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Review

The cell cycle and development: Lessons from *C. elegans*

David S. Fay *

University of Wyoming, College of Agriculture, Department of Molecular Biology, Dept 3944, 1000 E. University Avenue, Laramie, WY 82071, USA

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Abstract

The invariant developmental cell lineage of *Caenorhabditis elegans* (and other similar nematodes) provides one of the best examples of how cell division patterns can be precisely coordinated with cell fates. Although the field has made substantial progress towards elucidating the many factors that control the acquisition of individual cell or tissue-specific identities, the interplay between these determinants and core regulators of the cell cycle is just beginning to be understood. This review provides an overview of the known mechanisms that govern somatic cell growth, proliferation, and differentiation in *C. elegans*. In particular, I will focus on those studies that have uncovered novel genes or mechanisms, and which may enhance our understanding of corresponding processes in other organisms.

Keywords: Cell cycle; *Caenorhabditis elegans*; Development; Review

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1. Introduction to *C. elegans* development

Just how a typical worm goes about generating 558 cells during embryonic development as well as an additional 401 somatic cells (plus ∼2000 germ cells) during its four postembryonic larval stages has been a subject of great interest for nearly 40 years. Aiding researchers in this ambitious goal has been the worm itself, both through its amenability to genetic approaches as well as its quasi-fixed or "hard-wired" developmental lineage. Briefly, during the first ∼1.5 h of embryogenesis, six "founder" cells are generated that will subsequently give rise to all cell types within the embryo [1]. The specific timing of founder cell establishment ranges from ∼30 min (in the case of AB) to ∼90 min (for D and P4; Fig. 1). Three of the founder cells will produce differentiated cell types of a single class, e.g. E, from which the intestine is derived. Three others

* Tel.: +1 307 766 4961; fax: +1 307 766 5098.
E-mail address: davidfay@uwyo.edu.

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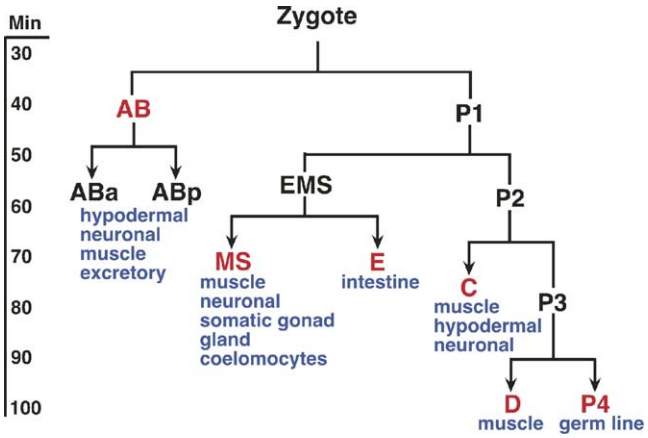

Fig. 1. Cell lineage of the early *C. elegans* embryo. Founder cells (red) and their derivatives (blue) are indicated along with the approximate timing of divisions after fertilization (at 25 °C). Left and right placements of daughter cells indicate their relative anterior and posterior locations within the embryo, respectively. Adapted from [1].

will generate diverse cell types, such as AB, whose descendents include skin, neurons, and muscle cells. After hatching, 53 cells produced during embryogenesis (termed "blast cells") will undergo subsequent rounds of division over the course of four larval stages (designated L1–L4) to generate the cell types and structures associated with the adult animal [2]. Two other embryonically derived cells (Z2 and Z3) are responsible for populating the germ line.

In examining the lineage of *Caenorhabditis elegans*, three things become apparent: (1) the relative timing of all (somatic) cell divisions is invariant; (2) the orientation planes of the cell divisions (with respect to the major animal axes) are also highly reproducible; and (3) the ultimate fates assumed by individual cells are invariant and correlate with the specific position of a cell within the greater lineage. As described below, by altering any single aspect of the lineage, other characteristics of the lineage may experience consequences. For example, by changing the plane of cell division, differentiation may be affected because of the abnormal segregation of cell fate determinants. In addition, by shifting cell fates (most commonly through loss of gene function), the subsequent timing of cell divisions will typically (and predictably) be altered. It is important to note that whereas the fixed lineage of *C. elegans* is suggestive of a model that could rely exclusively on the activities of asymmetrically segregated differentiation factors, in fact, cell signaling and inductive events play a major role in determining developmental outcomes during early embryogenesis, as well as later during postembryonic development. It is the invariance of the lineage with respect to both timing and orientation that leads to a reproducible pattern of cell-cell contacts, thereby ensuring consistency of the inductive events.

In addition to the actions of cell fate determinants and instructive signaling molecules, more global controls exist to guide the relative timing of postembryonic cell divisions. Such regulation is provided primarily by the heterochronic genes (so named for their striking defects in developmental timing), which include a number of micro RNAs as well as their presumptive targets. Mutations in the heterochronic genes lead to juxtapositions of developmental events, such that divisions typical of the L2 stage may occur during L1, or to patterns that are characteristic of one stage being reiterated throughout multiple stages, producing the equivalent of a developmental stutter [3]. Of particular significance is the implication that heterochronic genes must ultimately interface with cell cycle regulators to control both re-entry into and withdrawal from the cell cycle [4,5]. The exact mechanism by which this occurs, however, remains largely unsolved (also see below).

Components of the dauer pathway, the core portion of which includes an insulin-like signaling pathway, provides a necessary degree of flexibility to postembryonic development, allowing animals to temporarily withdraw from the normal course of development in times of food shortage or other environmental challenges [6]. Similar to the situation for heterochronic genes, entry into the dauer state (following L2) must necessarily be coordinated with cell cycle regulators, such that cells withdraw from the cell cycle and remain quiescent until re-entry into the L3 stage.

2. Control of embryonic cell fates and divisions

Prior to the isolation of informative mutations, several early studies suggested a role for asymmetrically distributed cytoplasmic determinants in governing the duration of individual cell cycles [7,8]. Using several different manipulation techniques, it was found that nuclei within a common cytoplasm divide synchronously, whereas enucleated cells continue to cycle (based on surface contractions) with a timing that is characteristic of their normal lineage. Furthermore, the duration of cell cycles can be greatly altered by the introduction of cytoplasm from cells with different inherent periodicities. Notably, these studies failed to detect alterations in the timing of blastomere divisions based solely on changes in nuclear-to-cytoplasmic ratios [7].

Initial studies also demonstrated that lineage-specific differences in cell cycle lengths could be attributed solely to disparities in the duration of S phase; the early cycles of *C. elegans*, like those of *Drosophila*, lack detectable gap phases [9]. True gap phases are first observed in the daughters of the E cell, and this delay (which corresponds with gastrulation) is dependent on embryonic transcription [10]. More recently, it has been reported that the duration of S phase in the two-cell-stage blastomeres AB and P1, depends on the actions of several conserved checkpoint genes including *C. elegans* homologs of Chk1 and ATM/ATR [11]. In the absence of checkpoint function, normal differences in the timing of these divisions were substantially, although not completely, abrogated. This study provided further evidence that the longer cell cycle associated with P1 may be the indirect effect of the smaller size of P1 relative to AB; a phenomenon that is