Multi-author Review
Telomeres and meiosis in health and disease

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Telomeres and meiosis in health and disease

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Meiosis is a specialized form of cell division in which the DNA copy number first doubles, then undergoes two reductive divisions, ending in a haploid state, to be restored to the diploid state by the act of fertilization [1]. In addition to facilitating genetic diversity through breeding, meiosis also reshuffles the specie's genome through recombination, in which chromatids pair, join, undergo double-strand breaks and reanneal to form a new, unique, haploid genome. The evolutionary advantages of meiosis are evidenced by its wide prevalence throughout nature. Species as diverse as yeast, plants, mice and man undergo meiotic reproduction. Many of the most important features of meiosis are conserved across phyla, while other features are unique to specific species. This creates ideal opportunities to employ model species to develop a broad-based, fundamental understanding of meiosis, as demonstrated by three of the reviews which follow.

Meiosis is an important topic not only because of its ubiquitous presence in nature, but also because it presents an important cause of disease and human suffering when it goes awry [1]. Aneuploidy, the presence of an abnormal chromosome number, especially trisomy, is the most common genetic disease, and the most common cause of mental retardation in humans. Aneuploidy occurs in 3–4% of clinical pregnancies, 15% of miscarriages and almost all preimplantation embryos from women at the end of their reproductive lives. As women increasingly delay attempts at child bearing, the clinical and public health importance of aneuploidy becomes increasingly apparent. In mammals, the critical, early steps of meiosis, in particular chromosome pairing, synapsis and chiasmata formation, occur in the fetal gonad, inside the uterus, a compartment particularly inaccessible to experimental study. Until recently, the technical challenges of studying early meiosis in mammals posed significant challenges to investigators. However, that many of the most important aspects of meiosis are conserved across species, and the growing availability of genetic manipulation in the mouse, have greatly advanced our understanding of early mammalian meiosis [1, 2].

Early studies demonstrated that during early meiosis telomeres cluster and attach to the nuclear envelope [3–5]. The diversity of species subsequently found to exhibit these chromosome bouquets provides testimony to the power of the comparative approach to biology. Genetic manipulation in yeast, combined with cytogenetic studies of early meiosis in plants and mammals, and genetic manipulation of mice, have all contributed to our understanding of this rapidly evolving field, and shown conclusively that telomeres align chromosomes to facilitate pairing of homologous chromosomes, an important step in facilitating recombination during early meiosis.

'Telomere attachment and clustering in meiosis', by Harry Scherthan, describes the fascinating behavior of telomeres during early meiosis, when they attach to and move along the nuclear envelope during the so-called bouquet stage. Scherthan provides a comprehensive overview of this widely conserved phenomenon among the various species in which it has been studied. He then goes on to report recent studies, many from his own work, elucidating the molecular mechanisms of telomere movement during early meiosis. Both actin and microtubules appear to be involved in telomere motion. He also discusses the impact of these processes on recombination.

In their review, Arthur Lustig and his colleague, Immanual Joseph, focus on telomeres and recombination in two species of yeast. When the awesome power of yeast genetics is focused on the analysis of telomeres in meiosis, the results are illuminating. Joseph and Lustig report that meiotic recombination, known to be facilitated through telomere-mediated chromosome pairing, also occurs between telomeres themselves. They review the role of meiotic-specific genes in mediating recombination, including how recombination between non-sister chromatids is favored over sister chromatids. Finally, this review places recombination in the context of other meiotic landmark

events, i.e. telomere clustering and dispersion, and homologue alignment and pairing. Though this review focuses on telomeres and meiosis in just two unicellular yeasts, *Schizosaccharomyces pombe* and *Saccharomyces cerevisiae*, the widely divergent meiotic machineries and processes employed by these two species provide a remarkably broad perspective on how telomeres function during meiosis.

The review by Tej Panjita and colleagues, 'Regulation of telomere movement by telomere chromatin structure', illustrates the particular structural and functional complexity of telomeres. They point out that telomeres share features characteristic of heterochromatin. Panjita and his team have begun to interpret the information contained in the complex, higher-order structure of telomeres. This structure may play important roles not only in meiotic chromosome pairing and segregation but also in the organization of the nucleus itself. Panjita et al.'s review focuses primarily on meiosis, but also draws from research on somatic cells to show that the positions of telomeres within the nucleus are highly specific, and depend on interactions between telomeres and the nuclear envelope.

That telomeres should play such an important role during early meiosis is intriguing, since in somatic cells, telomeres also mediate cellular aging. With each successive division of DNA, telomeres lose sequence. Even non-dividing cells, such as mammalian oocytes, can lose telomeric sequence by the damaging effects of reactive oxygen, the inevitable consequence of living. Thus, the two most widely established mechanisms of cellular aging – replicative senescence and reactive oxygen damage – converge on the telomere. The final review in this series, by Keefe et al., attempts to focus light provided by current research on the biology of telomeres in meiosis on the problem of aging-related meiotic dysfunction in women.

One of the most dramatic aspects of meiotic dysfunction in humans is the powerful, detrimental effect of aging. Since telomeres play important roles in both meiosis and aging, could telomere dysfunction mediate the effect of aging on meiosis in women? At first blush, the answer would have to be no – oocytes don't divide, presumably sparing them from replicative senescence, and they are hermetically sealed inside the ovary, presumably protected from the toxic effects of oxygen by their limited blood supply. However, during early oogenesis in the fetal gonad, female germ cells do replicate [6, 7]. Moreover, several studies have shown that in mammals, the last eggs to ovulate are the last to have exited the gamete production line in the fetal ovary [6, 7]. Thus, eggs ovulated from older women would have started life having gone through more replications than eggs ovulated from younger women. Oocytes are also long-lived, up to 50 years in the human ovary, making it impossible for them to completely avoid prolonged exposure to reactive oxygen. Do telomeres mediate reproductive aging in women? Preliminary evidence suggests that may be the case, but clearly more studies are needed.

What is the basis of telomere dysfunction with aging? For telomeres, does size itself matter, or is telomere function related more to the function of associated proteins? Telomere shortening from replicative senescence and/or the damage response to reactive oxygen could play a role in reproductive aging, but the story is likely to be more complex. A host of proteins decorate telomeres and regulate cellular function, including motility during early meiosis, homologue pairing, generation of the telomeric DNA loop (which caps and protects the chromosome) and regulation of more complex, heterochromatin-like structures [8]. Telomeres even undergo recombination themselves [9].

While the articles in this multi-author presentation review many exciting, new findings, perhaps more important, they raise many additional questions about the roles of telomeres and meiosis in health and disease, which should provide a robust stimulus for future research.

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