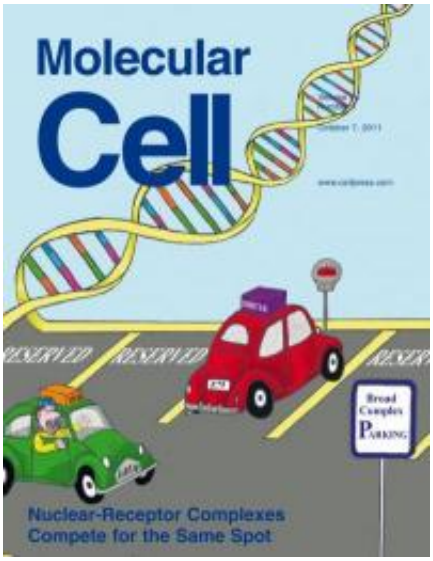
Nuclear receptors battle it out during metamorphosis in new fruit fly model

October 6 2011



This is an illustration and *Molecular Cell* cover art for "Ecdysone- and NO-mediated gene regulation by competing EcR/Usp and E75A nuclear receptors during *Drosophila* development." Credit: D. Johnston/TJU and *Molecular Cell*

Growing up just got more complicated. Thomas Jefferson University biochemistry researchers have shown for the first time that the receptor for a major insect molting hormone doesn't activate and repress genes as once thought. In fact, it only activates genes, and it is out-competed by a heme-binding receptor to repress the same genes during the larval to pupal transition in the fruit fly.

For the last 20 years, the nuclear receptor known as EcR/Usp was thought to solely control gene transcription depending on the presence or absence of the hormone ecdysone, respectively. But it appears, researchers found, that E75A, a heme-binding receptor that represses genes, replaces EcR/Usp during metamorphosis when ecdysone is absent.

The findings, which could shed light on new ways to better understand and treat hormone-dependent diseases, such as cancer, were published in the online October 6 issue of *Molecular Cell*.

"This is the first time we've shown that a steroid hormone receptor and heme-binding nuclear receptor are even interacting with each other," said Danika M. Johnston, Ph.D. "We didn't really think the two were competing against each other to bind to the same sequence of DNA and regulate the same genes."

More specifically, in the absence of ecdysone, both ecdysone receptor subunits localize to the cytoplasm, and the heme-binding nuclear receptor E75A replaces EcR/Usp at common target sequences in several genes. During the larval-pupal transition, a switch from gene activation by EcR/Usp to gene repression by E75A is triggered by a decrease in ecdysone concentration and by direct repression of the EcR gene by E75A.

An important nuance of this system is that the heme-binder E75A is sensitive to the amount of nitric oxide in the cell, and it cannot completely fulfill its repressive potential at high levels of this important molecule. Thus, the uncovered system uses changing amounts of two ligands, a steroid hormone and a gas, to regulate transcription during development.

"These were quite unexpected findings, given the longstanding thoughts

of this process," said Dr. Johnston, "but we just didn't have the tools in the past to figure out what was going on mechanistically. We're painting a clearer picture now."

Knowing how nuclear receptors regulate gene expression in animal models can provide useful information in the development of drugs. Today, the molecular targets of roughly 13 percent of U.S. Food and Drug Administration approved drugs are nuclear receptors.

"It's very possible that similar situations exist in the mammalian system. That could ultimately lead to different treatments that regulate hormone levels in hormone-dependent diseases, such as cancer," said Dr. Johnston.

Provided by Thomas Jefferson University