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SPOTLIGHT

From a syncytium to mononucleate cells and back: Yki and JNK in symphony

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Alary muscle syncytia in *Drosophila* larvae undergo a remarkable process of dedifferentiation into single cells that then fuse to become ventral longitudinal muscle in the adult. In this issue, Schaub et al. (2019. *J. Cell Biol.* https://doi.org/10.1083/jcb.201905048) identify the Hippo and JNK signaling pathways as key regulators of this process of developmental remodeling of cell fate.

The Waddington landscape offers an elegant simile for the progressive specification of form and function among the lineages of a zygote; i.e., how one cell with a fixed genotype can give rise to a multitude of cells with remarkably different behavior and physiology within the same organism (1). Once an organism attains a "stable" morphology, maintenance and repair mechanisms are activated. The Waddington landscape leaves an impression that the metaphorical ball cannot roll back up the hill and land in a different spot; i.e., the cell fate of an adult cell is fixed.

Decades of research in several species has shown that under extraordinary circumstances like tumorigenesis and injury, cells can "step back" transcriptionally in the differentiation program to take up a different cell fate. For instance, fragments of planaria and hydra can regenerate entire individuals complete with all tissue types. Less dramatic, but no less extraordinary, is the ability of starfish and salamanders to regenerate limbs and for geckos to regenerate tails (2). In these cases, cells at the site of injury dedifferentiate to form a blastema that subsequently differentiates to regenerate a lost organ. In mice, repair of the liver, bone, and neonatal heart and regeneration of digit tips in post-weaned animals is the extent of regeneration that has been documented, though injuries in skin and muscles are repaired by local stem cells (3).

Skeletal muscles are considered the epitome of differentiated cells. These are syncytia formed by the fusion of numerous mononucleate myoblasts. Most skeletal muscle development in *Drosophila melanogaster* takes the same route. Myoblasts specified in embryonic development fuse to give rise to syncytia that help with larval locomotion, among other functions (4). Alary muscles are a scaffolding muscle type that hold the larval heart attached to the body wall. In addition to the scaffolding function of alary muscles in larvae, ventral longitudinal muscles surround the heart in adult fruit flies and assist in hemolymph movement.

Schaub et al. in 2015 uncovered a peculiar step in the course of alary and ventral longitudinal muscle development (5). They showed that anterior alary muscle syncytia disaggregate into single cells and fuse again to form ventral longitudinal muscle. The disaggregation step is dependent on the transcription regulators Org1, the single *Drosophila* T box transcription factor, and Tailup (Tup). This breakdown of a muscle syncytium and the refusion of the resulting mononucleate cells to form a new syncytium as part of normal development was a unique observation, at least in *Drosophila*, if not other species. This step in development is reminiscent of dedifferentiation and redifferentiation, but in a fundamentally unique homeostatic context.

In this issue, Schaub et al. now identify new molecular players that are responsible for this reprogramming (Fig. 1; 6). They present data showing that the reprogramming and disaggregation of larval anterior alary muscle, which is the first step in ventral longitudinal muscle formation, are regulated in concert by Hippo and JNK signaling pathways. Atypical PKC (aPKC) acts upstream of Hippo to activate the transcription factors Yorkie (Yki) and Scalloped, and transcription of their target genes *Myc* and *Piwi* (known from other contexts) influences anterior alary muscle reprogramming. In parallel, active *Drosophila* JNK (dJNK) signaling mediated by the proteins Basket (Bsk) and AP-1 (Jra and Kay) exerts similar control over this process. Bsk also clearly influences the derepression of Yki. Future investigations may explore which of the target genes of these pathways (other than *Myc* and *Piwi*) can influence the subsequent stages of muscle reprogramming that manifest in syncytial disaggregation and subsequent fusion to form ventral longitudinal muscle.

The new molecular details of this dedifferentiation process presented in this paper are about as startling as the discovery of anterior alary muscle reprogramming itself (6). In *Drosophila*, Yki and Myc activity are widely known to promote proliferation and prevent apoptosis in the developing brain, eye, and wing (7, 8). The observation that Hippo-regulated Yki activity induces syncytial breakdown into fusion-competent myoblasts suggests that Hippo and JNK signaling in concert may promote cytokinesis-like processes in a syncytium without DNA replication, but the nature of this remains to be explored.

Changes in Yki function in muscles are associated with catastrophic outcomes. In the context of mouse skeletal muscles, native expression of the mammalian homologue of Yki (Yes-associated protein; YAP) in adult mice muscles is elevated upon

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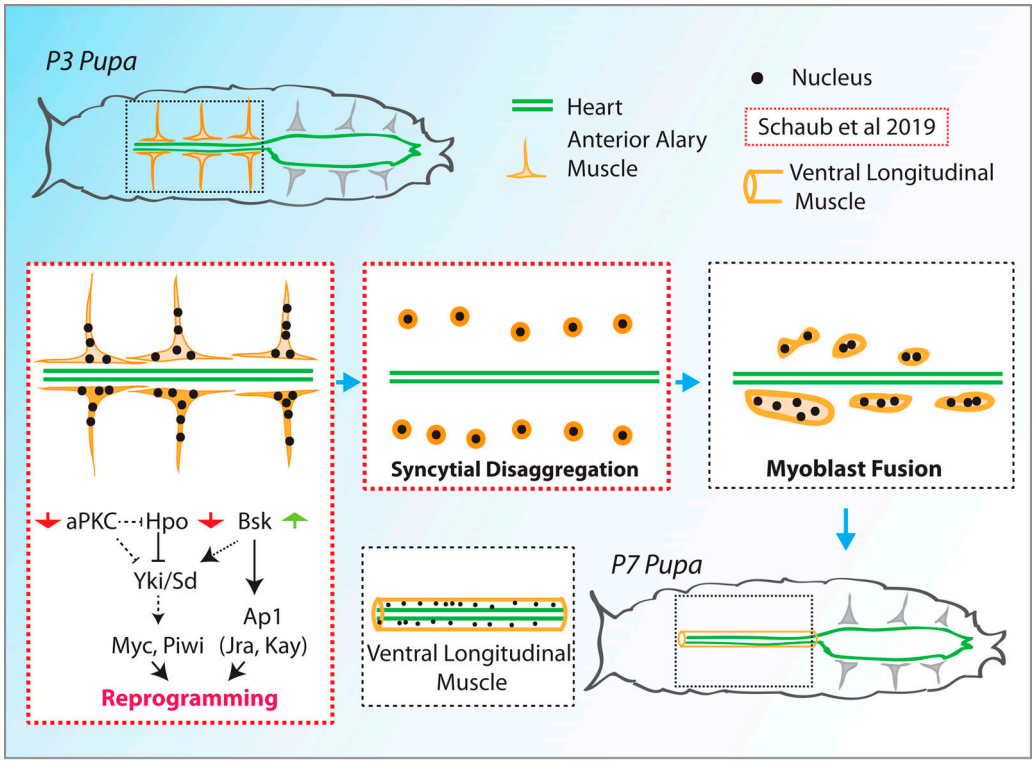

Figure 1. **AM disaggregation to VLM formation.** At the P3 stage in *Drosophila* pupal development, anterior alary muscle syncytia undergo reprogramming (through Hippo and JNK signaling proteins) to disaggregate into mononucleate myoblasts, which, by the P7 stage, fuse among themselves to form the ventral longitudinal muscle. Hpo, Hippo; Sd, Scalloped.

denervation, ostensibly to prevent atrophy (9). However, constitutive expression of activated YAP in mouse skeletal muscles leads to muscle degradation, although muscle stem cell–associated transcripts are elevated (10). The concerted function of Hippo and JNK signaling resulting in syncytial reprogramming that is not associated with cell proliferation makes this report by Schaub et al. particularly new and noteworthy.

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