CDB SEMINAR

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Monday, October 3, 2016

16:00~17:00 Auditorium C1F

In for the long haul: Maintaining chromosome cohesion in mammalian oocytes

Summary

Female reproductive lifespan is curtailed by exhaustion of the stock of ovarian germ cells established during fetal development, and by an increased incidence of chromosome segregation errors during meiosis. Meiosis generates haploid gametes by driving diploid precursors to undergo two rounds of chromosome segregation without an intervening round of DNA replication. Errors in meiosis almost always result in early embryonic lethality. Rare exceptions include trisomy 13, 18 and 21, which can develop to term. The vast majority of meiotic errors in human embryos are maternally transmitted and the risk is markedly increased as women get older.

In mammals, as in most organisms, accurate segregation of chromosomes during meiosis depends on the formation of bivalent chromosomes during meiotic recombination. Bivalents consist of replicated maternal and paternal homologues linked at sites of reciprocal DNA exchange and stabilised by cohesion between sister arms. As in mitosis, cohesion is mediated by the cohesin complex, which forms a tripartite ring thought to entrap sister chromatids from S phase until anaphase. During anaphase of meiosis I, separase cleaves cohesin, converting bivalents to dyad chromosomes. Dyads consist of a pair of chromatids linked by centromeric cohesin, which is protected by Sgol2/PP2A until anaphase of the second meiotic division when chromatids segregate to form single copy genomes.

While the mechanisms of meiosis are broadly conserved, female meiosis has several unique features, which may render it inherently error prone. Particularly relevant to the age-effect is the fact that bivalent chromosomes formed during foetal life are stabilized by Rec8-containing cohesin complexes until anaphase I, which occurs shortly before ovulation some decades later. According to our current understanding, cohesive cohesin is not replenished during the prolonged period of arrest in prophase of meiosis I. Moreover, evidence from our previous studies indicates that female ageing is accompanied by a decline in levels of oocyte chromosomal cohesin (Rec8), which in turn results in reduced recruitment of its protector Sgo2. Lack of replenishment, together with its essential role in maintaining bivalent and dyad chromosomes, makes cohesin unique among candidates for the molecular target of the maternal age effect. However, the mechanisms and timing of cohesin depletion during oogenesis are currently unknown. From a clinical perspective, a key question is whether the "cohesin clock" is already ticking during the relatively quiescent non-growing state in which the oocyte spends decades. I will present our recent work towards addressing these questions.

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