

Genetic Control of Cell Division Patterns in the *Drosophila* Embryo

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Summary

In *Drosophila* embryogenesis, mitotic control undergoes a significant transition during the 14th interphase. Mitoses before interphase 14 run on maternal products, and occur in metasynchronous waves. Mitoses after interphase 14 require zygotic transcription, and occur asynchronously in an intricate, highly ordered spatio-temporal pattern. Mutations at the string (*stg*) locus cause cell-cycle arrest during this transition, in G2 of interphase 14, yet do not arrest other aspects of development. This phenotype suggests that *stg* is required specifically for initiating mitosis. We describe the cloning of *stg*, and show that its predicted amino acid sequence is homologous to that of *cdc25*, a regulator of mitotic initiation in the yeast *S. pombe*. In addition, we show that zygotic expression of *stg* mRNA occurs in a dynamic series of spatial patterns which anticipate the patterns of the zgotically driven cell divisions. Therefore we suggest that regulated expression of *stg* mRNA controls the timing and location of these embryonic cell divisions.

Introduction

The development of a multicellular organism from a single egg cell involves an extended series of precisely regulated cell divisions. Cell lineages leading to different organs and tissue types divide according to distinct spatial and temporal patterns, which we assume are somehow specified in the "genetic program" development. Although the patterns of embryonic cell divisions have been studied in detail in several organisms (Sulston et al., 1983; Hartenstein and Campos-Ortega, 1985; Weisblat et al., 1980), very little is known about their regulation by molecular and genetic mechanisms. We are studying this problem in *Drosophila* embryos because they have a well-characterized pattern of cell proliferation which may be investigated using an excellent array of cytological, genetic, and molecular techniques. Moreover, certain features of the embryonic cell division program in *Drosophila* seem to be evolutionarily conserved. A period of rapid synchronous cleavages followed by a transition to slower, asynchronous cell divisions, for instance, occurs during early development in organisms as distantly related as marine invertebrates, insects, amphibians, and birds (Mita, 1983; Edgar et al, 1986a; Newport and Kirschner, 1982; Olszanska et al., 1984). Such phenomenological similarities may well reflect common molecular mechanisms, since many of the genes involved in mitotic control are highly conserved in eukaryotic as diverse as

yeast, flies, and human (Lee and Nurse, 1988; Lehner and O'Farrell, 1989; Dunphy and Newport, 1988c).

Drosophila development begins with 13 extremely rapid mitotic waves that traverse the embryo, dividing the nuclei in a single cytoplasm without cytokinesis (Rabinowitz, 1941). The first extended interphase (interphase 14) occurs about 2 hr after fertilization, and it is during this period that high levels of transcription first occur and cells form around the embryonic nuclei. Following interphase 14, these cells enter mitosis over a period of about 2 hr, in a precisely regulated, spatio-temporal pattern that reflects newly established differences in cell identities (Foe and Alberts, 1983; Foe, 1989). Most cell lineages have three embryonic divisions after interphase 14, but some, such as the neurogenic lineages, undergo as many as six divisions, and others, such as the amnioseroses, never divide again (Hartenstein and Campos-Ortega, 1985).

While previous studies revealed little about how the patterns of these divisions are controlled, they suggested that cell-cycle progression in the early embryonic is regulated by factors that trigger mitosis. Experiments with translation inhibitors, for instance, showed that during the rapid cleavages in *Drosophila* and *Xenopus* embryonic new proteins are required for the initiation of each mitosis, but not for the initiation or completion of S phases (Newport and Kirschner, 1984; Edgar and Schubiger, 1986). In accordance with this result, Harland and Laskey (1980) and Blow and Laskey (1988) found that the cytoplasm of cleavage-stage *Xenopus* embryos is constitutive in its ability to support DNA replication, and proposed that S phases during the cleavages are triggered simply by nuclear envelope breakdown during mitosis.

This simple mode of regulation, with a single control point at the G2/M transition, seems to continue during the later asynchronous cell cycles. Cycle 14, the first spatially patterned cell cycle in *Drosophila*, begins after a synchronous mitosis, lacks G1 and has a short S phase that begins and ends virtually synchronously in all the embryonic nuclei (Blumenthal et al., 1984; McKnight and Miller, 1977; Edgar and Schubiger, 1986; Edgar, unpublished data). Consequently, patterned variation in cell-cycle lengths during cycle 14 results from differences in the lengths of G2 periods, which vary between 30 and >150 min in different cells. This may continue to be true at least throughout cycle 15, which also lacks a detectable G1 phase (Edgar, unpublished data). A in the early synchronous divisions, blocking protein synthesis including cycle 14 results in G2 arrest, and suggesting that new factors are required only to initiate mitosis (Edgar, unpublished data). This type of cell-cycle regulation is strikingly different from that found in budding yeast and many types of cultured cells, where control occurs, primarily at the G1/S boundary (see Murray, 1985, for review). Another clue to the developmental regulation of the cell-cycle comes from experiments with the translation inhibitor -amanitin. These experiments indicate that maternal mRNAs are sufficient to drive