Steroids Make You Bigger? Fat Chance Says Myc

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In flies, ecdysone integrates growth with developmental transitions by antagonizing insulin signaling, which links growth with nutritional status. Work in *Developmental Cell* (Delanoue et. al, 2010) finds that ecdysone represses the transcription factor Myc in the larval fat body to inhibit systemic growth, revealing a mechanism for such coordination.

Animals develop from a single cell into adults with dramatically different ranges in size. One of the most intriguing but largely unresolved questions in biology is how multicellular organisms achieve their final adult size. The size of an organism is determined by two main factors: growth rate and duration of such growth. Past studies have uncovered a crucial role for the insulin/insulin-like growth factor signaling pathway (IIS) in regulating growth rates in response to nutritional status, and other studies have shown that cessation of growth coincides with the rise of circulating steroid hormone levels. A fundamental and unanswered question is how growth, nutrient availability, and maturation are coordinated in order to determine the overall size of an organism. A recent study by Delanoue and coauthors (Delanoue et al., 2010) published in *Developmental Cell* demonstrates that, in *Drosophila*, downregulation of the transcription factor Myc in fat cells is sufficient to mediate the systemic inhibitory effects of the steroid hormone 20-hydroxyecdysone (ecdysone) on growth. Previous studies have shown that insulin signaling coordinates nutritional availability with protein synthesis via Myc (Teleman et al., 2008). Given that IIS is antagonized by ecdysone signaling during maturation (Caldwell et al., 2005; Colombani et al., 2005; Mirth et al., 2005), the study by Delanoue and colleagues provides a mechanistic link between nutrition sensing, growth, and maturation.

Drosophila is used extensively as a system to address questions related to mechanisms underlying size control of the cell, organ, and organism (Edgar, 2006). Although the physiology of growth control in insects is very different from that of mammals, many of the basic signaling pathways involved are similar. For example, the evolutionarily conserved IIS system controls cell growth in flies by regulating the activity of the phosphatidylinositol 3-kinase (PI3K) signaling cascade. Further, the transition through the different developmental stages (from embryo to larvae, through the three larval instars, and from larvae to pupae) is stimulated by pulses of the steroid hormone ecdysone (Thummel, 1996). These ecdysone pulses are reminiscent of the spikes of gonadotrophin (a mammalian steroid hormone) that enable the transition from childhood to puberty to adulthood in humans.

Similar to vertebrate steroids, ecdysone signals through nuclear hormone receptors, which are ligand-gated transcription factors that regulate crucial developmental and metabolic pathways. Ecdysone is produced by the prothoracic gland (PG) and released into the hemolymph (fly blood), where it is then transported to peripheral tissues and binds to a heterodimer of two nuclear receptors, the ecdysone receptor (EcR) and ultraspiracle (USP), resulting in the expression of target genes that execute morphological changes specific to each developmental stage (King-Jones and Thummel, 2005).

Three previous reports have shown that ecdysone can modulate growth rate and developmental transitions to determine final size (Caldwell et al., 2005; Colombani et al., 2005; Mirth et al., 2005). The PG emerged from these studies as the weight sensor that determines whether the larvae is at an ideal weight to metamorphose into a pupae, at which point the PG upregulates ecdysone synthesis and its release. These studies further showed that ecdysone then signals to the fat body (FB)—the equivalent of the vertebrate liver and adipose tissue—where it positively regulates the transcription factor dFoxO, which in turn antagonizes IIS. Altogether, these studies led to a model whereby ecdysone limits systemic growth by antagonizing IIS in the FB. However, the mechanism by which circulating ecdysone stops systemic growth remained unclear.

The authors of this *Developmental Cell* study (Delanoue et al., 2010) report that dMyc, a positive regulator of the G1-to-S transition (Johnston et al., 1999), is repressed by ecdysone signaling in the FB and mediates the systemic effects of steroid signaling on growth. Using a series of insightful experiments, the authors first confirm that the FB mediates the ecdysone response, as feeding larvae ecdysone inhibits growth, an effect that is suppressed when EcR expression is reduced in FB, but not in some other tissues such as the gut. To test whether EcR signaling directly antagonizes IIS in a cell-autonomous fashion, the authors knocked down EcR function in FB cells. Surprisingly, under these conditions, FB cells are smaller than wild-type and resemble the phenotype associated with loss of IIS signaling. Further, because previous work had shown that activating IIS in the PG produces smaller flies because of increased ecdysone expression in the PG (Colombani et al., 2005), the authors tested whether activation of IIS in the FB suppresses the activation of IIS in the PG. Interestingly, concomitant activation of IIS in both PG and FB does not suppress the ecdysone-induced

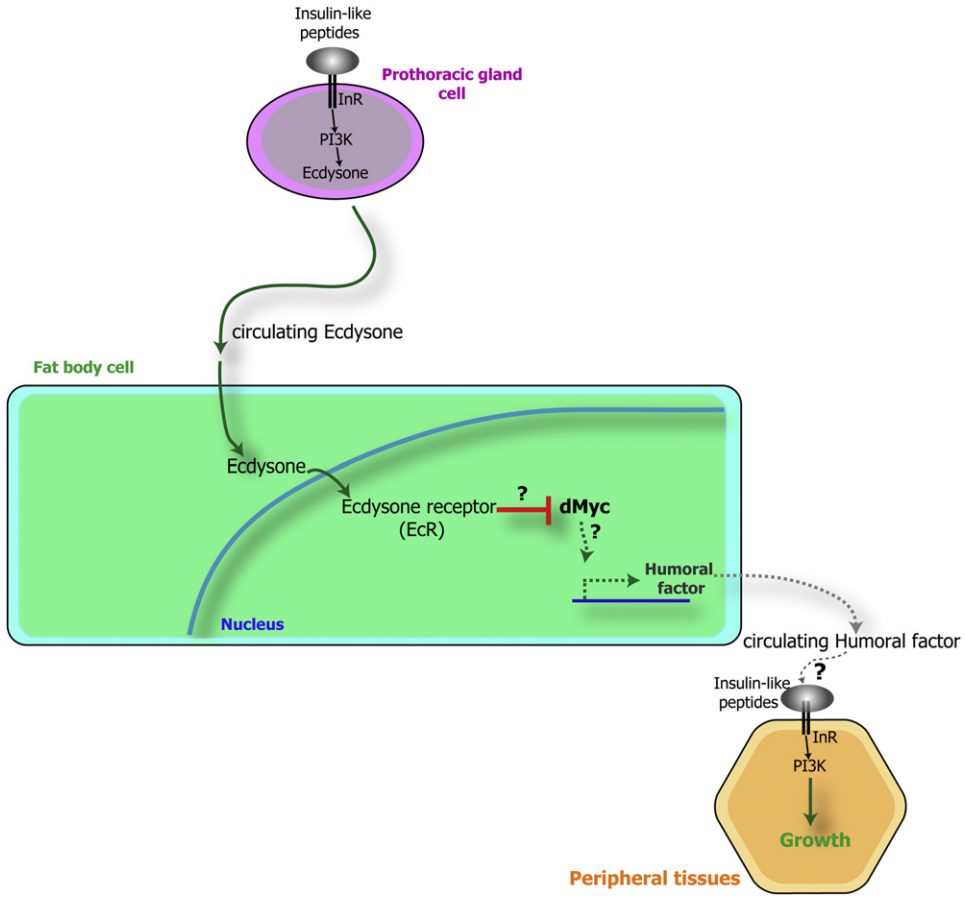

Figure 1. Ecdysone Signaling Represses dMyc Expression in the Fat Body during the Larval-Pupal Transition to Limit Systemic Growth
The prothoracic gland releases ecdysone, which in turn activates the EcR in fat body cells. EcR represses dMyc expression either directly or indirectly. In turn, dMyc has been proposed to upregulate the expression of an unknown humoral signal that activates, either directly or indirectly, IIS in peripheral tissues.

growth retardation phenotype, suggesting that IIS in the FB cells is not the target of EcR signaling in ecdysone-induced systematic growth retardation. However, the authors did find that, in response to EcR signaling in the FB, IIS is inhibited in peripheral tissues.

To identify factors that respond to ecdysone signaling in the FB, the authors compared the transcriptome of FB with reduced EcR activity to wild-type and discovered a striking upregulation of the growth regulator dMyc. Consistent with a role for dMyc in the regulation of systemic growth (Demontis and Perrimon, 2009), dMyc overexpression in the FB led to an increase in overall animal size, whereas a decrease was associated with a reduction in growth. Finally, both genetic and physiological experiments suggested that dMyc is a target of EcR signaling. In particular, as the level of ecdysone increases during the larval-pupal transition, dMyc protein was found to decrease in fat cells. Altogether, these studies establish a link between ecdysone and dMyc and help explain how steroid hormone signaling limits systemic growth.

The phenotypes of dMyc in regulating systemic growth in the FB reported in this study are consistent with previous observations that reduction of dMyc in the muscles affects systemic growth (Demontis and Perrimon, 2009). This raises the question as to whether muscle is also a sensor of ecdysone during metamorphosis. Another area that will need further clarification is how dMyc transcription is regulated in response to ecdysone signaling. It has been well documented during nutrient sensing in the FB that dMyc is negatively regulated by FoxO at the transcriptional level and positively regulated by TOR at a posttranscriptional level (Teleman et al., 2008). Thus, the role of TOR in EcR signaling needs to be clarified. An exciting additional mechanism that needs to be characterized is the nature of the humoral signal from the FB downstream of dMyc that regulates growth of peripheral tissues (Figure 1). Given that the FB is at the crossroads of nutrient sensing (Colombani et al., 2003) and systemic growth regulation, future studies using this system will enable us to understand how organisms coordinate growth and maturation in response to nutrients.

To what extent are these findings in flies relevant to human biology? In humans, somatotrophin (also known as human growth hormone hGH, secreted by the pituitary gland) and insulin-like growth hormone (IGF-1, secreted by the liver) act on most tissues to stimulate cell proliferation and growth during adolescence before gradually decreasing during adulthood. Given that the genes and signaling pathways controlling the processes such

as nutrition sensing, growth (IIS), and maturation (nuclear hormones) are conserved between flies and vertebrates, recent findings from flies may provide useful directions for studies in mammalian systems.

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