38 Georges-Labouesse, E. *et al.* (1996) Absence of integrin alpha 6 leads to epidermolysis bullosa and neonatal death in mice. *Nat. Genet.* 13, 370–373
39 DiPersio, C.M. *et al.* (1997) alpha3beta1 Integrin is required for normal development of the epidermal basement membrane. *J. Cell Biol.* 137, 729–742
40 Dowling, J. *et al.* (1996) Beta4 integrin is required for hemidesmosome formation, cell adhesion and cell survival. *J. Cell Biol.* 134, 559–572
41 van der Neut, R. *et al.* (1996) Epithelial detachment due to absence of hemidesmosomes in integrin beta 4 null mice. *Nat. Genet.* 13, 366–369
42 Murgia, C. *et al.* (1998) Cell cycle and adhesion defects in mice carrying a targeted deletion of the integrin beta4 cytoplasmic domain. *EMBO J.* 17, 3940–3951
43 Williamson, R.A. *et al.* (1997) Dystroglycan is essential for early embryonic development: disruption of Reichert's membrane in Dag1-null mice. *Hum. Mol. Genet.* 6, 831–841
44 Henry, M.D. and Campbell, K.P. (1998) A role for dystroglycan in basement membrane assembly. *Cell* 95, 859–870
45 Gardner, H. *et al.* (1996) Deletion of integrin alpha 1 by homologous recombination permits normal murine development but gives rise to a specific deficit in cell adhesion. *Dev. Biol.* 175, 301–313
46 Pozzi, A. *et al.* (1998) Integrin alpha1beta1 mediates a unique collagen-dependent proliferation pathway *in vivo*. *J. Cell Biol.* 142, 587–594
47 Baudoin, C. *et al.* (1998) Knockout and knockin of the beta1 exon D define distinct roles for integrin splice variants in heart function and embryonic development. *Genes Dev.* 12, 1202–1216
48 Li, X. *et al.* (1998) Requirements for the cytoplasmic domain of the alphaPS1, alphaPS2 and betaPS integrin subunits during *Drosophila* development. *Development* 125, 701–711
49 Martin-Bermudo, M.D. and Brown, N.H. (1999) Uncoupling integrin adhesion and signaling: the betaPS cytoplasmic domain is sufficient to regulate gene expression in the *Drosophila* embryo. *Genes Dev.* 13, 729–739
50 Muller, U. and Brandli, A.W. (1999) Cell adhesion molecules and extracellular-matrix constituents in kidney development and disease. *J. Cell Sci.* 112, 3855–3867
51 Hemler, M.E. (1998) Integrin associated proteins. *Curr. Opin. Cell Biol.* 10, 578–585
52 Hobert, O. *et al.* (1999) A conserved LIM protein that affects muscular adherens junction integrity and mechanosensory function in *Caenorhabditis elegans*. *J. Cell Biol.* 144, 45–57
53 Gettner, S.N. *et al.* (1995) Characterization of beta pat-3 heterodimers, a family of essential integrin receptors in *C. elegans*. *J. Cell Biol.* 129, 1127–1141
54 Miner, J.H. and Sanes, J.R. (1996) Molecular and functional defects in kidneys of mice lacking collagen alpha 3(IV): implications for Alport syndrome. *J. Cell Biol.* 135, 1403–1413
55 Noakes, P.G. *et al.* (1995) The renal glomerulus of mice lacking s-laminin/laminin beta 2: nephrosis despite molecular compensation by laminin beta 1. *Nat. Genet.* 10, 400–406
56 Patton, B.L. *et al.* (1997) Distribution and function of laminins in the neuromuscular system of developing, adult, and mutant mice. *J. Cell Biol.* 139, 1507–1521
57 Libby, R.T. *et al.* (1999) Disruption of laminin beta2 chain production causes alterations in morphology and function in the CNS. *J. Neurosci.* 19, 9399–9411
58 Costell, M. *et al.* (1999) Perlecan maintains the integrity of cartilage and some basement membranes. *J. Cell Biol.* 147, 1109–1122
59 Arikawa-Hirasawa, E. *et al.* (1999) Perlecan is essential for cartilage and cephalic development. *Nat. Genet.* 23, 354–358
60 Arroyo, A.G. *et al.* (1996) Differential requirements for alpha4 integrins during fetal and adult hematopoiesis. *Cell* 85, 997–1008
61 Arroyo, A.G. *et al.* (1999) Alpha4 integrins regulate the proliferation/differentiation balance of multilineage hematopoietic progenitors *in vivo*. *Immunity* 11, 555–566
62 Goh, K.L. *et al.* (1997) Mesodermal defects and cranial neural crest apoptosis in alpha5 integrin-null embryos. *Development* 124, 4309–4319
63 Muller, U. *et al.* (1997) Integrin alpha8beta1 is critically important for epithelial-mesenchymal interactions during kidney morphogenesis. *Cell* 88, 603–613
64 Littlewood Evans, A. and Muller, U. (2000) Stereocilia defects in the sensory hair cells of the inner ear in mice deficient in integrin alpha8beta1. *Nat. Genet.* 24, 424–428
65 Schon, M.P. *et al.* (1999) Mucosal T lymphocyte numbers are selectively reduced in integrin alpha E (CD103)-deficient mice. *J. Immunol.* 162, 6641–6649
66 Etzioni, A. *et al.* (1999) Of man and mouse: leukocyte and endothelial adhesion molecule deficiencies. *Blood* 94, 3281–3288
67 Rosenkranz, A.R. and Mayadas, T.N. (1999) Leukocyte-endothelial cell interactions – lessons from knockout mice. *Exp. Nephrol.* 7, 125–136
68 Brakebusch, C. *et al.* (1997) Genetic analysis of beta1 integrin function: confirmed, new and revised roles for a crucial family of cell adhesion molecules. *J. Cell Sci.* 110, 2895–2904
69 Hodivala-Dilke, K.M. *et al.* (1999) Beta3-integrin-deficient mice are a model for Glanzmann thrombasthenia showing placental defects and reduced survival. *J. Clin. Invest.* 103, 229–238
70 McHugh, K.P. *et al.* (2000) Mice lacking beta3 integrins are osteosclerotic because of dysfunctional osteoclasts. *J. Clin. Invest.* 105, 433–440
71 Huang, X. *et al.* (2000) Normal development, wound healing, and adenovirus susceptibility in beta5-deficient mice. *Mol. Cell Biol.* 20, 755–759
72 Huang, X.Z. *et al.* (1996) Inactivation of the integrin beta 6 subunit gene reveals a role of epithelial integrins in regulating inflammation in the lung and skin. *J. Cell Biol.* 133, 921–928
73 Wagner, N. *et al.* (1996) Critical role for beta7 integrins in formation of the gut-associated lymphoid tissue. *Nature* 382, 366–370
74 Huang, X.Z. *et al.* (2000) Fatal bilateral chylothorax in mice lacking the integrin $\alpha 9\beta 1$. *Mol. Cell. Biol.* 20, 5208–5215

The pachytene checkpoint

The pachytene checkpoint prevents meiotic nuclear division in cells that fail to complete meiotic recombination and chromosome synapsis. This control mechanism prevents chromosome missegregation that would lead to the production of aneuploid gametes. The pachytene checkpoint requires a subset of proteins that function in the mitotic DNA damage checkpoint. In budding yeast, the pachytene checkpoint also requires meiosis-specific chromosomal proteins and, unexpectedly, proteins concentrated in the nucleolus. Progress has been made in identifying components of the cell-cycle machinery that are impacted by the checkpoint.

In eukaryotic organisms, the integrity of genetic information is maintained through the operation of cell-cycle checkpoints. Checkpoint controls ensure the proper order of events in the mitotic cell cycle by arresting or delaying the cycle in response to defects in cellular processes[1]. The term checkpoint is sometimes used to describe the specific time during the cell cycle at which cells arrest[2]. Here, we use the term checkpoint to refer to the control mechanisms that enforce the proper order of cell-cycle events[1].

Checkpoints are not confined to cells that divide mitotically. They also operate during meiosis, the specialized cell division cycle that generates haploid gametes from diploid parental cells (Fig. 1a). In particular, a checkpoint prevents exit from the pachytene stage of meiotic prophase when meiotic recombination and chromosome synapsis are incomplete[3]. This 'pachytene checkpoint' has also been referred to as the meiotic recombination checkpoint[4].

During meiotic prophase, homologous chromosomes synapse and undergo genetic recombination[3]. Synapsis is defined as the close association of homologous chromosomes through a proteinaceous structure called the synaptonemal complex (Fig. 1b). Pairs of homologous chromosomes are fully synapsed along their lengths at the

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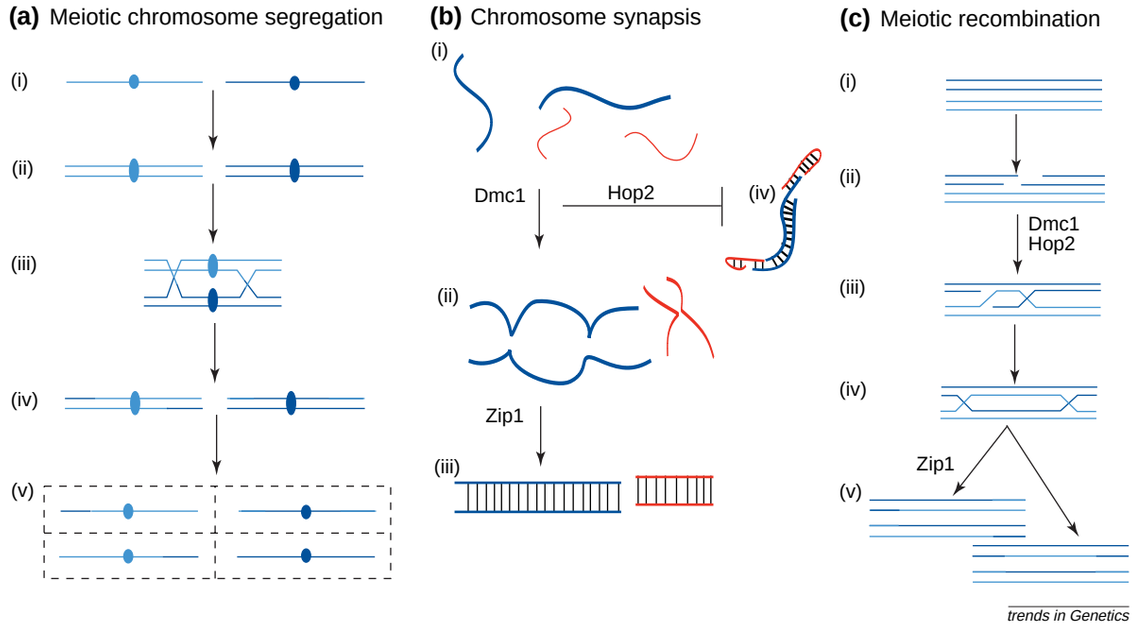
FIGURE 1. Meiotic chromosome segregation, chromosome synapsis and meiotic recombination



(a) Meiotic chromosome segregation. Shown is a single pair of homologous chromosomes, one in light blue and one in dark blue; each line represents a chromatid (i.e. a double-stranded DNA molecule) (i). After DNA replication, each chromosome consists of two sister chromatids (ii). Homologs then pair, synapse and recombine (iii). At meiosis I, homologous chromosomes segregate from each other but sister chromatids remain associated (iv). At meiosis II, sister chromatids separate and segregate from each other to form four haploid products (v). (b) Chromosome synapsis. Shown are two pairs of homologous chromosomes, one in blue and one in red. Each line represents the proteinaceous core shared by a pair of sister chromatids (i). Synapsis initiates at a few sites along each chromosome pair (ii) and then extends along their full length (iii). In the absence of Hop2, nonhomologous chromosomes synapse (iv). (c) Meiotic recombination. Shown are two homologous DNA duplexes, one in dark blue and one in light blue (i). Meiotic recombination initiates with a double-strand break in one duplex. Processing of the ends results in single-stranded tails (ii). A single-stranded tail then invades the homologous duplex (iii). Repair synthesis results in a double Holliday junction (iv) that can be resolved to generate either crossover or noncrossover products (v). The budding yeast Dmc1, Hop2 and Zip1 proteins are positioned at their points of action; the corresponding mutants are blocked at the indicated stages in synapsis and recombination.

pachytene stage of meiotic prophase but they desynapse before the first meiotic division. Meiotic recombination initiates with DNA double-strand breaks (DSBs)[3,5,6] that are repaired by recombination with homologous sequences on a nonsister chromatid (Fig. 1c). Recombination establishes chromatin bridges, called chiasmata, that hold homologs together after recombination has been completed and chromosomes have desynapsed. Chiasmata ensure the proper orientation of chromosomes on the meiosis I spindle and thereby promote correct segregation.

The pachytene stage of meiotic prophase is an important control point during meiosis. In budding yeast, this is the last stage before cells become committed to undergo meiotic chromosome segregation[7]. Mutations in the major cyclin-dependent kinase Cdc28 cause arrest at pachytene[7]. Yeast mutants that are unable to complete meiotic recombination and chromosome synapsis undergo checkpoint-induced arrest at pachytene[3].

This review emphasizes the progress made in understanding the pachytene checkpoint in budding yeast, where several meiotic checkpoint factors have been characterized. Key advances in understanding the pachytene checkpoint in other organisms are also presented. Note that many of the yeast checkpoint proteins have homologs in other organisms (Table 1).

Mutants that undergo checkpoint-mediated arrest at pachytene

Several meiotic mutants of budding yeast activate the pachytene checkpoint, although the severity of arrest varies with yeast strain background. This review focuses on the *dmc1*, *zip1* and *hop2* mutants because these mutants exhibit tight arrest in at least one strain background and they have been used to identify genes required for pachytene checkpoint function. Two observations indicate that these mutants arrest at the pachytene stage of meiotic prophase. Cells from both *dmc1* and *hop2* contain extensive synaptonemal complex at the arrest point[8,9]. All three mutants arrest at the stage of maximum chromatin condensation[8–10], which corresponds to pachytene in yeast.

The *dmc1* mutant lacks a meiosis-specific homolog of the RecA strand exchange enzyme[11]. *dmc1* cells process DSBs to expose extensive single-stranded tails, but subsequent steps in DSB repair are blocked[11]; additionally, chromosome synapsis is delayed in *dmc1* cells[8]. Synapsis does not occur in the *zip1* mutant, which lacks a major component of the synaptonemal complex[10]. *zip1* cells arrest with incomplete recombination[10]; most of the events are delayed as Holliday junctions, but a small percentage (~10%) persist as unrepaired DSBs[12,13]. In the *hop2* mutant, DSBs with long single-stranded tails

TABLE 1. Homologs of *Saccharomyces cerevisiae* proteins implicated in pachytene checkpoint function or activation

Saccharomyces cerevisiae	*Schizosaccharomyces pombe*	*Drosophila melanogaster*	*Caenorhabditis elegans*	Mammals	Function in *S. cerevisiae*
DNA damage checkpoint proteins					
Ddc1	Rad9	Rad9		Rad9	Sensor of DNA damage; complexes with Mec3 and Rad17
Chk1	Chk1			Chk1	Protein kinase involved in signal transduction
Mec1	Rad3	Mei-41		Atr/Atm	Lipid/protein kinase
Mec3	Hus1			Hus1	Sensor of DNA damage; complexes with Rad17 and Ddc1
Rad17	Rad1		Mrt-2	Rad1	Putative exonuclease; complexes with Mec1 and Ddc1
Rad24	Rad17	Rad17	Hpr-17	Rad17	Homology to clamp loader (DNA polymerase processivity factor)
Meiotic chromosomal proteins					
Hop1			Him-3		Associated with meiotic chromosome cores; required for synapsis
Hop2					Prevents synapsis between nonhomologous chromosomes
Mek1					Meiosis-specific protein kinase that phosphorylates Red1
Red1					Essential building block of cores of meiotic chromosomes
Zip1					Major building block of SC central region
Recombination proteins					
Dmc1		Spn-B	Rad-51	Dmc1	Meiosis-specific RecA homolog
Mlh1				Mlh1	MutL homolog; involved in mismatch repair
Msh5				Msh5	MutS homolog; required for wild-type level of crossing over
Rad51	Rhp51		Rad-51	Rad51	RecA homolog; strand exchange enzyme
Rad54	Rhp54	Okr		Rad54	Helicase homolog; facilitates Rad51-promoted strand exchange
Chromatin-silencing factors					
Sir2					Chromatin silencing factor; protein deacetylase
Pch2					Nucleolar protein; represses meiotic recombination in rDNA
Dot1					Represses transcription of telomeric-proximal DNA sequences
Cell-cycle proteins					
Cdc28	Cdc2		Ncc-1	Cdc2	Cyclin-dependent protein kinase
Clb1		[a]	[a]	[a]	G2/M-specific cyclin
Glc7		[a]	[a]	[a]	Protein phosphatase type I
Ndt80					Meiosis-specific transcription factor
Swe1	Wee1	Wee1	Wee-1	Wee1	Protein kinase that phosphorylates and inactivates Cdc28

Homologs of *S. cerevisiae* proteins are listed only in cases where they have been described in the published literature. Searches of sequence data bases will reveal additional homologs.
[a]Note that the genomes of higher eukaryotes contain multiple genes encoding type I protein phosphatases, but it is not known which (if any) of these is the functional homolog of Glc7; similarly, it is not clear which of the cyclins in other organisms correspond to Clb1.

accumulate, and chromosomes synapse with nonhomologous partners[9].

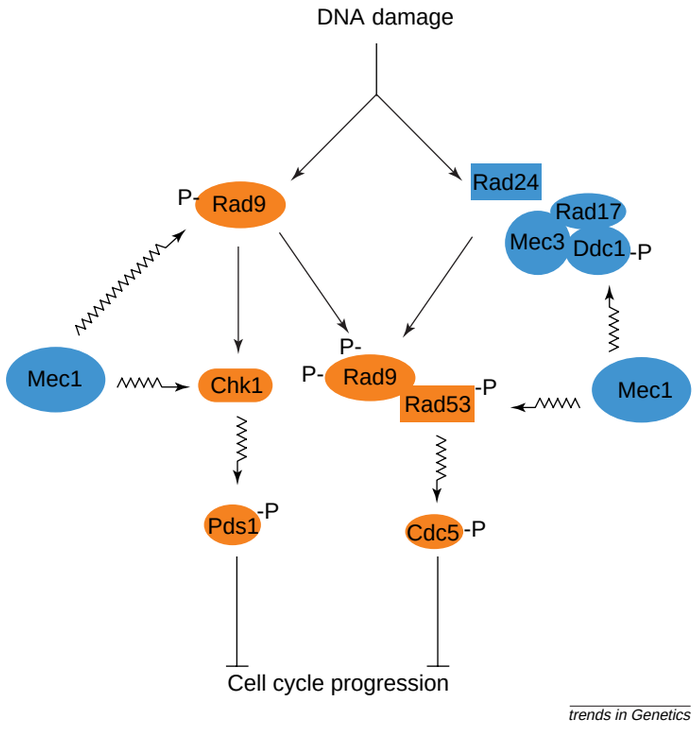
Numerous observations indicate that the *dmc1*, *zip1* and *hop2* mutants arrest at pachytene because of a checkpoint that is triggered by the accumulation of intermediates in recombination and synapsis (Fig. 1). The arrest of each of these mutants is alleviated by preventing the initiation of meiotic recombination[9–11]. Mutant cells retain viability at the arrest point and can resume mitotic cell division if returned to growth medium, presumably because DSBs are repaired by mitotic recombination. Arrest in the *dmc1*, *zip1* and *hop2* mutants is also abolished by mutation of certain genes required for checkpoints that operate in vegetative cells[4,14,15]. In addition, arrest in *dmc1* is bypassed by overproduction of the Rad54 protein, which promotes DSB repair by recombination between sister chromatids and therefore provides an alternative to the meiotic interhomolog recombination pathway[16].

The existence of a checkpoint that prevents entry into meiosis I when defects in meiotic prophase occur is not unique to budding yeast. In recent years, knockout mice have been generated in which spermatocytes and oocytes arrest at mid-meiotic prophase. In contrast to the situation in yeast, however, mammalian germ cells in which the checkpoint is triggered undergo apoptosis. This phenotype is observed in Dmc1-deficient mice and in mice lacking Msh5 or Mlh1, which are homologs of the *Escherichia coli* mismatch repair proteins MutS and MutL, respectively[17–21]. Spermatocytes and oocytes lacking Dmc1 or Msh5 arrest in meiotic prophase with unsynapsed chromosomes[18–20]; however, the cores of meiotic chromosomes are fully developed, which is not normally the case until pachytene[18]. Foci corresponding to the strand-exchange enzyme Rad51 persist on meiotic chromosomes prepared from Dmc1- and Msh5-deficient spermatocytes, suggesting that recombination is incomplete[18,20] (Rad51 serves as a marker for ongoing recombination events[4]). By contrast, chromosome synapsis occurs normally in Mlh1-deficient mice[17,22] but there is a failure of meiotic crossing over and chiasma formation[22,23]. Meiotic arrest and apoptosis in mice lacking Dmc1, Msh5 or Mlh1 are attributed to activation of a checkpoint[17,18], analogous to that operating in the *dmc1* mutant of yeast.

The pachytene checkpoint also operates in other organisms. In *Drosophila*, the *okr*, *spn-B* and *spn-C* mutations confer meiotic prophase arrest in oocytes[24]. Both *okr* and *spn-B* are homologous to yeast genes required for DSB repair (Table 1), suggesting that meiotic arrest is due to defects in meiotic recombination[24]. Unexpectedly, the *okr*, *spn-B* and *spn-C* mutants also display egg-patterning defects. The meiotic arrest and developmental defects are alleviated either when the initiation of meiotic recombination is prevented or when a checkpoint gene is disrupted[24]. Thus, the *okr*, *spn-B* and *spn-C* mutants confer phenotypes that are analogous to those of the *dmc1*, *zip1* and *hop2* mutants in yeast.

Evidence for a pachytene checkpoint operating in *Caenorhabditis elegans* comes from the study of the single worm gene that encodes a homolog of the RecA-related proteins, Dmc1 and Rad51. Mutation of this gene prevents pachytene exit in oocytes and results in increased

FIGURE 2. DNA damage checkpoint pathway



In the DNA damage checkpoint, signals indicating damage are detected by sensor proteins. This information is then transduced to the cell-cycle machinery to effect cell-cycle arrest and transcriptional induction of repair genes. Proteins known to interact with each other are indicated by overlapping symbols. Proteins required for both the DNA damage checkpoint and the pachytene checkpoint are shown in blue. The wavy lines indicate protein phosphorylation.

apoptosis[25,26]. Mutation of a *C. elegans* checkpoint gene (e.g. *mrt*-2; see Table 1) prevents the germ cell apoptosis observed in *rad51* mutants[26].

The role of DNA damage checkpoint proteins in the pachytene checkpoint

In budding yeast, several proteins involved in the DNA damage checkpoint also participate in the pachytene checkpoint (Fig. 2; Table 1). In mitotic cells, sensing of DNA damage requires the Rad9 protein acting in parallel with the Rad24 group of proteins, which consists of Rad24, Rad17, Mec3 and Ddc1 (Refs 27–29). Both Rad9 and Ddc1 are phosphorylated by the Mec1 kinase[28,29]. Transduction of the checkpoint signal requires the parallel action of two additional protein kinases, Rad53 and Chk1, both of which undergo Mec1-dependent phosphorylation[28–30]. Modification of Rad53 requires the Rad24 group of proteins and direct association of Rad53 with phosphorylated Rad9 (Refs 28,29). The downstream target of Rad53 might be Cdc5, a kinase that blocks mitotic exit by preventing activation of the anaphase-promoting complex[30]. The activated Chk1 kinase phosphorylates the anaphase inhibitor Pds1[30]; modification of Pds1 (and presumably Chk1) requires Rad9 but is independent of the Rad24 group of proteins[28,29]. As a consequence of Pds1 activation and Cdc5 inhibition, a high level of cyclin-dependent kinase activity is maintained and the separation of sister chromatids is prevented, leading to cell-cycle arrest in mitosis.

The Rad24, Rad17, Mec3, Ddc1 and Mec1 proteins also function in the pachytene checkpoint[4,14,31]. By contrast, the checkpoint activities of Rad9, Rad53 and Chk1 are not required to arrest meiotic cells at pachytene[4] (P.A. San-Segundo and G.S. Roeder, unpublished data). If a checkpoint mutation (such as *rad24*) is combined with *dmc1*, cells of the resulting double mutant undergo meiotic nuclear division, even though recombination is incomplete[4]. In wild type, the Rad51 strand-exchange enzyme localizes to foci on meiotic chromosomes early in meiotic prophase but dissociates from chromosomes by pachytene[32]. By contrast, in the *dmc1 rad24* double mutant, Rad51 foci are found on chromosomes even in nuclei that are dividing[4]. The meiotic products of *dmc1 rad24* (and *dmc1 rad17*, *zip1 rad24*, etc.) strains are inviable[4], as expected if cells undergo meiotic nuclear division before recombination is complete.

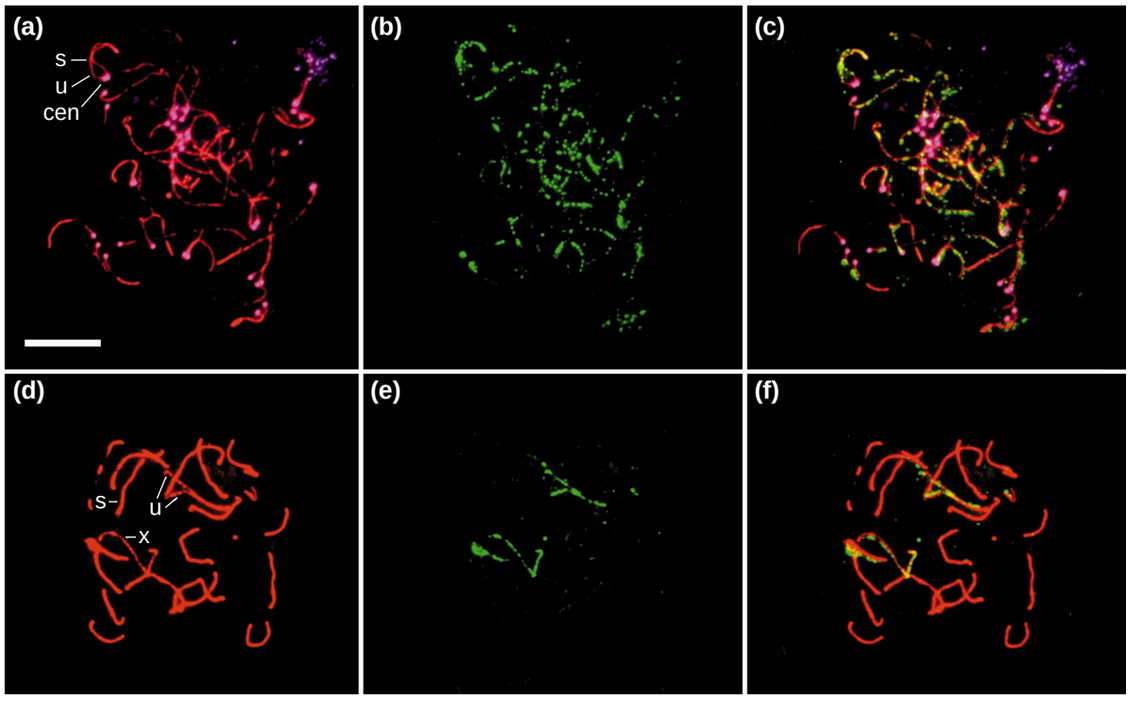
Analysis of single mutants in checkpoint genes suggests that gene products required for the pachytene checkpoint play additional roles during meiosis. In *Drosophila*, mutation of the *mei-41* gene (Table 1) leads to reduced levels of meiotic recombination and altered placement of recombination events[33]. In budding yeast, *rad17*, *rad24* and *mec1* mutants exhibit decreased recombination, reduced spore viability and aberrant chromosome synapsis[4,34,35]. The defects in these mutants cannot be accounted for solely by checkpoint defects, arguing that these checkpoint genes function in meiotic recombination and/or chromosome synapsis in addition to their role in regulating cell-cycle progression. Unexpectedly, germ cells in Atm-deficient mice undergo pachytene arrest and apoptosis[36]. Thus, although Atm (like Mec1) is required for normal meiosis, proteins might function redundantly with Atm to prevent exit from pachytene when defects in recombination and synapsis occur. Alternatively, Atm might not be needed for the pachytene checkpoint in mice.

The roles of checkpoint proteins during meiosis in mammals have been inferred in part from immunolocalization studies. The protein kinases Atm (Ref. 37, but see Ref. 38), Chk1 (Ref. 39) and Atr (Refs 37,38), and the Rad1 protein[40] (Table 1), have been reported to localize to foci on meiotic chromosomes in mouse spermatocytes. Chromosomes that undergo delayed synapsis seem to accumulate Atr along the unsynapsed chromosome axes (Fig. 3), raising the possibility that Atr serves to monitor synapsis[37,38]. Neither Atr nor Rad1 colocalize with Dmc1 or Rad51, indicating that Atr and Rad1 foci do not mark the sites of recombination events[38,40].

Links between chromatin silencing and the pachytene checkpoint

The localization of several checkpoint proteins along meiotic chromosomes is consistent with a role for these proteins in monitoring recombination and synapsis. Unexpectedly, however, other proteins required for the pachytene checkpoint localize primarily to the nucleolus. In budding yeast, the meiosis-specific protein Pch2 and the chromatin-silencing factor Sir2 are found predominantly in the nucleolus, with additional foci localized along meiotic chromosomes[14] (Fig. 4a). Mutation of *PCH2* or *SIR2* bypasses checkpoint-induced pachytene arrest of the *zip1* and *dmc1* mutants[14]. Pch2 is detected only in the nucleolus in *zip1* cells, in which the checkpoint is operating (Fig. 4b). By contrast, Pch2 is delocalized from the nucleolus in the *sir2* mutant, in which the checkpoint is

FIGURE 3. Localization of Atr to meiotic chromosomes in mice



(a)–(c) A mid-zygotene nucleus stained with antibodies to (a) Cor1 (red; a component of meiotic chromosome axes) and centromeres (purple). s indicates a synapsed region; u indicates an unsynapsed region; cen indicates a centromere. (b) Atr (green); (c) merged image of Atr, Cor1 and centromere staining. Atr localizes to numerous foci on chromosomes. (d)–(f) A late-zygotene nucleus stained with antibodies to (d) Cor1 (red); (e) Atr (green); (f) merged image of Cor1 and Atr staining. Most chromosomes are fully synapsed. Chromosomal segments that remain unsynapsed (a) stain intensely with anti-Atr antibodies; in addition, Atr accumulates on the unsynapsed regions of the X and Y chromosomes (x). Regions of overlap between Atr and Cor1 are yellow. Scale bar = 10 μm. Figures provided by Peter Moens.

inactive[14] (Fig. 4c). Thus, the nucleolar localization of Pch2 seems to be important for checkpoint function. A possible explanation for the function of Pch2 is suggested by studies of the yeast Cdc14 protein that is required for the exit from mitosis[41,42]. Cdc14 is sequestered in the nucleolus, and thereby prevented from accessing its substrates, until the point in the mitotic cell cycle when it is required to act. Perhaps Pch2 sequesters within the nucleolus a protein required for the exit from pachytene.

Interestingly, Pch2 and Sir2 are needed to prevent meiotic interhomolog recombination within the repeated ribosomal RNA genes present in the nucleolus[14]. In wild-type cells, the meiosis-specific Hop1 protein that promotes recombination between homologous chromosomes[43] is excluded from the nucleolus[44]. However, mutation of *PCH2* or *SIR2* results in Hop1 localization to the nucleolus and consequently increases recombination within the ribosomal DNA array[14].

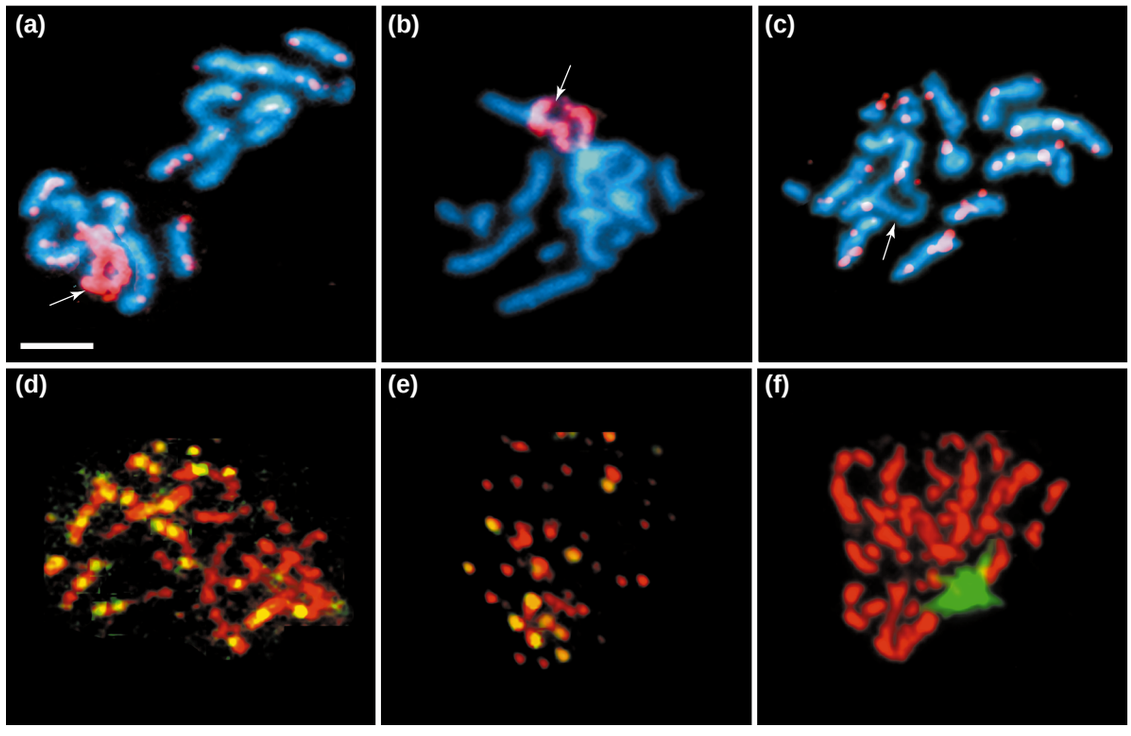
Several recent observations provide additional evidence for links between chromatin silencing and checkpoint control. Mutations in budding yeast *MEC1* or fission yeast *rad3*$^+$ (Table 1) lead to reduced silencing of telomere-proximal DNA sequences[45,46]. In addition, in budding yeast, the Mec3 checkpoint protein interacts physically with Set1, a protein required for telomeric silencing[47]. Finally, the Dot1 protein that is required for silencing at telomeres and the mating-type loci[48] is also required for the pachytene checkpoint (P.A. San-Segundo and G.S. Roeder, submitted).

The role of meiotic chromosomal proteins in the pachytene checkpoint

In budding yeast, the meiotic chromosomal proteins Red1, Mek1 and Hop1 are required for the pachytene checkpoint. Red1 is a major component of meiotic chromosome axes[44]; Mek1 is a protein kinase that phosphorylates Red1 (Refs 49,50). Hop1 colocalizes with Red1 in early meiotic prophase but dissociates from chromosomes at or before pachytene, as chromosomes synapse[44]. Deletion of *RED1*, *MEK1* or *HOP1* allows wild-type levels of meiotic nuclear division in mutants that undergo checkpoint-mediated arrest[13,51]. Overproduction of Red1 or Mek1, but not Hop1, also promotes nuclear division in the *zip1* mutant[52]. However, *zip1* arrest is not bypassed by co-overproduction of both Red1 and Mek1 or by co-overproduction of Hop1 with either Red1 or Mek1, suggesting that the stoichiometry of Red1, Hop1 and Mek1 is important for checkpoint function[52].

Kleckner and colleagues[13] proposed that a properly developed recombination complex emits an inhibitory signal to delay meiotic progression until recombination is complete. Recent observations suggest that phosphorylated Red1 might be such an inhibitory signal. Red1 is phosphorylated by Mek1 and localized to chromosomes early in meiotic prophase[44,49] (Fig. 4d; Fig. 5), but is dephosphorylated by the Glc7 phosphatase and delocalized from chromosomes around the end of pachytene[31,44] (Fig. 4e; Fig. 5). Cells delay or arrest with phosphorylated Red1 if the checkpoint is triggered (Fig. 4f), Mek1 is rendered

FIGURE 4. Localization of the yeast Pch2 and Red1 proteins to meiotic chromosomes



(a)–(c) Pch2 staining patterns. Spread meiotic nuclei were stained with a DNA-binding dye (blue) and with antibodies to Pch2 (pink). In wild type, Pch2 localizes primarily to the nucleolus (arrows), but also to chromosomal foci (a). Pch2 is found only in the nucleolus in the *zip1* mutant (b); Pch2 is absent from the nucleolus but still present on chromosomes in a *zip1 sir2* double mutant (c). (d)–(f) Red1 localization. In spread nuclei from wild type, (d) Mek1 (green) colocalizes with Red1 (red) in early prophase, and (e) Glc7 (green) colocalizes with Red1 (red) in late pachytene/early diplotene. Regions of overlap between Red1 and Mek1, or Red1 and Glc7, are yellow. Red1 (red) remains localized to chromosomes in the *zip1* mutant (f); staining with anti-tubulin antibodies (green) reveals a tubulin bush indicative of duplicated but unseparated spindle pole bodies. Scale bar = 2 μm. (a)–(c) provided by P.A. San-Segundo; (a)-(c), (e) reprinted with permission from *Cell*.

constitutively active or Glc7 is inactivated by mutation[31]. However, this arrest is suppressed by overproduction of Glc7 (Ref. 31). Taken together, these observations suggest that phosphorylated Red1 signals a defect in meiotic chromosome metabolism to downstream components of the checkpoint pathway.

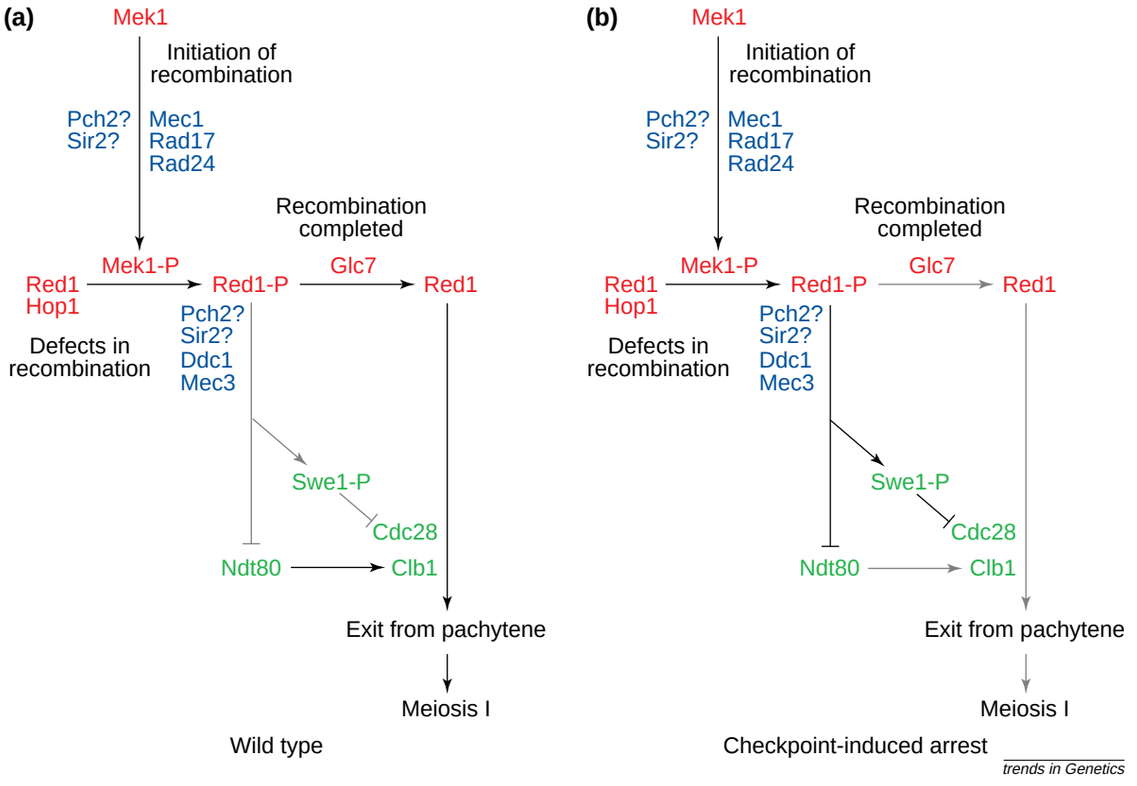
The Hop1 protein is not normally associated with chromosomes late in pachytene, suggesting that Hop1 is not involved directly in checkpoint activation. However, the checkpoint is inactivated by a *red1* mutation (*red1–K348E*) that abrogates the Red1–Hop1 interaction[51]. In this mutant, the Red1 protein is still modified by Mek1, but chromosomes fail to synapse. These observations demonstrate that phosphorylated Red1 is not sufficient to inhibit pachytene exit and suggest that the Red1 protein must be present within a specific chromosomal context in order to be monitored by the checkpoint machinery.

Requirements for generation and monitoring of the inhibitory signal

The pachytene checkpoint is not activated in the absence of meiotic recombination but only when recombination has been initiated, but not completed. Phosphorylation of Mek1 requires the initiation of meiotic recombination[31], suggesting that an inhibitory signal is not generated in the absence of recombination. Mek1 also fails to become phosphorylated in certain checkpoint mutants (*rad17*, *rad24* and *mec1-1*)[31]. In mitotic cells, the Rad17 and Rad24 proteins are thought to be involved in the generation and/or recognition of single-stranded DNA[27,29]; in meiosis, these proteins might interact with regions of single-stranded DNA present in recombination intermediates. In response, the checkpoint kinase Mec1 could phosphorylate and activate downstream kinases such as Mek1. Mek1 is highly homologous to Rad53, both in the kinase domain and in the forkhead-associated domain[53], raising the possibility that Mek1 functions in the pachytene checkpoint pathway as a counterpart to Rad53 in the DNA damage checkpoint pathway (Fig. 2). A forkhead domain in the Rad53 sequence mediates its interaction with phosphorylated Rad9 (Ref. 54); perhaps the forkhead-associated domain of Mek1 is also important for interactions with checkpoint proteins.

Ddc1 and Mec3 also act in the pachytene checkpoint, although these proteins are not required for Mek1 phosphorylation[14,31]. This raises the intriguing possibility that Ddc1 and Mec3 act downstream of Mek1, perhaps as sensors or transducers of Red1 phosphorylation. Although the Rad24, Rad17, Mec3 and Ddc1 proteins are thought to act together in the DNA damage checkpoint pathway (Fig. 2), analysis of Mek1 phosphorylation suggests that these checkpoint proteins act at different steps during meiosis.

FIGURE 5. Model for the pachytene checkpoint pathway in budding yeast



Red1 and associated proteins are shown in red; checkpoint proteins are shown in blue; and downstream targets of the checkpoint are shown in green.

Downstream targets of the pachytene checkpoint

Two downstream targets of the pachytene checkpoint have been identified in budding yeast: Swe1 and Ndt80. In mitosis, the Swe1 kinase phosphorylates and inactivates the cyclin-dependent kinase Cdc28 (Ref. 55). In meiosis, Swe1 is required for checkpoint-induced arrest at pachytene[15]. When the pachytene checkpoint is activated, Swe1 accumulates and becomes hyperphosphorylated, causing Cdc28 to become phosphorylated and presumably inactivated[15]. This result points to another difference between the pachytene checkpoint and the DNA damage checkpoint, which is known not to involve inhibitory phosphorylation of Cdc28 (Refs 56,57).

Ndt80 is a meiotic transcription factor that activates genes required for the exit from pachytene[58], including *CLB1*, which encodes the major cyclin required for meiosis I (Refs 59,60). When the pachytene checkpoint is triggered, Ndt80 target genes are not transcribed; however, if the checkpoint is inactivated by mutation, Ndt80-promoted transcription is restored[58,61]. These observations suggest that the activity of Ndt80 is down-regulated by the pachytene checkpoint. Consistent with this hypothesis, overproduction of the Ndt80 protein increases meiotic nuclear division in mutants that would otherwise undergo checkpoint-induced pachytene arrest (K-S. Tung and G.S. Roeder, unpublished data). Recent evidence suggests that the transcriptional activity of the Ndt80 protein is regulated by post-translational modification (Ref. 58; K-S. Tung and G.S. Roeder, unpublished data).

In higher eukaryotes, gene products involved in regulating cell-cycle progression are not the only targets of the pachytene checkpoint. In *Drosophila*, a regulator of protein translation, called Vasa[62], is inactivated by post-translational modification when the checkpoint is activated[24]. As a consequence, translational targets of Vasa are not produced, including the Gurken protein that is required to initiate dorsoventral patterning during oogenesis[63]. It is the absence of Gurken that accounts for the egg-patterning defects observed in the *okr*, *spn-B* and *spn-C* mutants[24].

In mice, meiotic cell-cycle arrest is followed rapidly by apoptosis[17–21], suggesting that gene products involved in programmed cell death are targets of the pachytene checkpoint. One of these targets is likely to be p53, a protein known to promote apoptosis[64]. In Atm-deficient mice, p53 is increased in abundance; furthermore, mutation of p53 decreases substantially the apoptosis of meiotic prophase cells that is observed normally in Atm-deficient mice[65].

A model for the pachytene checkpoint pathway in *Saccharomyces cerevisiae*

A working model for the pachytene checkpoint pathway in budding yeast is presented in Fig. 5. Early in meiotic prophase, meiotic recombination initiates. This initiation generates an inhibitory signal – phosphorylated Red1 – indicating that recombination is ongoing. Some checkpoint proteins, including Rad17, Rad24 and Mec1, are required to generate this inhibitory signal. If recombination is completed successfully, the inhibitory signal is eliminated (presumably by Glc7-dependent dephosphorylation of Red1)

and exit from pachytene is promoted. However, if recombination cannot be completed, Red1 phosphorylation persists, leading to activation of the checkpoint. It is possible that other signals, not shown in this model, can also trigger the pachytene checkpoint. Proteins such as Ddc1 and Mec3 might function in detection and/or transduction of the signal to the downstream components of the checkpoint pathway. The point of action of Pch2 and Sir2 remains to be determined: these proteins could function either in generating the signal or in transducing the signal to the checkpoint machinery. Ultimately, the downstream targets of the checkpoint, Swe1 and Ndt80, are affected. Swe1 inactivates Cdc28 (Ref. 15), and Ndt80 is prevented from transcribing Clb1 (Refs 58,61). Thus, inhibition of cell cycle progression is enforced by limiting the abundance or activity of both components of the cyclin-dependent kinase complex (Cdc28 and Clb1).

Other meiotic checkpoints

In addition to the pachytene checkpoint, checkpoints operate at a number of other points in meiosis. A premeiotic replication checkpoint has been described in both budding and fission yeasts[66,67]. Activation of the replication checkpoint requires initiation of replication[66], analogous to the requirement for initiation of meiotic recombination for activation of the pachytene checkpoint. In addition, meiotic budding yeast cells that sustain chromosomal lesions early in meiosis undergo a *RAD9*-dependent checkpoint that arrests cells after DNA replication but before recombination and synapsis[68].

Checkpoints also operate at metaphase I. The metaphase I checkpoint blocks the metaphase to anaphase transition if spindle formation is defective[23] or if one or more chromosomes are misaligned on the spindle apparatus[69–71]. Proper orientation of chromosomes on the meiotic spindle results in tension because homologous chromosomes are being pulled toward opposite spindle poles, but this pulling is resisted by the chiasmata that hold homologs together[72]. If a single chromosome is not under tension, it emits a signal that prevents the metaphase–anaphase transition[69]; the signal is thought to be a kinetochore-associated protein that is phosphorylated specifically on chromosomes that are misaligned[73].

It is a biological curiosity that the checkpoint that responds to misaligned chromosomes in mammals operates in males but not females. In mice carrying a chromosome that lacks a pairing partner, spermatocytes arrest at metaphase I (Ref. 71), whereas oocytes continue to progress though meiosis[70]. It has been suggested that failure of the metaphase checkpoint provides an explanation for the remarkably high rate of meiosis I chromosome missegregation observed in human females[70].

Perspectives

Although considerable progress has been made in elucidating the pachytene checkpoint pathway, there is still much to learn. Most important, it remains to be determined whether the principles that operate in budding yeast are conserved in other organisms.

A critical question that remains to be addressed in all systems is the nature of the signal(s) that triggers arrest. Differences between meiotic mutants in yeast suggest that more than one signal can trigger arrest and that different signals might be transduced through different pathways. For example, pachytene arrest in the *hop2* mutant (unlike the *zip1* and *dmc1* mutants) is not alleviated by a *pch2* mutation or by overproduction of the Red1 or Mek1 protein[14,52]. In meiotic mutants of mammals, arrest is associated clearly with synaptic failure; however, the recombination defects in these mutants are not well characterized. In budding yeast (and probably mammals), synapsis and recombination are linked intimately, and mutants that affect one process usually affect the other. For these reasons, it is not yet clear whether defects in recombination and/or synapsis cause checkpoint-mediated arrest. It might be easier to determine whether defects in recombination, synapsis, or both, trigger the checkpoint by studying flies or worms, in which recombination and synapsis can be separated cleanly by mutation[5,6].

Even in budding yeast, many components of the pachytene checkpoint pathway remain to be identified. In addition, the functions of many of the known checkpoint proteins, and their interactions with each other, have yet to be elucidated. In particular, the role of nucleolar proteins in the pachytene checkpoint is a mystery that remains to be solved.

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References

1 Hartwell, L.H. and Weinert, T.A. (1989) Checkpoints: controls that ensure the order of cell cycle events. *Science* 246, 629–634

2 Carr, A.M. (1996) Checkpoints take the next step. *Science* 271, 314–315

3 Roeder, G.S. (1997) Meiotic chromosomes: it takes two to tango. *Genes Dev.* 11, 2600–2621

4 Lydall, D. *et al.* (1996) A meiotic recombination checkpoint controlled by mitotic checkpoint genes. *Nature* 383, 840–843

5 McKim, K.S. and Hayashi-Hagihara, A. (1998) *mei-W68* in *Drosophila melanogaster* encodes a Spo11 homolog: evidence that the mechanism for initiating meiotic recombination is conserved. *Genes Dev.* 12, 2932–2942

6 Dernburg, A.F. *et al.* (1998) Meiotic recombination in *C. elegans* initiates by a conserved mechanism, and is dispensable for homologous chromosome synapsis. *Cell* 94, 387–398

7 Shuster, E.O. and Byers, B. (1989) Pachytene arrest and other meiotic effects of the start mutations in *Saccharomyces cerevisiae*. *Genetics* 123, 29–43

8 Rockmill, B. *et al.* (1995) Roles for two RecA homologs in promoting meiotic chromosome synapsis. *Genes Dev.* 9, 2684–2695

9 Leu, J-Y. *et al.* (1998) The meiosis-specific Hop2 protein of *S. cerevisiae* ensures synapsis between homologous chromosomes. *Cell* 94, 375–386

10 Sym, M. *et al.* (1993) ZIP1 is a synaptonemal complex protein required for meiotic chromosome synapsis. *Cell* 72, 365–378

11 Bishop, D.K. *et al.* (1992) DMC1: a meiosis-specific yeast homolog of *E. coli recA* required for recombination, synaptonemal complex formation, and cell cycle progression. *Cell* 69, 439–456

12 Storlazzi, A. *et al.* (1996) Synaptonemal complex (SC) component Zip1 plays a role in meiotic recombination independent of SC polymerization along the chromosomes. *Proc. Natl. Acad. Sci. U. S. A.* 93, 9043–9048

13 Xu, L. *et al.* (1997) Meiotic cells monitor the status of the interhomolog recombination complex. *Genes Dev.* 11, 106–118

14 San-Segundo, P. and Roeder, G.S. (1999) Pch2 links chromatin silencing to meiotic checkpoint control. *Cell* 97, 313–324

15 Leu, J-Y. and Roeder, G.S. (1999) The pachytene checkpoint in *S. cerevisiae* depends on Swe1-mediated phosphorylation of the cyclin-dependent kinase Cdc28. *Mol. Cell* 4, 805–814

16 Bishop, D.K. *et al.* (1999) High copy number suppression of the meiotic arrest caused by a *dmc1* mutation: *REC114* imposes an early recombination block and *RAD54* promotes a *DMC1*-independent DSB repair pathway. *Genes Cells* 4, 425–443

17 Edelmann, W. *et al.* (1996) Meiotic pachytene arrest in MLH1-deficient mice. *Cell* 85, 1125–1134

18 Pittman, D.L. *et al.* (1998) Meiotic prophase arrest with failure of chromosome synapsis in mice deficient for *Dmc1*, a germline-specific RecA homolog. *Mol. Cell* 1, 697–705

19 Yoshida, K. *et al.* (1998) The mouse *RecA*-like gene *Dmc1* is required for homologous chromosome synapsis during meiosis. *Mol. Cell* 1, 707–718

20 Edelmann, W. *et al.* (1999) Mammalian MutS homologue 5 is required for chromosome pairing in meiosis. *Nat. Genet.* 21, 123–127

21 de Vries, S.S. *et al.* (1999) Mouse MutS-like protein Msh5 is required for proper chromosome synapsis in male and female meiosis. *Genes Dev.* 13, 523–531

22 Baker, S.M. *et al.* (1996) Involvement of mouse *Mlh1* in DNA mismatch repair and meiotic crossing over. *Nat. Genet.* 13, 336–342
23 Woods, L.M. *et al.* (1999) Chromosomal influence on meiotic spindle assembly: abnormal meiosis I in female *Mlh1* mutant mice. *J. Cell Biol.* 145, 1395–1406
24 Ghabrial, A. and Schupbach, T. (1999) Activation of a meiotic checkpoint regulates translation of Gurken during *Drosophila* oogenesis. *Nat. Cell Biol.* 1, 354–357
25 Takanami, T. *et al.* (1998) Characterization of a *Caenorhabditis elegans recA*-like gene *Ce-rdh-1* involved in meiotic recombination. *DNA Res.* 5, 373–377
26 Gartner, A. *et al.* (2000) A conserved checkpoint pathway mediates DNA damage-induced apoptosis and cell cycle arrest in *C. elegans*. *Mol. Cell* 5, 435–443
27 Lydall, D. and Weinert, T. (1995) Yeast checkpoint genes in DNA damage processing: implications for repair and arrest. *Science* 270, 1488–1491
28 Longhese, M.P. *et al.* (1997) The novel DNA damage checkpoint protein Ddc1p is phosphorylated periodically during the cell cycle and in response to DNA damage in budding yeast. *EMBO J.* 16, 5216–5226
29 Weinert, T. (1998) DNA damage and checkpoint pathways: molecular anatomy and interactions with repair. *Cell* 94, 555–558
30 Sanchez, Y. *et al.* (1999) Control of the DNA damage checkpoint by Chk1 and Rad53 protein kinases through distinct mechanisms. *Science* 286, 1166–1171
31 Bailis, J.M. and Roeder, G.S. (2000) Pachytene exit controlled by reversal of Mek1-dependent phosphorylation. *Cell* 101, 211–221
32 Bishop, D.K. (1994) RecA homologs Dmc1 and Rad51 interact to form multiple nuclear complexes prior to meiotic chromosome synapsis. *Cell* 79, 1081–1092
33 Carpenter, A.T.C. (1979) Recombination nodules and synaptonemal complex in recombination-defective females of *Drosophila melanogaster*. *Chromosoma* 75, 259–292
34 Kato, R. and Ogawa, H. (1994) An essential gene, *ESR1*, is required for mitotic cell growth, DNA repair and meiotic recombination in *Saccharomyces cerevisiae*. *Nucleic Acids Res.* 22, 3104–3112
35 Grushcow, J.M. *et al.* (1999) *Saccharomyces cerevisiae* checkpoint genes *MEC1*, *RAD17* and *RAD24* are required for normal meiotic recombination partner choice. *Genetics* 153, 607–620
36 Xu, Y. *et al.* (1996) Targeted disruption of *ATM* leads to growth retardation, chromosomal fragmentation during meiosis, immune defects, and thymic lymphoma. *Genes Dev.* 10, 2411–2422
37 Keegan, K.S. *et al.* (1996) The Atr and Atm protein kinases associate with different sites along meiotically pairing chromosomes. *Genes Dev.* 10, 2423–2437
38 Moens, P.B. *et al.* (1999) The association of ATR protein with mouse meiotic chromosome cores. *Chromosoma* 108, 95–102
39 Flaggs, G. *et al.* (1997) Atm-dependent interactions of a mammalian Chk1 homolog with meiotic chromosomes. *Curr. Biol.* 7, 977–986
40 Freire, R. *et al.* (1998) Human and mouse homologs of *Schizosaccharomyces pombe rad1*$^{+}$ and *Saccharomyces cerevisiae RAD17*: linkage to checkpoint control and mammalian meiosis. *Genes Dev.* 12, 2560–2573
41 Shou, W. *et al.* (1999) Exit from mitosis is triggered by Tem1-dependent release of the protein phosphatase Cdc14 from nucleolar RENT complex. *Cell* 97, 233–244
42 Visintin, R. *et al.* (1999) Cfi1 prevents premature exit from mitosis by anchoring Cdc14 phosphatase in the nucleolus. *Nature* 398, 818–823
43 Hollingsworth, N.M. and Byers, B. (1989) *HOP1*: a yeast meiotic pairing gene. *Genetics* 121, 445–462
44 Smith, A.V. and Roeder, G.S. (1997) The yeast Red1 protein localizes to the cores of meiotic chromosomes. *J. Cell Biol.* 136, 957–967
45 Matsuura, A. *et al.* (1999) Genetic control of telomere integrity in *Schizosaccharomyces pombe*: *rad3*$^{+}$ and *tel1*$^{+}$ are parts of two regulatory networks independent of the downstream protein kinases *chk1*$^{+}$ and *cds1*$^{+}$. *Genetics* 152, 1501–1512
46 Craven, R.J. and Petes, T.D. (2000) Involvement of the checkpoint protein Mec1p in silencing of gene expression at telomeres in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* 20, 2378–2384
47 Corda, Y. *et al.* (1999) Interaction between Set1p and checkpoint protein Mec3p in DNA repair and telomere functions. *Nat. Genet.* 21, 204–208
48 Singer, M.S. *et al.* (1998) Identification of high-copy disruptors of telomeric silencing in *Saccharomyces cerevisiae*. *Genetics* 150, 613–632
49 Bailis, J.M. and Roeder, G.S. (1998) Synaptonemal complex morphogenesis and sister-chromatid cohesion require Mek1-dependent phosphorylation of a meiotic chromosomal protein. *Genes Dev.* 12, 3551–3563
50 de los Santos, T. and Hollingsworth, N.M. (1999) Red1p, a *MEK1*-dependent phosphoprotein that physically interacts with Hop1p during meiosis in yeast. *J. Biol. Chem.* 274, 1783–1790
51 Woltering, D. *et al.* Meiotic segregation, synapsis and recombination checkpoint functions require physical interaction between the chromosomal proteins Red1p and Hop1p. *Mol. Cell. Biol.* (in press)
52 Bailis, J.M. *et al.* (2000) Bypass of a meiotic checkpoint by overproduction of meiotic chromosomal proteins. *Mol. Cell. Biol.* 20, 4838–4848
53 Cherry, J.M. *et al.* (1998) Saccharomyces Genome Database. http://genome-www.stanford.edu/Saccharomyces
54 Sun, Z. *et al.* (1998) Rad53 FHA domain associated with phosphorylated Rad9 in the DNA damage checkpoint. *Science* 281, 272–274
55 Booher, R.N. *et al.* (1993) Properties of *Saccharomyces cerevisiae* wee1 and its differential regulation of p34^{CDC28} in response to G_1 and G_2 cyclins. *EMBO J.* 12, 3417–3426
56 Amon, A. *et al.* (1992) Regulation of p34^{CDC28} tyrosine phosphorylation is not required for entry into mitosis in *S. cerevisiae*. *Nature* 355, 368–371
57 Sorger, P.K. and Murray, A.W. (1992) S-phase feedback control in budding yeast independent of tyrosine phosphorylation of p34^{cdc28}. *Nature* 355, 365–368
58 Chu, S. and Herskowitz, I. (1998) Gametogenesis in yeast is regulated by a transcriptional cascade dependent on Ndt80. *Mol. Cell* 1, 685–696
59 Grandin, N. and Reed, S.I. (1993) Differential function and expression of *Saccharomyces cerevisiae* B-type cyclins in mitosis and meiosis. *Mol. Cell. Biol.* 13, 2113–2125
60 Dahmann, C. and Futcher, B. (1995) Specialization of B-type cyclins for mitosis or meiosis in *S. cerevisiae*. *Genetics* 140, 957–963
61 Hepworth, S.R. *et al.* (1998) *NDT80* and the meiotic recombination checkpoint regulate expression of middle sporulation-specific genes in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* 18, 5750–5761
62 Lasko, P.F. and Ashburner, M. (1988) The product of the *Drosophila* gene *vasa* is very similar to eukaryotic initiation factor-4A. *Nature* 335, 611–617
63 Gonzalez-Reyes, A. *et al.* (1997) Oocyte determination and the origin of polarity in *Drosophila*: the role of the *spindle* genes. *Development* 124, 4927–4937
64 Jacks, T. and Weinberg, R.A. (1996) Cell-cycle control and its watchman. *Nature* 381, 643–644
65 Barlow, C. *et al.* (1997) Partial rescue of the prophase I defects of *Atm*-deficient mice by *p53* and *p21* null alleles. *Nat. Genet.* 17, 462–466
66 Stuart, D. and Wittenberg, C. (1998) *CLB5* and *CLB6* are required for premeiotic DNA replication and activation of the meiotic S/M checkpoint. *Genes Dev.* 12, 2698–2710
67 Murakami, H. and Nurse, P. (1999) Meiotic DNA replication checkpoint control in fission yeast. *Genes Dev.* 13, 2581–2593
68 Weber, L. and Byers, B. (1992) A *RAD9*-dependent checkpoint blocks meiosis of *cdc13* yeast cells. *Genetics* 131, 55–63
69 Li, X. and Nicklas, R.B. (1995) Mitotic forces control a cell-cycle checkpoint. *Nature* 373, 630–632
70 LeMaire-Adkins, R. *et al.* (1997) Lack of checkpoint control at the metaphase/anaphase transition: a mechanism of meiotic nondisjunction in mammalian females. *J. Cell Biol.* 139, 1611–1619
71 Odorisio, T. *et al.* (1998) The meiotic checkpoint monitoring synapsis eliminates spermatocytes via p53-independent apoptosis. *Nat. Genet.* 18, 257–261
72 Hawley, R.S. (1988) In *Genetic Recombination* (Kucherlapati, R. and Smith, G.R., eds), pp. 497–527, American Society for Microbiology
73 Nicklas, R.B. *et al.* (1995) Kinetochore chemistry is sensitive to tension and may link mitotic forces to a cell cycle checkpoint. *J. Cell Biol.* 130, 929–939