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Reproductive biology: A genetic recipe for parthenogenesis

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Abstract

New work reveals differences in oogenic gene expression between parthenogenetic and sexually reproducing *Drosophila mercatorum* strains. Recapitulating those changes in *D. melanogaster* oocytes induced parthenogenesis in this normally sexually reproducing species, providing molecular insight into how these reproductive modes arise.

Most animals derive from the union of an egg and a sperm. Combining genetic material from two parents into a single offspring contributes to genetic diversity and allows for generation of potentially advantageous allelic combinations and removal of disadvantageous alleles/combinations by recombination. Given the advantages of biparental reproduction, it is not surprising to find cellular mechanisms that render it obligatory. Such mechanisms include genomic imprinting in mammals[1] and the need for sperm to provide important molecules that 'activate' eggs to start embryogenesis. For example, sperm-derived phospholipase C raises calcium levels in mammalian eggs, thereby activating them[2], and sperm organelles such as centrioles are needed for embryonic divisions in many taxa (e.g.[3]).

However, as with many biological phenomena, there is immense variation in reproductive strategies. In bees and their relatives, females develop from the standard egg-meets-sperm situation, but males develop from unfertilized eggs that initiate development and make their own centrioles *de novo*[4]. In 'gynogenetic' species, such as the crucian carp[5], female progeny develop from eggs fertilized by sperm from another species. The eggs are activated, but the heterospecific sperm's genome is not incorporated into that of the offspring. Conversely, progeny in 'androgenetic' species have paternally derived genomes, again by exploiting gametes from the opposite sex[6].

A particularly intriguing method of reproduction is parthenogenesis. Here, progeny develop from a female's oocytes with no involvement of a male. Parthenogenesis occurs in numerous insect species (e.g.[7,8]) as well as in reptiles, birds, and fishes (e.g.[9,10]). Although parthenogenesis lacks some of the genome-diversifying advantages of biparental inheritance, it has its own advantages: it allows progeny production without finding and mating with a male — an expedient strategy if animals are very dispersed. Some species are obligatorily parthenogenetic, others obligatorily sexually reproducing. So-called

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DECLARATION OF INTERESTS

The authors declare no competing interests.

'facultatively parthenogenetic' species avail themselves of the benefits of each reproductive mode, generating biparental offspring when males are available and conditions warrant, and undertaking parthenogenesis when they are not.

Despite its existence in many taxa, mechanisms of parthenogenesis and its regulation have remained mysterious. We know that parthenogenesis often produces diploid progeny from diploid mothers by mechanisms ranging from suppression of meiosis to fusion of meiotic products; the latter can also give rise to higher-ploidy offspring. But, while previous studies have associated candidate loci or chromosomal regions with parthenogenesis, the molecular mechanisms that control the switch between the production of biparental vs. parthenogenetic progeny remain unknown. A new paper by Sperling *et al.*[11] in this issue of *Current Biology* takes the first molecular steps towards solving this mystery, by taking advantage of the existence of parthenogenetic, sexually reproducing, and facultatively parthenogenetic strains within *Drosophila mercatorum*[8].

To search for a parthenogenesis-promoting gene(s) or genomic region(s), Sperling *et al.* sequenced and compared genomes of the different *D. mercatorum* strains. The genomes' contents and karyotypes were remarkably similar across strains, apart from some inversions in one chromosome arm; no obvious 'parthenogenesis gene(s)' jumped out. The authors then wondered whether a parthenogenesis-regulating gene might differ in expression in the germline of parthenogenetic vs. sexually reproducing strains. Accordingly, they determined and compared the transcriptomes of mature oocytes between strains. They observed expression differences, often in conserved genes with known functions. Though many of those genes were not obviously connected to parthenogenesis, some — namely cell-cycle regulators and centriole and spindle factors — hinted at a role in early development.

The authors then took a brave leap. They hypothesized that the differential expression of these genes might underlie parthenogenetic ability and decided to test this with *Drosophlia melanogaster*, a species that is simple to genetically manipulate in the lab. *D. melanogaster* is normally considered obligately sexually reproducing, although an early report documented that some wild-caught strains show a low level of parthenogenesis[12]. Sperling *et al.* tested whether altering the expression of genes discovered as differentially expressed in *D. mercatorum* oocytes could induce parthenogenesis in *D. melanogaster*. They used publicly available as well as 'homemade' strains to increase or decrease expression of the candidate genes in the *D. melanogaster* germline, looking for cases where unmated females laid unfertilized eggs that developed to adulthood.

This investigation would have been impossible in any other insect, but even in *D. melanogaster* it was not easy. Expecting induced parthenogenesis to be rare, the authors screened tens of thousands of female flies to find conditions that switched on parthenogenesis. Excitingly, 16 genes, when manipulated to echo the expression in parthenogenetic *D. mercatorum*, converted *D. melanogaster* eggs to parthenotes at low rates: these included cell-cycle or centriole regulatory genes. As a proxy for manipulating many of the latter, the authors focused on Polo kinase, a known centriole regulator[13]. Increasing *polo* expression, and thus modulation of its targets, in *D. melanogaster* eggs resulted in parthenogenesis, but at a low (0.1%) rate. The authors then tested whether

manipulating other candidates in combination with increased Polo could increase the rate of *D. melanogaster* parthenogenesis.

Combining increased *polo* dosage with knockouts of fatty acid desaturases (*desat1/2*) increased parthenogenesis; 0.6% of unfertilized eggs developed to adulthood. Parthenogenesis increased further (to 1.4% surviving adults) upon the addition of an extra copy of *Myc*, a transcriptional regulator of cell cycle/proliferative genes[14], and a homolog of one of the original Yamanaka pluripotency factors[15]. This is, to our knowledge, the first identification of genetic changes that can trigger parthenogenesis and modulate its rate.

How could these genes trigger parthenogenetic development? The transition from differentiated oocyte to early embryo normally involves at least two distinct processes. First, eggs must be activated by a calcium-triggered event that relieves meiotic arrest and alters the egg's transcriptome, proteome, and membranes/envelopes to support development (e.g.[16]). Second, the activated eggs must begin embryogenesis by generating a zygotic nucleus from egg- and sperm-derived pronuclei, making centrioles if necessary, and undertaking mitotic divisions. While egg activation and the initiation of embryo development are often tightly coupled, they are separate in some species. In particular, egg activation in numerous insects including *D. melanogaster* is independent of fertilization; it is induced instead by physical forces that eggs experience as they move through the reproductive tract[17,18]. Thus, to trigger parthenogenetic development, a *D. melanogaster* egg only needs what is necessary to start embryo development.

It is not simple to come up with a model for how Polo, Myc, and Desat2 levels could promote parthenogenesis. Sperling *et al.* propose that each of these genes contributes in a different way (Figure 1). Higher Myc may 'prime' the parthenogenetic egg for mitotic divisions by ensuring abundant cell-cycle gene products in the egg, thereby supporting later proliferation. Increased amounts of Polo kinase, which has roles in mitotic entry and whose activity may be regulated during egg activation[19], are suggested to drive the centriole biogenesis needed for parthenogenetic embryos to undertake mitosis. The authors' images of Polo puncta at sites of centriole formation support this model. How decreasing Desat1/2 levels promotes parthenogenesis seems more mysterious. The authors suggest it might alter membrane fluidity, allowing polar body nuclei to fuse or engage in mitosis.

Sperling *et al.*'s exciting results will motivate many fascinating future studies of cell, developmental, reproductive, and evolutionary questions. For example, although a few parthenogenetic *D. melanogaster* embryos can develop to adulthood (and are fertile, either by sexual or parthenogenetic reproduction), many arrest development very early, around the time of the initiation of mitotic divisions. Among embryos that proceed beyond that point, the authors saw intriguing deviations from stereotypical spindle distribution and organization. *D. melanogaster* sperm normally provide centrioles for the embryos[3]. Do the spindle abnormalities in the later-arresting parthenogenetic embryos reflect inefficiencies in *de novo* centriole generation or function?

It will also be interesting to know whether additional 'ingredients' improve the 'recipe' for parthenogenesis (a pinch of extra Polo and Myc, a little less Desat2). Does parthenogenesis

efficiency in *D. melanogaster* increase if the expression of additional candidates is manipulated along with these three genes? The full molecular instructions will be important to know for their significance to fundamental and applied reproductive/developmental biology and to compare to gene expression changes in other situations in which non-dividing cells are induced to proliferate, such as cancer initiation or tissue regeneration.

It is also tempting to wonder whether manipulating analogous genes in eggs of other organisms could induce parthenogenesis, although success is uncertain given potential technical barriers and biological differences (e.g. imprinting in mammals, but see[20]). The results of such studies would interest not only developmental, cell, and evolutionary biologists but also people looking to reproduce without the need for sperm-meets-egg: same-sex couples who desire biologically related offspring, or people who can produce eggs and would like a biological child without a partner or with a partner who is infertile due to sperm defects.

Sperling *et al.*'s important findings bring a new understanding of how parthenogenesis can be induced. Now that we know some of the genes involved, it will be intriguing to determine what causes their germline gene expression differences between sexually reproducing and parthenogenetic species or strains. Did the changes arise individually and accumulate with selection? Or is there an upstream regulator — intrinsic or extrinsic — that controls them all? The answers will illuminate the genesis of this aspect of the amazing diversity in reproductive strategies across the animal kingdom.

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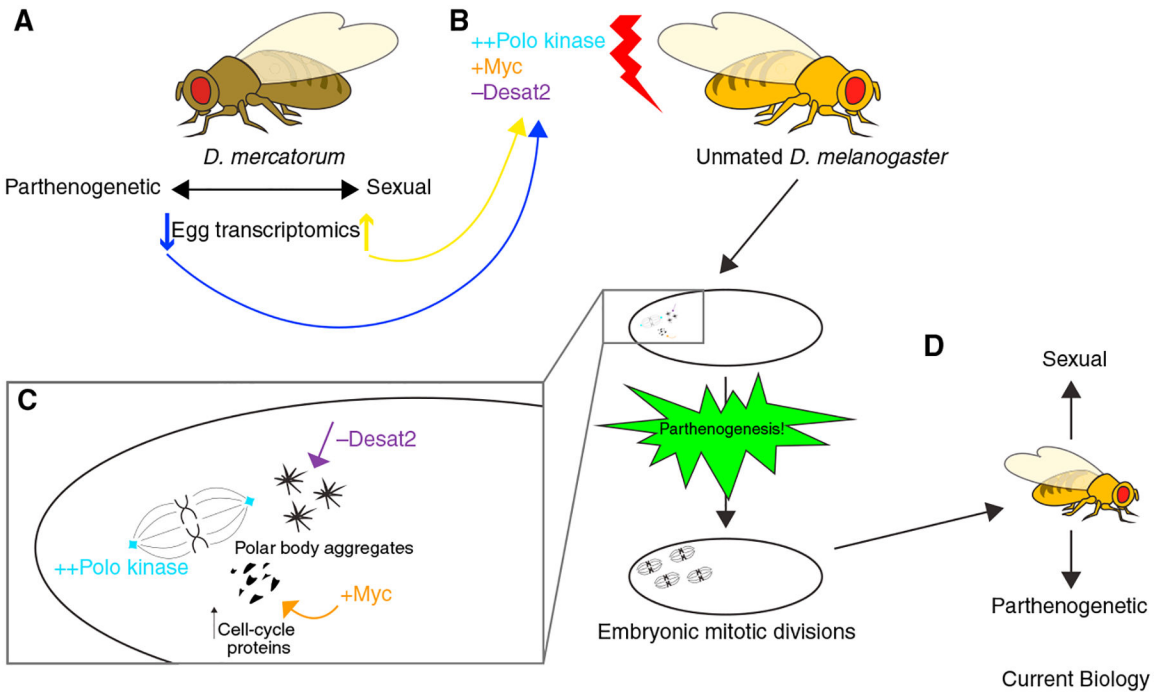

Figure 1. Inducing parthenogenesis in *D. melanogaster*.

(A) Sperling *et al.*[11] performed RNA sequencing analysis to compare transcriptomes of sexually reproducing and parthenogenetic (obligatory and facultative) *D. mercatorum* eggs. (B) They mimicked the differential expression of some of these genes in the germline of female *D. melanogaster*, a normally sexually reproducing species. (C) Unfertilized eggs from *D. melanogaster* females overexpressing Polo kinase and Myc, and deficient for desaturase 2 (Desat2), became parthenogenetic. The authors suggest that these genetic manipulations promote centriole biogenesis (Polo), 'prime' the embryo with abundant cell-cycle proteins to increase proliferative capacity (Myc), and allow polar bodies to participate in mitosis by altering membrane fluidity (Desat2). (D) Adult flies that develop from these parthenogenetic embryos can reproduce both sexually and by parthenogenesis.