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Letter to the Editor

Meiosis-II and mitosis have different molecular formats

Although we have come very far in the molecular biology of cell division, the idea that meiosis-II (MII) and mitosis are fundamentally same, since both involve chromatid segregation (see Nasmyth, 2002), keeps surfacing in new contexts. Notwithstanding the different pathways of achieving haploidy from diploidy, the attendant complexities due to sex chromosomes and inverted meiosis (John, 1990; Maguire, 1995), segregation of chromatids of maternal and paternal chromosomes on two separate bipolar spindles is a defining feature of MII as compared to mitosis where chromatids of both maternal and paternal chromosomes are segregated on the same bipolar spindle. This is true even in complex plant heterozygotes such as Oenotheras and *Rhoeo spathacea* which show a ring of all chromosomes instead of bivalents during MI and female meiosis in animals where polar bodies are eliminated. Exceptional instances such as sciarid insects show a single bipolar spindle during MII of male meiosis, but it is used only to segregate chromatids of maternal chromosomes since paternal ones are eliminated during MI (see Esteban et al., 1997).

Recent work has also shown that the proteins controlling the mitotic cycle are either replaced by homologous proteins that are expressed only during meiotic cell cycle or modulated by meiosis-specific factors to create a specialized cell cycle (Lee and Amon, 2001). Unlike mitosis, MII lacks a G1 phase. G1 functions are absolutely required for an entry into S-phase during a mitotic cell cycle. In eukaryotes, a ‘pRb (retinoblastoma)—E2F—cyclin D’ pathway primes the cell for DNA replication during G1 phase of a mitotic cell cycle (den Boer and Murray, 2000). Since all the DNA required is made available at the time of commitment to meiosis itself, there is no DNA replication, and therefore no G1 phase, during MII. The side stepping of G1 phase is a major deviation from the mitotic cycle and has a significant bearing on gametophyte development and evolution of higher plants. As compared to animals, higher plant meiosis is a transient phase where the products have to undergo a determined number of mitotic cycles before differentiating gametes. This poses special challenges on higher plant cell cycles since the DNA replication origins which are shut off during MII have to be reactivated by the pRb- pathway in such a manner that a recommitment to meiosis is avoided and a commitment to mitosis is promoted for a determined number of cycles (reviewed by Ranganath, 2003).

Most of the information about suppression of DNA replication in MII comes from yeasts and animals. In both vertebrates and invertebrates *Mos*, the c-mos protooncogene product, is a key regulator of meiosis. In the absence of *Mos* in oocytes, meiosis-I is followed directly by repeated embryonic mitotic cycles and its reinstatement restores meiosis-II. This implies that oocytes have a competence to undergo mitosis but the meiosis–mitosis transition is prevented by *Mos* until after fertilization (Tachibana et al., 2000). In the absence of *Mos*-dependent maintenance of cyclinB or removal of the chromokinesin—Xkid, *Xenopus* oocytes enter S-phase after MI (see Perez et al., 2002). Suppression of DNA replication by *Mos*/MAPK pathway might be mediated by p90rsk, which partially inhibits the action of anaphase promoting complex/cyclosome (APC/C) and hence cyclinB destruction (Gross et al., 2000). In addition, ectopic expression of the mitotic inhibitor *Wee1* in oocytes of *Xenopus* induces DNA replication after MI. Absence of *Wee1* during MI in mice, starfish and yeast indicates that it may be a conserved mechanism to ensure the absence of S-phase between MI and MII (Nakajo et al., 2000; Nebreda and Ferby, 2000). The absence of the essential pre-replication complex component Cdc6 and, cytoplasmic delocalization of the Orc proteins and Cdc7, are responsible for replication competence (see Petronczki and Siomos, 2003 and the references therein). In budding yeast, CDK1 might also interact with FEAR (For *Cdc14* EArly Release) network to act as a binary molecular switch by dropping to low levels so as to allow exit from MI but sufficient enough to prevent a S-phase between MI and MII whereas both FEAR and MEN (mitotic exit network) interact with CDK1 in mitosis (see Stern, 2003). It is also known that the *nix* mutants of *Drosophila* undergo an additional division subsequent to a normal MII (see O’Connell and Nurse, 1994). These instances show that the chromatid segregation events of MII and mitosis are driven by different molecular machines for entry, maintenance and/or exit. The question to be resolved therefore is whether the parallel observed in chromatid segregation should be the sole criterion to equate MII and mitosis or they should be

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assessed and compared on a wider molecular canvas with the ultimate rewards determined by development and evolution?

Interestingly, the elegant spermatocyte fusion experiments in grasshopper (Paliulis and Nicklas, 2000) have shown a 'mixed' chromosome segregation pattern that apparently blurs the molecular identity of MI and MII. A MI bivalent placed on an MII spindle or MII chromosomes placed on an MI spindle behave as they would have on their native spindle. Although, it may be argued that such blurring of the cell cycle boundaries between MI and MII may be partly due to forcible merging of their proteomes (expressed protein component of a cell), it is intriguing that the native chromosomes of either MI or MII also remain unaffected in their 'normal' behaviour. For instance, the precocious availability of APC due to proteome mixing may perhaps explain chromatid segregation of a MII chromosome on an MI spindle, but how the homologous chromosomes protect their chromatids from the APC remains to be resolved. Similarly, how the MI bivalent placed on an MII spindle protects its chromatids from separating when the APC is globally active in a MII meiocyte? These aspects, although an artifact, assume significance in view of the regulation of APC during meiosis of some organisms in such a manner that it is activated only during MII to effect chromatid segregation and not earlier (see Yu, 2002; Peter et al., 2002). A similar 'mixed' chromosome segregation pattern on a single spindle is also known to occur in two natural yeast mutants, *spo12* and *spo13* as well as cell cycle mutants for the polo-like kinase *Cdc5*, the kinetochore protein *Slk19* and the phosphatase *Cdc14* (see Stern, 2003; Marston et al., 2003; Buonomo et al., 2003). It is suggested that alterations in the FEAR network along with the presence of lagging chromosomes of MI persisting on MII spindle result in the mixed segregation pattern seen (Stern, 2003). How could these results be reconciled with spermatocyte fusion experiments of Paliulis and Nicklas (2000)?

The inverted meiotic sequence seen in some of the holokinetic systems, such as species of *Luzula* (Juncaceae) among the higher plants and many animal species including insects, worms and homopteran bugs (see John, 1990 and the references therein), presents an additional layer of complexity. Following anaphase-I the homologous chromatids separate only to pair again before prophase-II and then segregate during anaphase-II. In such systems, the organization and function of kinetochore as well as sister chromatid cohesion during mitosis and meiosis have remained an enigma. In *Luzula purpurea* ($2n = 6$) for example, the kinetochore is organized as a discontinuous plate along the length of the mitotic metaphase/anaphase (see Braselton, 1971, 1981) chromosome whereas in *L. nivea*, the kinetochore is organized along most of the chromosome (Bokhari and Godward, 1980). The ability to attach to MTs anywhere on the holokinetochore helps the chromosome to survive autonomous or even experimental fragmentation/breakage. X-irradiated fragments of a single chromosome of *L. purpurea* were not only successful in mitosis but also in meiosis where the breakage products paired with their (partly) homologous chromosome to form a technical trivalent (Nordenskiold, 1963). The successful meiosis also indicated the fitness of the progeny/hybrids recovered from X-irradiated experiments in this taxon.

Recent work has also shown that many components of kinetochore (ZW10, CENP-A, CENP-C, Bub1, aurora kinase, INCEPs) are highly conserved between the monocentric and holocentirc chromosomes (see Dernburg, 2001 and the references therein). However, the defining features of meiosis in holokinetic systems, particularly the flexibility of kinetochore activity, telokinetic in MI and holokinetic in MII, raise fundamental questions regarding the kinetochore organization and functions. The unique molecular requirements for the sister chromatid cohesion in such an altered kinetochore organization and functional environment also need to be understood in the context of cohesion in localized, monocentric systems. In these latter organisms, meiosis-specific cohesion components such as *Rec-8* ensure homolog separation in MI and chromatid separation in MII (see Nasmyth, 2002). In addition, MI-specific monopolins, identified by functional genomics (see Toth et al., 2000) and, polo-like kinase Cdc5 and related protein network (Lee and Amon, 2003 and the references therein) ensure sister kinetochore coorientation necessary for homolog separation. These aspects pose conceptual and experimental challenges for our understanding of the basic biology of meiosis in holocentric systems with flexible kinetic activity.

Future research has implications across different fields seeking to illuminate the molecular formats of cell division at different levels, with some of the cherished ideas about mitosis and meiosis coming under intense focus.

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