Germ Versus Soma Decisions: Lessons from Flies and Worms
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The early embryo is formed by the fusion of two germ cells that must generate not only all of the nonreproductive somatic cell types of its body but also the germ cells for the next generation. Therefore, embryo cells face a crucial decision: whether to develop as germ or soma. How is this fundamental decision made and germ cell fate maintained during development? Studies in the nematode worm Caenorhabditis elegans and fruit fly Drosophila identify some of the decision-making strategies, including segregation of a specialized germ plasm and global transcriptional regulation.

Despite their different formation strategies, both worms and flies rely on the passage of specialized germ plasm from the oocyte to the future germ cells. Induction, an alternative mode of germ cell specification, operates in other organisms, including mice (3).

Newly Formed Germ Cells Are in a transcriptionally Repressed State
A common feature of early germ cells in worms and flies is their transcriptional quiescence (Figs. 1 and 2). One likely role is to protect early germ cells from expressing somatic differentiation genes. Transcriptional quiescence is achieved through a repression program that regulates the core transcriptional machinery as well as chromatin states.

The earliest phase of repression is mediated at the level of transcription elongation in both organisms, as the germ line and soma are being separated from each other (4). Proteins involved in preventing RNA polymerase II (Pol II) elongation in germ cells have been identified in both organisms. The zinc finger protein PIE-1 is a key regulator in worms (5). In embryos that lack PIE-1 activity, newly formed germ cells contain elongating Pol II and produce mature mRNAs (1, 4, 5). In these mutants, the development of germ cells is similar to that of their somatic sister cells, and the embryos die. Mechanistically, PIE-1 apparently competes with the tail of Pol II for the enzymes that modify Pol II and produce mature mRNAs (1, 4, 5).

A chromatin-based phase of transcriptional repression kicks in soon after P4 divides to generate the Z2 and Z3 cells, at the ~100-cell stage of worm embryogenesis, when PIE-1 activity and expression are absent (6). As in pie-1 mutants, germ cells that lack either Pgc or Nanos activity show elongating Pol II activity and express genes characteristic of somatic cells (7, 8, 10) (Fig. 2, A, C, D, and F). These “transformed” cells either undergo apoptosis, a somatic cell death pathway, or adopt somatic cell fates (10). The mechanism (or mechanisms) by which Pgc and the Nanos and Pumilio translational repressors prevent elongation and the relationship between these regulators are unclear.

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granule markers (e.g., PGL-1) are ectopically expressed and Nanos (H3K4me is absent from embryonic germ cells from conditions or signals that send them down a somatic differentiation pathway. In the adult worm, germ lines lacking the translational regulators GLD-1 and MEX-3 lose their germ granules and express markers characteristic of neurons and muscles (I2). Conversely, somatic cells may require protection from conditions or signals that send them down a germine differentiation pathway. Loss of some of the C. elegans synMuv B chromatin regulators, such as LIN-35/Retinoblastoma and members of the nucleosome remodeling and histone deacetylase (NuRD) complex (e.g., MEP-1), causes somatic cells to display germine traits, such as germ granules and enhanced RNA interference (I3, I4) (Fig. 2, H and I). This ectopic expression of germine traits by somatic cells depends on the histone H3K36 methyltransferase MES-4 and the chromodomain protein MRG-1 (13–15). These chromatin regulators are known to be critical for germine development, but the mechanistic details in the soma are unclear.

Roles of Germ Granules

A distinctive feature of germ cells is possession of specialized germ plasm, which contains unique cytoplasmic organelles generically referred to as germ granules and specifically called polar granules in flies and P granules in worms (Fig. 2, G and H). Polar granules and P granules share some components, such as the RNA helicase Vasa in flies and the related germine helicases (GLHs) in worms, and they contain numerous species-specific proteins, such as Oskar in flies and PGL-1 in worms (I, J, K). Although the precise roles of these granules are still being worked out, it is clear that they are intimately associated with germine fate in all organisms, including those organisms that specify germ cells by inductive signals (I).

What roles do germ granules play? Studies in flies and worms suggest that a primary role is in handling RNA. Germ granules are rich in RNA and predicted RNA-binding proteins, and many RNAs and proteins are either specifically localized to or protected from degradation in these granules (I6). The location of germ granules over nuclear pores positions them to encounter mRNAs during their transport from the nucleus and may contribute to control of mRNA translation and localization within the cytoplasm (I7, I8) (Fig. 2G). Functionally, germ granules may be related to P bodies. The latter have been shown in yeast and mammalian cells to participate in mRNA decay, RNA interference, and translation inhibition by microRNAs. Many P-body proteins are found in germ granules in worms and flies (I9–22). Germ cells appear to be particularly dependent on RNA-based regulation and may benefit from consolidating RNA-processing machinery into large granular assemblies. Throughout the life cycle, however, germ granules are dynamic in morphology, composition, and RNA regulatory function. P body–like activities may thus be only one aspect that regulates germine fate.

Summary and Outlook

Flies and worms share several strategies to establish and maintain germ cells and protect them from somatic fates. Both systems segregate specialized germ plasm to the PGCs. The RNA-rich granules in germ plasm serve roles in localization, protection, and translation of mRNAs. Although mammalian germ cells are not specified by segregated germ plasm, they do contain germ plasm components. Transcriptional repression in early PGCs is a common theme to prevent PGCs from differentiating in the same way as their somatic neighbors, although the regulators—worm PIE-1, fly Pgc, and mammalian Blimp1—differ between species (I3). Studies across species promise to provide more mechanistic insights into how germ plasm and transcriptional regulation specify germ cells in the early embryo and protect germ cell fate throughout life.

References and Notes

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