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Developmental Biology 279 (2005) 322–335

DEVELOPMENTAL BIOLOGY

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Caenorhabditis elegans germline patterning requires coordinated development of the somatic gonadal sheath and the germ line

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Received for publication 29 September 2004, revised 24 November 2004, accepted 9 December 2004
Available online 19 January 2005

Abstract

Interactions between the somatic gonad and the germ line influence the amplification, maintenance, and differentiation of germ cells. In *Caenorhabditis elegans*, the distal tip cell/germline interaction promotes a mitotic fate and/or inhibits meiosis through GLP-1/Notch signaling. However, GLP-1-mediated signaling alone is not sufficient for a wild-type level of germline proliferation. Here, we provide evidence that specific cells of the somatic gonadal sheath lineage influence amplification, differentiation, and the potential for tumorigenesis of the germ line. First, an interaction between the distal-most pair of sheath cells and the proliferation zone of the germ line is required for larval germline amplification. Second, we show that insufficient larval germline amplification retards gonad elongation and thus delays meiotic entry. Third, a more severe delay in meiotic entry, as is exhibited in certain mutant backgrounds, inappropriately juxtaposes undifferentiated germ cells with cells of the proximal sheath lineage, leading to the formation of a proximal germline tumor derived from undifferentiated germ cells. Tumors derived from dedifferentiated germ cells, however, respond to the proximal interaction differently depending on the mutant background. Our study underscores the importance of strict developmental coordination between neighboring tissues. We discuss these results in the context of mechanisms that may underlie tumorigenesis.

Keywords: Germline; Gonadal sheath cell; Soma/germline interaction; Tumor; Cell–cell interaction; Proliferation; Mitosis; Meiosis; Proximal proliferation

Introduction

The control of cell proliferation within a developing organ or tissue is a fundamental problem in developmental biology. Since proliferation is often influenced by signals coming from the surrounding cellular environment, this question becomes even more complex if cells experience changes in their environment as they proliferate. In addition to signals that dictate cell fate status such as competence to proliferate versus differentiate, an equally important and perhaps less well-understood aspect of development is the control of the rate or extent of proliferative growth. Many tissues and organ primordia undergo a period of proliferation during their development that later resolves into a slower rate of homeostatic stem cell-based maintenance (Fuchs et al., 2004). If cell–cell interactions guide the extent of proliferation during development, then correct temporal and spatial coordination of these interactions is critical to ensure sufficient growth and prevent inappropriate proliferation.

One example of cell proliferation that occurs in the context of a changing developmental environment is the early proliferation of the germ line (Saffman and Lasko, 1999). The germ line of many animals undergoes extensive proliferation prior to meiosis and gametogenesis. The extent of proliferation during development must be tightly controlled: insufficient proliferation could deplete reserves of germline stem cells and excessive proliferation could lead to formation of germline tumors. In mammals, the proliferation of undifferentiated germ cells occurs in the context of the still-developing somatic gonad (McLaren, 2003). In males, this proliferation resolves into stem cell proliferation followed by transit-amplifying divisions to maintain homeostasis. In female mammals, extensive proliferation early in development is countered by extensive cell death (McLaren, 2001, 2003).

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doi:10.1016/j.ydbio.2004.12.021

In *Caenorhabditis elegans*, a similar phase of germline amplification occurs within the developing somatic gonad and produces a stem cell population or proliferation zone (Fig. 1). In the wild-type hermaphrodite, two gonad arms elongate away from a medial (proximal) somatic gonad primordium. Germ cells proliferate throughout the gonad arm until mid-way through the third larval stage (L3), at which time the proximal-most germ cells enter meiosis (Fig. 1; Hansen et al., 2004a; Kimble and White, 1981). A distal proliferation zone is thereby established and is maintained by an interaction between the distal tip cell (DTC) and the germ line (Kimble and Hirsh, 1979; Kimble and White, 1981). The DTC/germline interaction is mediated by the GLP-1 receptor, a member of the LIN-12/Notch family (Austin and Kimble, 1987; Yochem and Greenwald, 1989).

An interaction between somatic cells of the gonadal sheath/spermatheca (SS) lineage and the germ line is also required to promote robust amplification of the germ line (McCarter et al., 1997). The SS lineage/germline interaction acts in parallel to the GLP-1-mediated interaction: in the

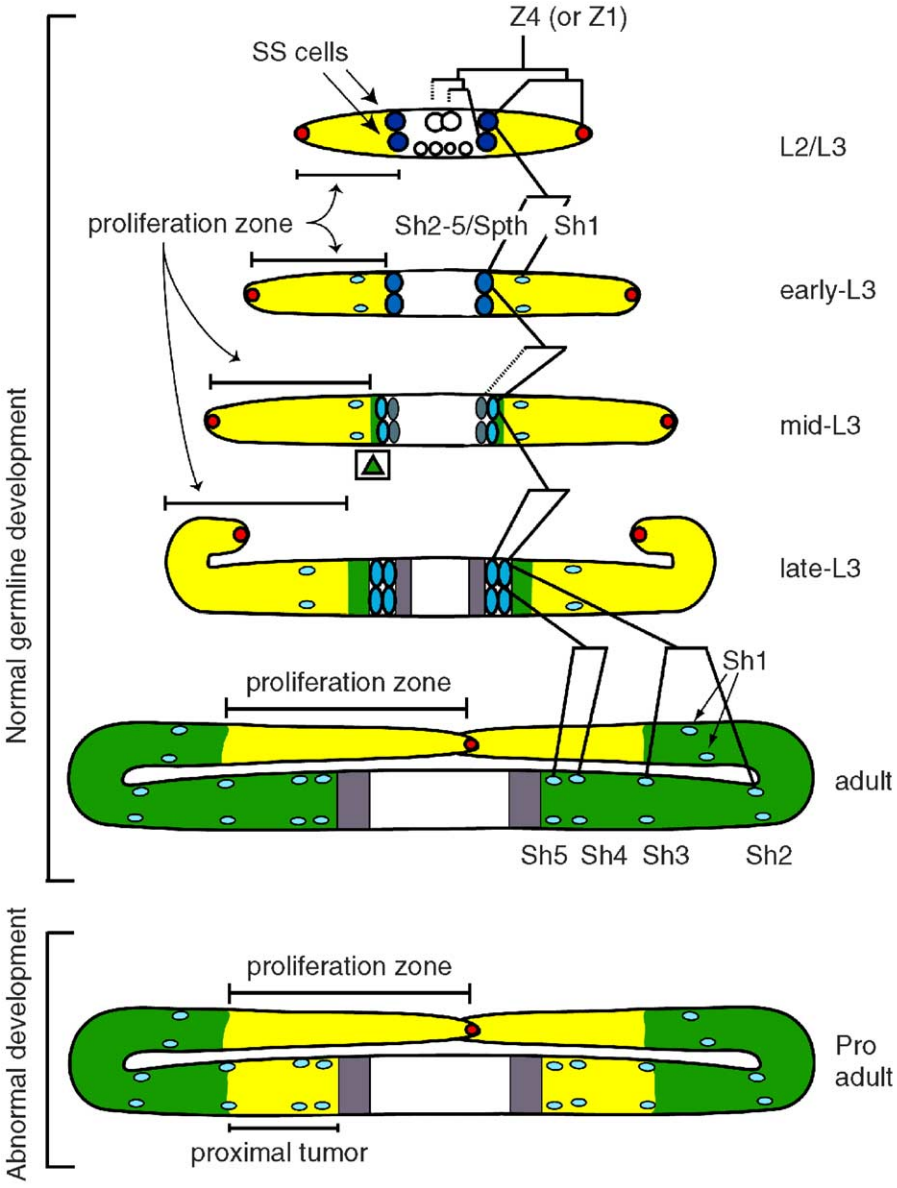

Fig. 1. Cartoon representation of hermaphrodite gonadogenesis. The positions of nuclei of SS cells and their descendents are shown with the sheath lineage connected by solid lines and additional lineages in dotted lines (the lineage is depicted in only one of the two SS cells after the L3). Vertical distance in the depicted lineage is not proportional to time between divisions. The sheath lineage nuclei are indicated in blue (increasingly light as the lineage progresses to differentiated sheath cells); the sheath cell bodies are not indicated (see Fig. 2). Yellow indicates germ cells in the mitotic cell cycle and green indicates germ cells in meiosis or gametogenesis or gametes. Grey represents the spermatheca and white represents the uterine and anchor cell lineages. The distal tip cell is indicated in red. Green boxed triangle indicates initial meiotic entry. Proximal germline tumors characteristic of the proximal proliferation (Pro) phenotype, are depicted in both gonad arms of the Pro adult. Lateral views are depicted for the L2/L3 and adult gonads. The proximal gonad of all other stages is depicted as a dorsal or ventral view, but the extent of gonad migration at each stage is represented laterally.