Making the commitment to meiosis

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Analysis of the phenotype of mouse germ cells deficient for the retinoic acid–responsive gene *Stra8* provides insight into the timing of the commitment to enter meiosis in mammals. The observations suggest that, as in other eukaryotes, this commitment precedes (or coincides with) the commitment to premeiotic DNA replication.

The question of what drives mammalian germ cells to cease their mitotic divisions and make the irreversible commitment to enter meiosis has remained a black box in the field of reproductive biology, despite extensive insight into the relevant signals gleaned from model eukaryotes such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe* and *Caenorhabditis elegans*[1,2]. The possibility that retinoic acid may function as a 'meiosis-inducing' substance was suggested in recent complementary studies from the laboratories of David Page[3] and Peter Koopman[4]. In the study on page 1430 of this issue, Andrew Baltus and colleagues[5] in the Page laboratory extend these earlier observations, describing the phenotype of the *Stra8* (stimulated by retinoic acid gene 8)-null mice that formed the basis for their previous work. In particular, they relate the phenotype to the timing of the onset of premeiotic DNA synthesis (or to the lack thereof).

The evolution of meiosis

The timing of the commitment to enter meiosis shows a striking dichotomy in the male and female germ cells in higher organisms[6–8]. In the mouse (and in humans), the mitotically dividing oogonia enter meiosis during embryonic development, whereas in the male germline, this occurs postnatally (**Fig. 1**). Many other interesting sexually dimorphic properties of differentiation follow, including the fact that a renewing stem cell population is maintained throughout the reproductive lifespan in the male but not in the female. The genetic control of this differentiation pathway has been the focus of many investigators, with the hope of understanding the cause of infertility and the identification of new targets for contraception[9]. The field has been advanced enormously by the fact that many genes implicated in the events of meiosis in simpler model organisms are evolutionarily conserved[10,11] (see also http://www.germonline.org/).

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Curiously, the molecular nature of the signals to enter meiosis, the very first step in triggering the subsequent differentiation, seems to be less well conserved. As noted by Baltus *et al.*[5], the molecules involved in this induction even differ between the two yeasts. It was thus of considerable interest when the two aforementioned groups reported that retinoic acid signaling through the *Stra8* gene may be involved with this signal in the mouse model. Specifically, they reported that retinoic acid could induce entry into meiosis in embryonic gonads of both males and females, although normally this would occur only in the female at this stage. Nonetheless, the prospermatogonia were capable of responding to the ectopic trigger. The *Stra8* gene, first identified as being induced by retinoic acid[12], was further implicated as a key to this commitment, as its expression precedes meiotic differentiation in both sexes.

Stra8 gets it started

The present study now details the reproductive phenotype of *Stra8*$^{-/-}$ mice: invariable sterility in both sexes and no other overt abnormalities. The authors did not detect any oocytes in adult

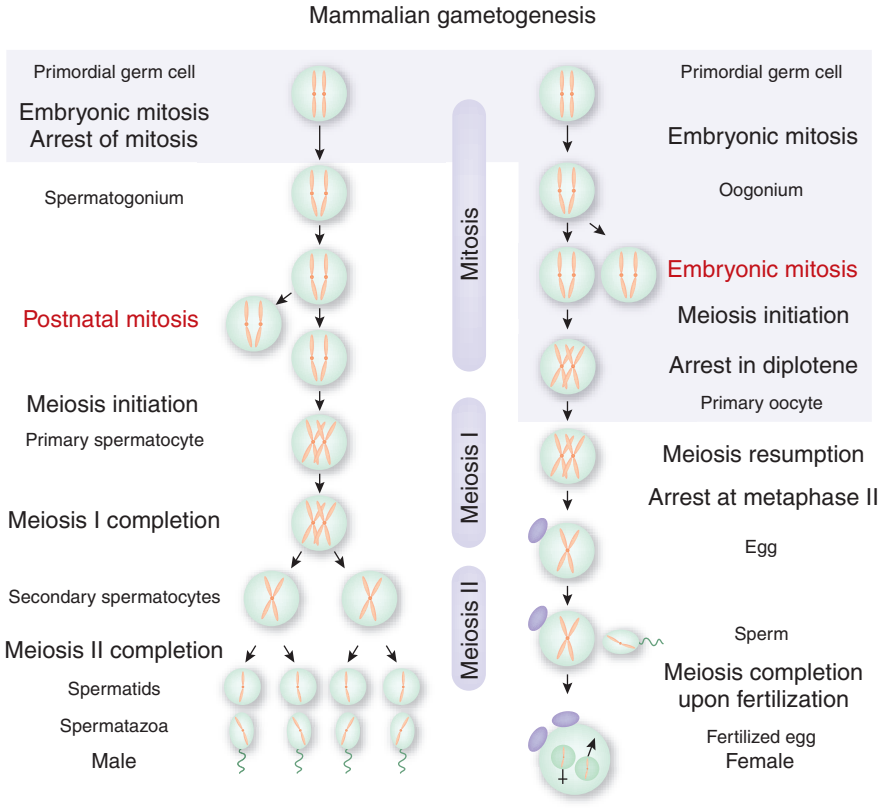

Figure 1 This flowchart depicts the steps of mammalian gametogenesis with an emphasis on the progression through mitosis and meiosis. The stages in the portion with the blue background typically occur during embryonic development. The paper by Baltus *et al.*[5] examines the question of whether the initiation of meiosis (highlighted in red) precedes or follows the premeiotic round of replication. Figure modified, with permission, from B.W. Alberts *et al. Molecular Biology of the Cell* (Garland, New York, 1983).

ovaries, and the only germ cells observed in adult testes resembled premeiotic spermatogonia. Characterization of the embryonic gonads showed that Stra8-deficient ovaries never contained germ cells with the morphology of meiotic prophase oocytes. Correspondingly, and not surprisingly, the chromosomes were neither condensed into characteristic leptotene, zygotene or pachytene configurations, nor were they decorated with meiotic prophase marker proteins, including the meiotic cohesion REC8 and the synaptonemal complex protein SCP3. The expression of several other markers of meiotic prophase was similarly negative—these cells do not enter meiosis.

The authors then went on to ask whether the cells nonetheless entered a round of DNA synthesis in preparation for this doomed meiotic differentiation, focusing on the question of commitment to meiosis as an event temporally distinct from the commitment to the round of DNA synthesis that precedes meiosis. Enriched populations of oocytes were isolated from embryonic ovaries and were essentially shown to have a 2C rather than a 4C content of DNA. The parallel experiment in the male germline could not be performed because of the inability to separate spermatogonia from spermatocytes before the cells underwent apoptosis. This brings up another interesting sexual dimorphism: the female germline seems to be much less robust in eliciting apoptosis in response to interruption of meiosis than in the male. Sexual dimorphism notwithstanding, the conclusion of the study was that the commitment to enter meiosis precedes the round of DNA synthesis before entry into meiosis.

Decisions, decisions

This argument assumes that premitotic DNA synthesis and premeiotic DNA synthesis are one and the same, using the same regulatory molecules and same machinery, because the conclusion hinges on the fact that the germ cells fail to undergo DNA replication and subsequent meiotic differentiation. What if the commitment to meiosis were, in fact, the decision to enter a unique premeiotic round of replication? There are scattered hints in the literature that premeiotic S-phase may be different from typical mitotic S-phases in diverse organisms[13–15]. This shifts the focus from the question of when the cells actually undergo DNA synthesis back to the original question of the critical signal that triggers the 'commitment to meiosis'. Here, the identification of retinoic acid as a potential key molecule is intriguing, and if this is verified, the even more challenging question is which molecules involved in retinoid metabolism—retinoid synthesis, degradation, intracellular transport or receptors—are required for its role in the induction of meiosis .

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New insights into the biological basis of genomic disorders

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Many clinical syndromes result from deletion or duplication of regions within the human genome. Two new studies demonstrate strong connections between such events and allelic recombination in humans, which in the future may enable researchers to better predict the locations of unstable genomic regions.

Many genetic diseases are caused by deletion or duplication of regions of the genome. These events are frequently associated with low-copy repeats (LCRs). One mechanism by which such repeats can mediate insertion and deletion events is nonallelic homologous recombination (NAHR). During meiosis, mispairing is thought to occur between paralogous repeats that are located on the same chromosome but separated by intervening DNA; subsequent crossing over between strands results in duplication or deletion of the intervening sequence (**Fig. 1**). In several cases, it has been observed that deletion and insertion breakpoints cluster in narrow 'hotspots' within such repeats, reminiscent of the clustering that takes place in allelic recombination, in which most human recombination is concentrated in narrow hotspots sharing a common 1- to 2-kb width[1,2]. Two studies, one by De Raedt *et al.*[3] on page 1419 of this issue and one by Lindsay *et al.*[4], advance our biological understanding of chromosomal rearrangement hotspots. They demonstrate that NAHR is highly similar in several ways to the process of allelic recombination, suggesting close mechanistic ties between the two.

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Targeting LCRs

Despite the large number of pathogenic deletions and duplications associated with LCRs, there has been little detailed exploration of variation in and around segmental duplications. One reason for this is the technical difficulty inherent in identifying polymorphisms and performing genotyping within these areas of the genome. This has meant that large-scale genetic surveys such as the HapMap often have poor coverage in duplicated regions, motivating the targeted, sequencing-based approach taken by the two new studies.

De Raedt *et al.* studied three copies of a human LCR: two present in direct orientation on chromosome 17, flanking the *NF1* gene, and one on chromosome 19. NAHR between the two chromosome 17 copies during meiosis can result in removal of the intervening sequence, including the *NF1* gene, a process responsible for the majority of cases of *NF1* microdeletion. In such individuals, the endpoints of the deleted