Cell cycle control during the development of the fruit fly, *Drosophila*

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The development of any metazoan requires a highly regulated program of cell proliferation. In insects, this program, although complex, is essentially invariant. We are characterizing the different modes of cell cycle control that occur during fly development and are learning how the cell cycle control apparatus interfaces with the systems that mediate patterning and cell specification during development.

The first 13 cell cycles of *Drosophila* embryogenesis are rapid and synchronous and are driven exclusively by maternal factors. One of these factors, still unidentified, is progressively depleted as nuclei divide. This slows the cell cycle and leads to the activation of zygotic transcription and the destabilization of many maternal mRNAs. One consequence of maternal mRNA degradation is the loss of the mitotic inducer String (Cdc25). This causes cell cycle arrest at a conserved stage termed the midblastula transition (MBT), and subsequent cell cycles require zygotically transcribed Cdc25/String. After the MBT cells divide in stereotypic spatiotemporal patterns that parallel patterns of cell fate specification. These patterns (the mitotic domains) arise from patterned transcription of *string*, which is, in turn, controlled through more than 35 kb of modular transcriptional control elements that serve to integrate patterning information by binding a plethora of position specific transcription factors. The final cessation of embryonic cell proliferation is effected by a distinct mechanism, which involves the coordinate loss of a limiting G1/S regulator, cyclin E, and the timed induction of $p27^{dacapo}$, a specific inhibitor of the CyclinE/CDK2 kinase.

After the *Drosophila* embryo hatches, the cell cycles resume in response to nutrition. Most larval tissues grow through DNA endoreplication, but stem cells that form the adult proliferate mitotically with a cycle that is regulated at both G1/S and G2/M and is coordinated with increases in cell and tissue mass (growth). The signals that drive growth in these tissues are homologues of those used during human development (WNTs, bone morphogenetic proteins, epidermal growth factors, etc.), but it remains obscure how these signals effect growth and cell proliferation in any system. As an initial test, we altered division rates in the developing *Drosophila* wing and measured the effects on growth. We found that the transcriptional regulator dE2F increased expression of the limiting S- and M-phase initiators, cyclin E and String, and thereby accelerated cell proliferation. The loss of dE2F or overproduction of its corepressor, the *retinoblastoma* homologue retinoblastoma binding factor (RBF), retarded cell proliferation. Although these manipulations altered cell numbers over a fourfold to fivefold range, they had little effect on the sizes of cell clones, compartments, or the final wing. Instead, changes in cell division rates were offset by changes in the cell size. Thus, we suggest that cell signaling modulates growth and that growth rates are monitored by an intermediary mechanism that regulates the activity of cell cycle control genes to match. dE2F and RBF may function in this growth-monitoring capacity. Finally, and somewhat paradoxically, we find that Wingless, a WNT homologue that acts as a mitogen in early wing development, also serves to arrest the cell cycle at the onset of wing cell differentiation.

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