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Meiosis: no end in sight

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Meiosis is an essential event that generates haploid gametes from diploid progenitors in all sexually reproducing organisms. It involves a single round of DNA replication followed by two rounds of chromosome segregation: separating homologous chromosomes (homologs; meiosis I [MI]), then sister chromatids (meiosis II [MII]). During the first meiotic prophase (MI prophase), homologs undergo recombination, pairing, and synapsis through the formation of the synaptonemal complex (SC). Recombination, the most prominent feature in meiosis, can increase genetic diversity during inheritance and generate physical connections between homologs to ensure their accurate segregation at MI prophase. In humans, meiotic errors can result in either infertility or gametic aneuploidy/mutation (hence, miscarriage or birth defects). With technological advances in the past few decades, researchers have made rapid progress in the field of meiosis. This special issue contains seven papers: five are reviews summarizing our current knowledge on meiosis (in particular mammalian MI prophase), and one is commentary highlighting an original research article on CRISPR-Cas9-based gene therapy for the treatment of meiotic arrest azoospermia in mice.

Given that meiosis is essential for sexual reproduction, it is important to understand how entry into meiosis is initiated. In budding

yeast, the gene inducer of meiosis 1 (*IME1*) is the master controller of meiotic initiation and encodes a transcriptional factor triggering the cascade expression of genes that is essential for meiosis. However, the factors that govern the initiation of meiosis are not conserved and mammals have no ortholog of *IME1*. It is well known that retinoic acid (RA)-induced genes, including stimulated by retinoic acid gene 8 (*Stra8*) and *Meiosin* (also named *Gm4969*), play crucial roles during mouse meiotic initiation.¹ However, the initiating factor(s) that control mitotic-to-meiotic switch remain unidentified in mammals. In their review, Gewiss and colleagues describe several key pathways controlled by RA and further discuss the major roles of RA and its downstream targets in regulating meiotic entry and completion.¹ They also raise an important question concerning the role of spermatogonial maturation for meiotic initiation.

In most mammals, meiotic recombination is initiated by programmed induction of double-strand break (DSB) at hotspots determined by PR domain-containing protein 9 (PRDM9). Few DSBs are subsequently repaired as crossovers, while others proceed to non-crossovers. The requirement for at least one crossover per homolog ensures their disjunction. The formation and repair of DSBs must be tightly controlled so that crossovers can occur at the right time, place, and frequency.^{2–4} Three reviews in this special issue provide comprehensive updated coverage on the key processes and players governing the DSB formation and repair from different aspects. The review by Li *et al.*² discusses recent advances regarding the formation of DSBs, compares the nature of meiotic DSBs in different organisms (highlighting evolutionary conservation and divergence), and further summarizes the mutations of genes necessary for DSB formation causing human infertility. Meanwhile, Wang *et al.*³ focus on the essential

features and the regulation of crossover – in particular crossover patterns – and how crossover patterns affect human fertility. They give special attention to the chromosome axis length that might be involved in the regulation of crossover frequency. At last, Qu *et al.*⁴ address the mechanisms underlying meiotic DSB formation and repair and the role of the genes that have been identified in mammalian meiosis. The three thought-provoking reviews also bring critical questions on meiotic recombination that remains to be explored in the future.

The SC, which normally initiates between the homologous axis and elongates along their full-length during MI prophase, provides a scaffold for meiotic recombination. The SC is thought to be required for meiotic recombination and MI prophase progression, and its defect(s) can result in aberrant meiosis. In an extensive and exciting review focusing on the SC, Zhang and colleagues provide an update on the current understanding of how the SC is formed and regulated, the functions of the SC, and its role in human infertility.⁵ They also discuss large gaps in knowledge pertaining to the regulation and function of the SC that need to be addressed by future research.

Genetic mutations and meiotic arrests play crucial roles in infertility and the etiology of developmental defects. As summarized in above reviews of this issue, a number of gene mutations in humans have been identified to account for meiosis-based infertilities. It will be challenging to develop safe methods for curing infertility by correction of a meiotic-causing genetic mutation. In the original article of this issue, Wang *et al.*⁶ open the possibility for the treatment of male azoospermia caused by monogenic mutation. They established a successful approach to correct an azoospermia patient-derived testis-expressed 11 (*TEX11*) mutation and restore fertility in mice through combining

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the cultured spermatogonial stem cells and CRISPR/Cas9-based gene editing. In their commentary, Lei and Hamer⁷ state that “Wang *et al.* have perfectly illustrated the possibilities and problems of using autotransplantation of genetically corrected male germline stem cells to restore spermatogenesis in men suffering from meiotic arrest.”

As highlighted in this issue, advances made in recent years are providing a better understanding of mammalian meiosis. However, many outstanding and fascinating questions remain to be explored. For example: how is meiosis initiated in mammals; how are DSB-forming complex proteins recruited to hotspots in mammals; what are the biochemical mechanisms involved in DSB formation and repair; and how is DSB fate controlled? As in 1974, Taylor⁸ said, “I will only remind you that meiosis is still a potential battleground where dead hypotheses litter the field or rest uneasily in shallow graves, ready to emerge and haunt any conscientious scientist who tries to consolidate a victory for any particular thesis.” Meiotic biology has thus no end in sight.

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