

# Meiosis



Published in final edited form as:
*Curr Biol*. 2009 January 27; 19(2): R74–R76. doi:10.1016/j.cub.2008.12.003.

# Meiosis: DDK Is Not Just for Replication

**Adele L. Marston**
The Wellcome Trust Centre for Cell Biology, School of Biological Sciences, University of Edinburgh, Michael Swann Building, Mayfield Road, Edinburgh EH9 3JR, UK.
adele.marston@ed.ac.uk

## Abstract

How is the chromosome segregation machinery modified to segregate homologs during meiosis I? The Dbf4-dependent Cdc7 kinase (DDK) has now been identified as a key regulator in this process.

Meiosis is a specialized cell cycle that generates haploid gametes from a diploid cell. This is achieved through two consecutive chromosome segregation events, meiosis I and meiosis II, which follow a single round of DNA replication. Meiosis I is a unique kind of segregation event because homologs are separated, in contrast to mitosis or meiosis II during which sister chromatids are separated (Figure 1). Recent reports by the Hollingsworth, Ohta and Zachariae labs [1–4] have established the Dbf4-dependent Cdc7 kinase (DDK), hitherto famous for its role in the initiation of DNA replication, as being important for setting up the so-called reductional pattern of chromosome segregation during meiosis I in budding yeast.

The segregation of homologs during meiosis I requires three modifications to the chromosome segregation machinery (Figure 1) [5]. First, meiotic recombination generates chiasmata, which hold homologs together owing to the sister-chromatid cohesion on chromosome arms. Second, sister kinetochores attach to microtubules from the same spindle pole body (monoorientation) during meiosis I, rather than opposite spindle pole bodies (biorientation) as they do in mitosis and meiosis II. Third, the cohesion that holds sister chromatids together is lost only from chromosome arms during meiosis I and is protected around centromeres to allow the accurate segregation of sister chromatids during meiosis II. In recent years, a basic molecular explanation for how these modifications are set up in budding yeast has emerged, but how they are coordinated with each other has remained less clear. DDK is now shown to control three events that promote meiosis I segregation: (1) the initiation of DNA replication, (2) the initiation of meiotic recombination, and (3) the recruitment of monopolin to kinetochores, which is required for monoorientation. The finding that DDK controls multiple processes necessary to prepare the chromosomes for reductional segregation during meiosis I [1–4] implicates DDK as a global coordinator of the meiosis I program.

DDK is a Ser/Thr kinase whose activity depends on the association of the constitutive Cdc7 catalytic subunit with a regulatory protein, Dbf4 [6], the levels of which are highest during metaphase I [4]. In vegetative cells, DDK phosphorylates components of the replicative complex, thereby triggering DNA replication. DDK also controls DNA replication during meiosis. Using an ‘analog sensitive’ version of the Cdc7 kinase (*cdc7-as*), which has an enlarged ATP-binding pocket and can be specifically inactivated by the addition of purine analogs to the medium, replication was shown to be greatly delayed, although it eventually occurred [7]. In a different approach, depletion of Dbf4 almost completely prevented DNA replication [8]. Therefore, DDK plays an important role in meiotic DNA replication, and an essential role cannot be ruled out as DDK may not be completely inactivated in these experiments.


Europe PMC Funders Author Manuscripts

After undergoing DNA replication, *cdc7-4* (a temperature-sensitive allele) and *cdc7-as* mutants arrest in prophase I [7,9]. To analyze the requirement for DDK in later meiotic events, the Ohta [2], Hollingsworth [3] and Zachariae [4] groups made use of the *bob1* allele. The *bob1* allele encodes a point mutation in a component of the Mcm complex (thought to constitute the replicative helicase), and completely bypasses the requirement for DDK in DNA replication [10]. Use of the *bob1* mutation relieved the delay in DNA replication caused by DDK inactivation [2–4]. However, in the Ohta [2] and Hollingsworth [3] studies, the *bob1* mutation did not bypass the prophase I arrest of *cdc7Δ* (a mutant lacking the *cdc7* gene) or *cdc7-as* mutants. The prophase I arrest appears to be due to a failure in inducing transcription of *NDT80* [2,3], a global meiotic transcriptional regulator that is required for exit from prophase I and progression into meiosis I [11]. Indeed, ectopic expression of *NDT80* in *bob1 cdc7-as* cells allowed progression beyond prophase I [3]. In contrast, the Zachariae group [4] observed no defect in either meiotic gene expression in *bob1 cdc7Δ* cells or the ability of *bob1 cdc7Δ* cells to exit prophase I. It was suggested [4] that replication defects activate checkpoints that cause the prophase I arrest and block *NDT80* transcription [12]. However, inactivation of various checkpoint genes did not relieve this arrest [3], so it is unclear whether DDK has a role in prophase I exit and, if so, whether this is direct or indirect.

DDK is required for the initiation of meiotic recombination [1,2,4,7]. Specifically, DDK inactivation abolishes the formation of double strand breaks (DSBs) by the Spo11 endonuclease [13]. DDK promotes meiotic recombination, in part, by phosphorylation of one of the Spo11 accessory factors, Mer2, on Ser29 [1,2]. The S-phase, cyclin-dependent kinase, Cdc28–Clb5,6 (S-CDK), which is required for DNA replication, also phosphorylates Mer2, but on Ser30 [14]. Furthermore, DDK-dependent phosphorylation of Mer2 on Ser29 is enhanced by prior S-CDK-dependent phosphorylation on Ser30 [1]. These phosphorylation events are essential for the recruitment of Spo11 to DSB sites [2]. The sequential phosphorylation of Mer2 by S-CDK and DDK may serve to coordinate DNA replication and recombination.

Using *bob1 cdc7Δ* cells [4] or *bob1 cdc7-as* cells ectopically expressing *NDT80* [3], the requirement for DDK in meiosis I chromosome segregation could be tested. Remarkably, sister chromatids were found to segregate to opposite nuclei in a single division, resulting in the formation of just two diploid spores (Figure 1) [3,4]. Using elegant live-cell imaging techniques, the Zachariae group [4] showed that homolog segregation fails in meiosis I and, rather, sister chromatids are segregated on a single spindle during meiosis II, although a second spindle does form (Figure 1). This phenotype can be explained by a failure to establish kinetochore monoorientation during meiosis I [3,4]. Chromosome segregation fails during meiosis I in *bob1 cdc7Δ* mutants because cohesion at centromeres holds bioriented sister chromatids together. It is only when centromeric cohesion is destroyed during meiosis II that sister chromatids can separate to opposite poles, resulting in the formation of two diploid spores. [4].

How does DDK specify monoorientation? In budding yeast, the monopolin complex, which consists of the casein kinase Hrr25, the meiosis-specific Mam1 protein, and two nucleolar proteins, Lrs4 and Csm1, must be recruited to kinetochores for monopolar attachment [15–17]. The Polo-like kinase (PLK), Cdc5, triggers release of Lrs4 and Csm1 from the nucleolus, leading to monopolin complex assembly [18,19]. DDK is not required for the assembly of the monopolin complex but is essential for its localization to kinetochores [3,4]. This could be explained by a requirement for DDK in Lrs4 phosphorylation [4], which also requires Cdc5 kinase in complex with a meiosis-specific protein, Spo13 [4,20]. Furthermore, DDK and Cdc5–Spo13 associate specifically in metaphase I cells, suggesting that they collaborate in promoting Lrs4 phosphorylation through physical association [4]. The dual

phosphorylation of Lrs4 by two different kinases is reminiscent of the phosphorylation of Mer2 by DDK and S-CDK, suggesting that cooperation with other kinases may be a general mechanism by which DDK executes the events of meiosis I.

The idea that cooperation between different kinases is a general paradigm for coordinating meiosis is an attractive one. By activating kinases in distinct but overlapping stages of meiosis and cellular compartments, a high degree of temporal and spatial flexibility in substrate activation can be achieved. This could explain how relatively few regulators, which are generally not meiosis-specific, execute the unique chromosome segregation pattern of meiosis I. DDK is highly conserved from yeast to human. These studies have underlined the importance of DDK as a link between DNA replication, recombination and monoorientation during meiosis I in budding yeast. Whether DDK plays a similar role in other organisms will be a fascinating question for the future.

## References


1. Wan L, Niu H, Futcher B, Zhang C, Shokat KM, Boulton SJ, Hollingsworth NM. Cdc28-Clb5 (CDK-S) and Cdc7-Dbf4 (DDK) collaborate to initiate meiotic recombination in yeast. Genes Dev. 2008; 22:386–397. [PubMed: 18245450]
2. Sasanuma H, Hirota K, Fukuda T, Kakusho N, Kugou K, Kawasaki Y, Shibata T, Masai H, Ohta K. Cdc7-dependent phosphorylation of Mer2 facilitates initiation of yeast meiotic recombination. Genes Dev. 2008; 22:398–410. [PubMed: 18245451]
3. Lo HC, Wan L, Rosebrock A, Futcher B, Hollingsworth NM. Cdc7-Dbf4 regulates NDT80 transcription as well as reductional segregation during budding yeast meiosis. Mol. Biol. Cell. 2008; 19:4956–4967. [PubMed: 18768747]
4. Matos J, Lipp JJ, Bogdanova A, Guillot S, Okaz E, Junqueira M, Shevchenko A, Zachariae W. Dbf4-dependent cdc7 kinase links DNA replication to the segregation of homologous chromosomes in meiosis I. Cell. 2008; 135:662–678. [PubMed: 19013276]
5. Marston AL, Amon A. Meiosis: cell-cycle controls shuffle and deal. Nat. Rev. Mol. Cell Biol. 2004; 5:983–997. [PubMed: 15573136]
6. Sclafani RA. Cdc7p-Dbf4p becomes famous in the cell cycle. J. Cell Sci. 2000; 113:2111–2117. [PubMed: 10825284]
7. Wan L, Zhang C, Shokat KM, Hollingsworth NM. Chemical inactivation of cdc7 kinase in budding yeast results in a reversible arrest that allows efficient cell synchronization prior to meiotic recombination. Genetics. 2006; 174:1767–1774. [PubMed: 17057233]
8. Valentin G, Schwob E, Della Seta F. Dual role of the Cdc7-regulatory protein Dbf4 during yeast meiosis. J. Biol. Chem. 2006; 281:2828–2834. [PubMed: 16319063]
9. Schild D, Byers B. Meiotic effects of DNA-defective cell division cycle mutations of Saccharomyces cerevisiae. Chromosoma. 1978; 70:109–130. [PubMed: 367734]
10. Hardy CF, Dryga O, Seematter S, Pahl PM, Sclafani RA. mcm5/cdc46-bob1 bypasses the requirement for the S phase activator Cdc7p. Proc. Natl. Acad. Sci. USA. 1997; 94:3151–3155. [PubMed: 9096361]
11. Xu L, Ajimura M, Padmore R, Klein C, Kleckner N. NDT80, a meiosis-specific gene required for exit from pachytene in Saccharomyces cerevisiae. Mol. Cell. Biol. 1995; 15:6572–6581. [PubMed: 8524222]
12. Hochwagen A, Amon A. Checking your breaks: surveillance mechanisms of meiotic recombination. Curr. Biol. 2006; 16:R217–R228. [PubMed: 16546077]
13. Murakami H, Keeney S. Regulating the formation of DNA double-strand breaks in meiosis. Genes Dev. 2008; 22:286–292. [PubMed: 18245442]
14. Henderson KA, Kee K, Maleki S, Santini PA, Keeney S. Cyclin-dependent kinase directly regulates initiation of meiotic recombination. Cell. 2006; 125:1321–1332. [PubMed: 16814718]
15. Toth A, Rabitsch KP, Galova M, Schleiffer A, Buonomo SB, Nasmyth K. Functional genomics identifies monopolin: a kinetochore protein required for segregation of homologs during meiosis I. Cell. 2000; 103:1155–1168. [PubMed: 11163190]

16. Rabitsch KP, Petronczki M, Javerzat JP, Genier S, Chwalla B, Schleiffer A, Tanaka TU, Nasmyth K. Kinetochore recruitment of two nucleolar proteins is required for homolog segregation in meiosis I. Dev. Cell. 2003; 4:535–548. [PubMed: 12689592]
17. Petronczki M, Matos J, Mori S, Gregan J, Bogdanova A, Schwickart M, Mechtler K, Shirahige K, Zachariae W, Nasmyth K. Monopolar attachment of sister kinetochores at meiosis I requires casein kinase 1. Cell. 2006; 126:1049–1064. [PubMed: 16990132]
18. Clyne RK, Katis VL, Jessop L, Benjamin KR, Herskowitz I, Lichten M, Nasmyth K. Polo-like kinase Cdc5 promotes chiasmata formation and cosegregation of sister centromeres at meiosis I. Nat. Cell Biol. 2003; 5:480–485. [PubMed: 12717442]
19. Lee BH, Amon A. Role of Polo-like kinase CDC5 in programming meiosis I chromosome segregation. Science. 2003; 300:482–486. [PubMed: 12663816]
20. Katis VL, Matos J, Mori S, Shirahige K, Zachariae W, Nasmyth K. Spo13 facilitates monopolin recruitment to kinetochores and regulates maintenance of centromeric cohesion during yeast meiosis. Curr. Biol. 2004; 14:2183–2196. [PubMed: 15620645]


Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

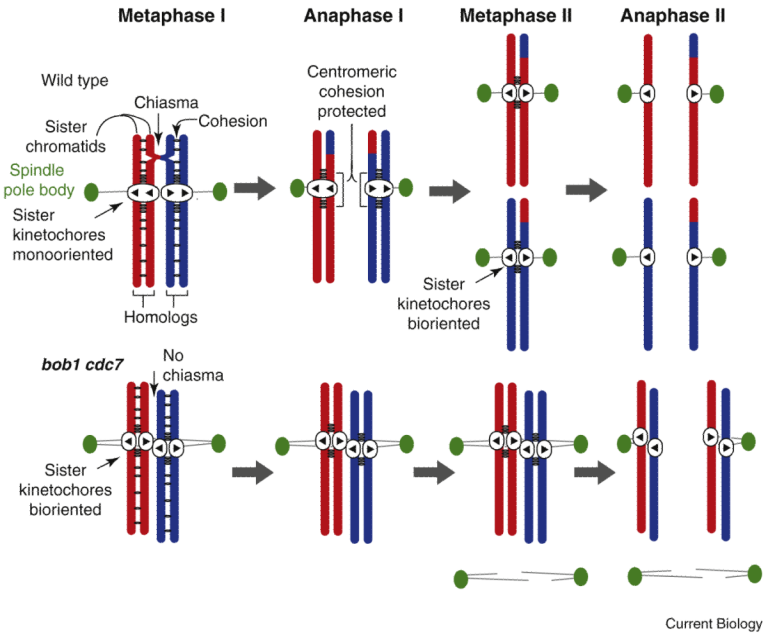


**Figure 1.**

Chromosome segregation during meiosis in wild-type and *bob1 cdc7* mutants.

The stages of meiosis after prophase I are shown. Homologs are colored red and blue, respectively, and spindle pole bodies are indicated in green. The direction of kinetochore attachment is indicated by the arrowheads. Cohesion is represented by black lines between sister chromatids. In *bob1 cdc7* mutants, the stepwise loss of cohesion occurs normally, but chiasmata do not form because recombination does not occur, and sister kinetochore monoorientation fails. Therefore, meiosis I chromosome segregation fails and a single nuclear division occurs in meiosis II with sister chromatids segregating to opposite poles, resulting in the production of diploid spores.