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Checking Your Breaks: Surveillance Mechanisms of Meiotic Recombination

Review

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Numerous DNA double-strand breaks (DSBs) are introduced into the genome in the course of meiotic recombination. This poses a significant hazard to the genomic integrity of the cell. Studies in a number of organisms have unveiled the existence of surveillance mechanisms or checkpoints that couple the formation and repair of DSBs to cell cycle progression. Through these mechanisms, aberrant meiocytes are delayed in their meiotic progression, thereby facilitating repair of meiotic DSBs, or are culled through programmed cell death, thereby protecting the germline from aneuploidies that could lead to spontaneous abortions, birth defects and cancer predisposition in the offspring. Here we summarize recent progress in our understanding of these checkpoints. This review focuses on the surveillance mechanisms of the budding yeast *S. cerevisiae*, where the molecular details are best understood, but will frequently compare and contrast these mechanisms with observations in other organisms.

Introduction

In most eukaryotic organisms, meiotic recombination is a crucial prerequisite for faithful gamete production. Meiosis is characterized by two consecutive division phases (meiosis I and II) during which homologous chromosomes, and then sister chromatids, are segregated (Figure 1A). Homologous chromosomes differ fundamentally from sister chromatids, because unlike sister chromatids, which are held together by cohesin complexes, homologous chromosomes are not initially linked to each other. To establish the connections between homologous chromosomes that are essential for their correct alignment on the metaphase I plate, most eukaryotes employ the system of controlled DNA breakage and homolog-directed repair known as meiotic recombination.

DNA breakage, while being necessary to connect homologous chromosomes, is nevertheless highly hazardous for genomic integrity. Incorrectly repaired DSBs can lead to mutations, loss of heterozygosity, and translocations. If cells initiate chromosome segregation before breaks are repaired, entire chromosomes or chromosome fragments may be lost or missegregated. The resulting aneuploidies are a hallmark of many diseases, most notably cancers. Consequently, surveillance mechanisms that control DSB formation and halt cell cycle progression to provide time for repair have a crucial role in guarding genome integrity. This is especially so during meiotic recombination, when often more than 200 DSBs are simultaneously introduced into the genome.

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Meiotic recombination is initiated after premeiotic DNA replication (Figure 1B), during a stage that has variably been called meiotic prophase and meiotic G2 phase. Prophase is cytologically defined as the stage during which meiotic chromosome morphology becomes apparent (due to chromosome condensation and formation of synaptonemal complexes). However, whereas chromosome morphology changes in mitotic prophase are induced by cyclin dependent kinase (CDK) activity, meiotic chromosomal changes occur when CDK activity is low, a characteristic of G2 phase [1–3]. Thus, depending on the marker that is used, recombination and the accompanying chromosomal changes occur during G2 (if assessed by CDK activity) or during prophase (if assessed by cytology). To accommodate both nomenclatures, we refer to the period of low CDK activity that follows premeiotic DNA replication as G2/prophase.

Meiotic recombination is initiated by the topoisomerase-like enzyme Spo11. This enzyme, in conjunction with a large number of accessory factors, introduces DSBs into the DNA that are subsequently resected in the 5′ to 3′ direction to expose 3′ single-stranded overhangs [4]. Single-stranded DNA (ssDNA) is incorporated into nucleoprotein filaments containing, among other proteins, the RecA-like strand invasion factors Rad51 and Dmc1. These filaments then engage in the search for homologous repair templates, with a strong bias towards the homologous chromosomes rather than the sister chromatid [5]. Template selection also requires factors, such as the chromosome-associated kinase Mek1, that block the sister chromatid as a possible repair template [5–8]. As DSBs are processed, a proteinaceous structure, the synaptonemal complex (SC), forms along meiotic chromosomes in many organisms [9,10]. Typically, SCs assemble between pairs of homologous chromosomes. However, in some mutant situations, such as yeast *hop2* mutants and *Msh5*$^{-/-}$ mice, synapsis can also occur between chromosomes that are not homologous [11,12]. Components of the SC, notably budding yeast Zip1, Zip2, and Zip3 proteins, as well as the Mer3 helicase and the Msh4/Msh5 complex, are required to ensure that recombination intermediates stably invade the homologous chromosomes and mature into crossovers [13]. Crossover formation is the crucial step in the establishment of physical links between homologous chromosomes, which are manifested cytologically as chiasmata. For an in-depth discussion of meiotic recombination, the reader should refer to a number of excellent reviews [4,9,10,14–16].

The sequence of events surrounding meiotic recombination is highly stereotyped. For example, DSB formation always occurs after DNA replication, and cells exit from G2/prophase only after all DSBs have been repaired. Research conducted in the past decade has uncovered some of the coupling mechanisms, so-called checkpoints, responsible for this temporal coordination

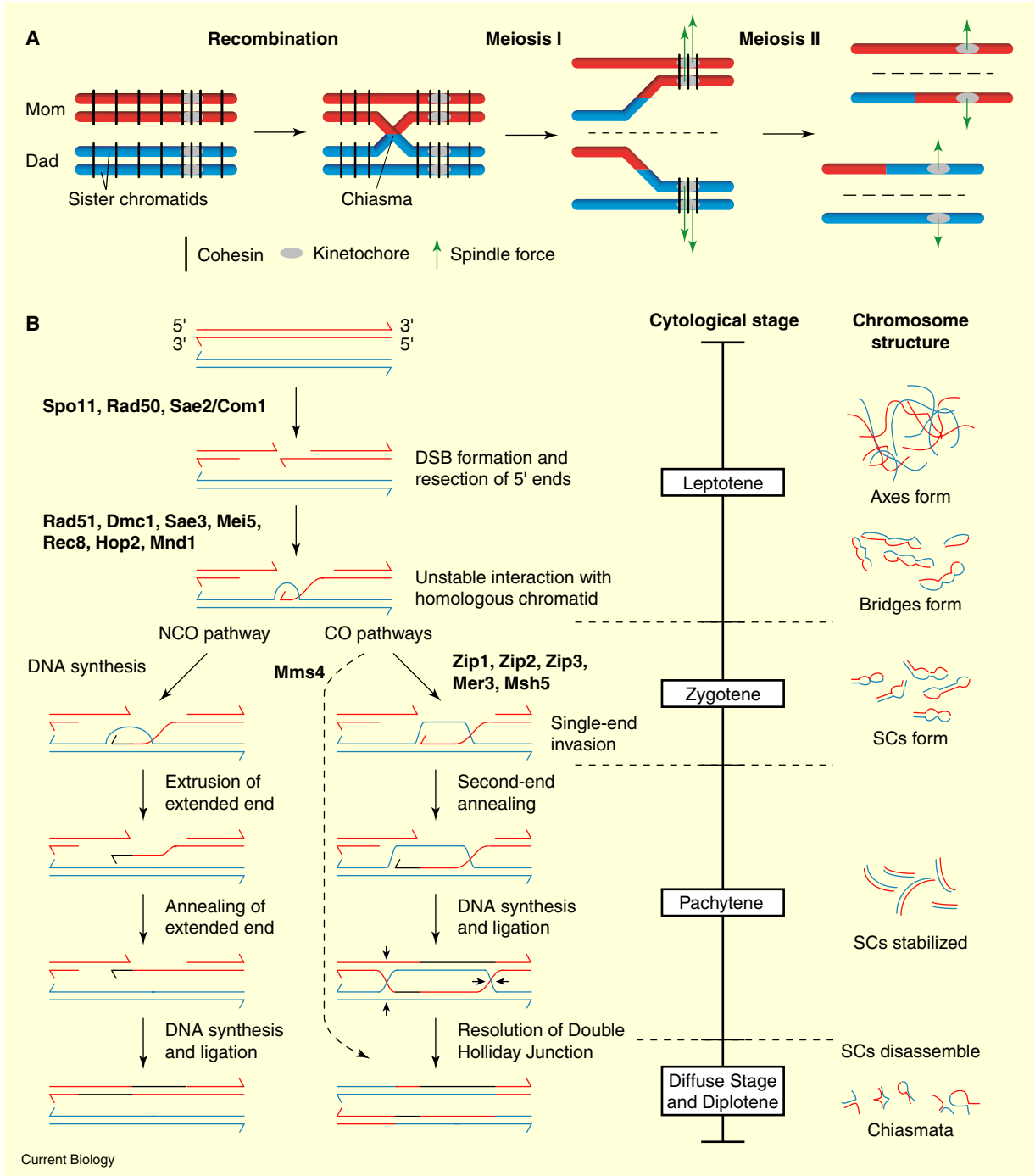

Figure 1. Major events in meiosis.

(A) Meiotic chromosome segregation. Following loss of cohesins at chromosome arms during meiosis I, homologous chromosomes segregate to opposite poles. Subsequently, sister chromatids segregate to opposite poles during meiosis II. (B) Meiotic recombination and corresponding changes in meiotic chromosome structure. DSBs can be processed to result in two types of recombination products: crossovers (COs), where flanking sequences are exchanged, and non-crossovers (NCOs), where flanking sequences are in the parental configuration. Unlike COs produced by the major *ZIP1*-dependent pathway (solid arrows), COs produced by the less active *MMS4*-dependent pathway (dashed arrows) may not be formed via a double-Holliday-junction intermediate and do not exhibit interference — that is, COs produced by the latter pathway are randomly distributed [128]. Recombination factors whose inactivation results in a checkpoint response are indicated next to the stage of recombination for which they are required. Adapted from [14].

between meiotic recombination and cell cycle progression. In the first part of this review, we summarize data that describe a still-poorly understood mechanism — here called the double-strand-break checkpoint — that couples DSB formation to DNA replication. In the subsequent sections, we review the checkpoint mechanisms monitoring DSB repair, commonly referred to as the recombination checkpoint or

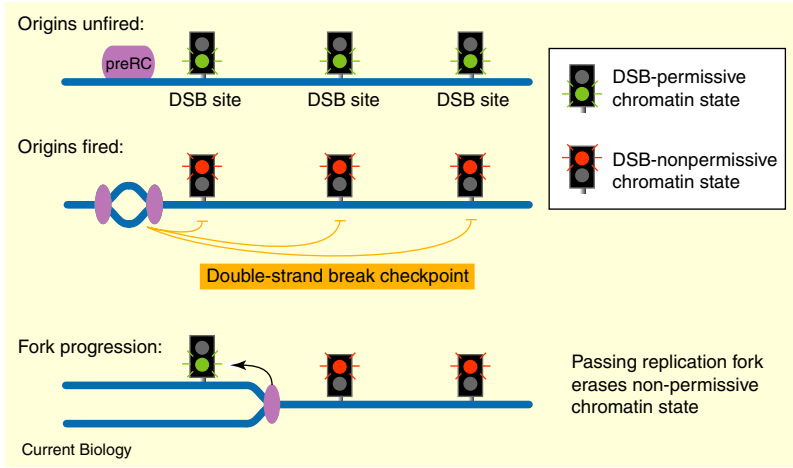

Figure 2. The double-strand-break checkpoint.

Prior to the initiation of DNA replication (pre-RC, pre-replicative complex), potential sites of DSB formation are permissive for DSB formation (indicated by green traffic lights). Once origins of replication have fired, a global signal prevents DSB formation at all potential sites (indicated by red traffic lights). Passage of the replication fork (indicated as purple oval) erases the checkpoint signal and resets potential sites of DSB formation to the permissive state.

pachytene checkpoint, and the possible conservation of these pathways across species.

Throughout this review we will use the term "checkpoint" to describe a mechanism that allows the coupling of two events. In this manner, a checkpoint comprises the following components: a signal (1), which is detected by signal sensors (2), which in turn activate signal-transduction pathways (3) that translate the signal into an output by modifying checkpoint targets (4). On the molecular level, different checkpoints can share sensors and signal-transduction pathways, and can impinge on the same targets. Here, we define checkpoints as distinct if they differ in the signal and at least one of the above components.

The Double-Strand-Break Checkpoint

DSB formation is coupled to the completion of premeiotic DNA replication, presumably to prevent aberrant replication across unrepaired DSBs or double Holliday junctions. Recent work in *S. cerevisiae* and *S. pombe* suggests that meiotic cells monitor the progression of the replication fork and permit DSB formation only once the replication fork has passed. If replication forks are stalled early in S phase as a result of mutations in ribonucleotide reductase (RNR) or the RNR inhibitor hydroxyurea [17,18], DSBs are not formed. Furthermore, Borde and colleagues showed that the coupling of DSB formation to DNA replication is a local chromosomal phenomenon. A delay in replication on one arm of chromosome III selectively delayed DSB formation on that arm without influencing the kinetics of DSB formation on other chromosomes, or even on the other (normally replicating) arm of chromosome III [17].

Interestingly, the mechanisms that ensure this coupling are only active once DNA replication has been initiated. If the firing of origins of replication is prevented — for example, by inactivating the *S. cerevisiae* pre-replication complex component *CDC6* [19] or its *S. pombe* homologue *CDC18* [20] — cells form nearly wild-type levels of DSBs, and, after a delay, repair these DSBs. Thus, the mechanism blocking premature meiotic DSB formation may require the presence of replication forks. This notion is highly reminiscent of the S-phase and DNA-damage checkpoint controls that couple mitosis to DNA replication. Cells preparing for mitosis are able to detect active and/or stalled replication forks, and delay entry into mitosis accordingly. Nevertheless, if DNA replication is does not occur, cells initiate mitosis with unreplicated chromosomes [21–25], presumably due to the absence of a signal that engages the S-phase and/or DNA-damage checkpoints.

The molecular details of the double-strand-break checkpoint are beginning to be understood in *S. pombe*. Inactivation of *S. pombe Atr* (*RAD3*) allows meiotic cells to form DSBs in the presence of stalled replication forks. A number of other DNA-damage checkpoint components, including Rad1, Rad9, Rad17, Rad26, Hus1 and Cds1, are also required for this double-strand-break checkpoint, while the checkpoint kinases Chk1 and Mek1 are not [18,26]. One potential target of the *S. pombe* double-strand-break checkpoint is Mei4, a meiotic transcription factor required for DSB formation [27]. *mei4*$^{+}$ expression levels are severely reduced in the presence of stalled meiotic replication forks, and this downregulation requires the checkpoint kinase Cds1 [26,28]. In *S. cerevisiae*, *Atr* (*MEC1*) does not appear to be required for the meiotic DSB block in response to stalled replication forks [17]. However, we speculate that a checkpoint similar to the *S. pombe* double-strand-break checkpoint may be dependent on redundant activities of both Mec1 and Tel1 (a checkpoint kinase closely related to Mec1). Such a checkpoint would presumably produce a global inhibitory signal preventing DSB formation once premeiotic DNA replication has been initiated (Figure 2). This block would then be inactivated locally by the passing replication fork, perhaps by the production of chromatin states permissive to DSB formation [29].

Checkpoints Monitoring DSB Repair

Once DSBs are introduced, entry into meiosis I is delayed until the completion of meiotic DSB repair. This coupling mechanism becomes apparent in mutants defective in DSB repair. If recombination intermediates persist, meiotic cells arrest or undergo programmed cell death. Such a checkpoint response can be observed in many organisms, including *S. cerevisiae*, *S. pombe*, *C. elegans*, *Drosophila*, and mouse [30–34]. However, over the past years, evidence has accumulated indicating that the response to DSB repair

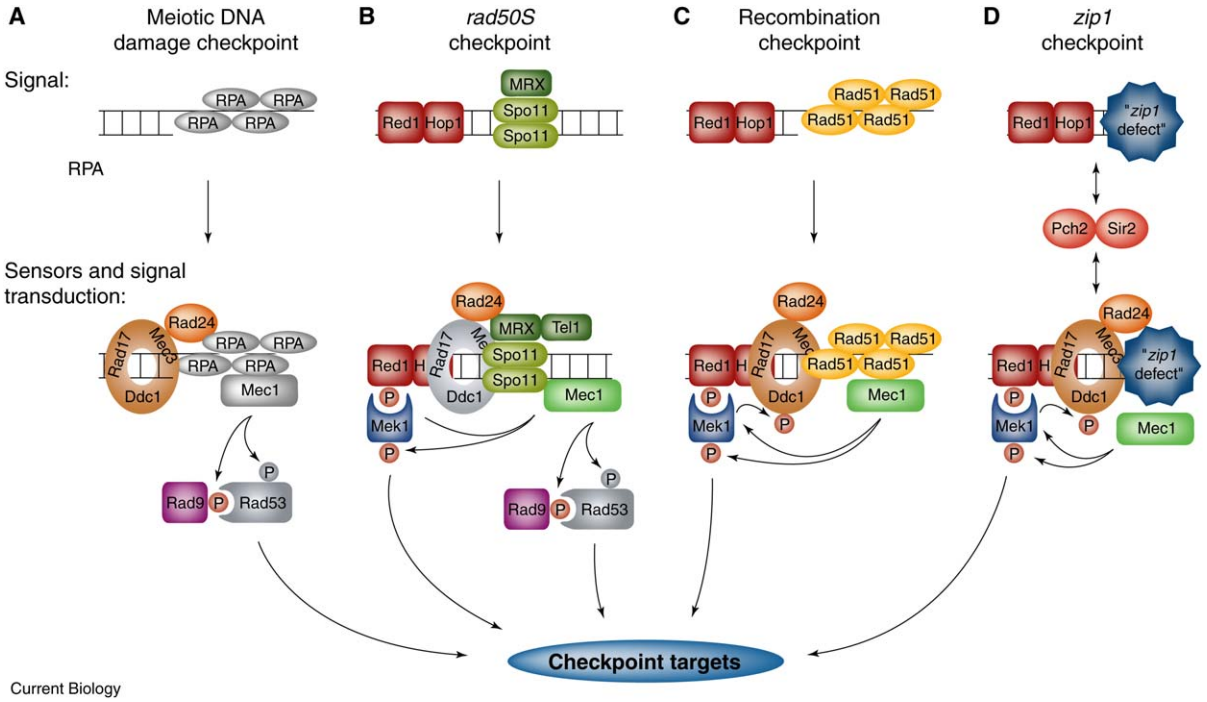

Figure 3. Surveillance of recombinatorial repair in budding yeast.

(A) Meiotic DNA damage checkpoint, (B) *rad50S* checkpoint, (C) recombination checkpoint, (D) *zip1* checkpoint. The potential signal activating each checkpoint is depicted at the top. The proteins comprising the sensors and signal transduction are listed below. Components that have been demonstrated to act in a particular checkpoint are depicted in color, predicted checkpoint components are depicted in grey. P indicates phosphorylation.

defects is far from homogeneous: frequently, both the exact arrest point and the duration of the delay vary depending on the nature of the defect. This could be explained by different severities of the respective defects, and hence quantitative differences in the signaling of a single checkpoint. Increasingly, however, checkpoint proteins are being identified that are only required for the response to a particular type of repair defect, and are dispensable for others. Thus, it appears that the recombination checkpoint or pachytene checkpoint needs to be thought of as a set of distinct pathways. Below, we attempt to define these checkpoint pathways, notably the meiotic DNA-damage checkpoint, the *rad50S* checkpoint, the recombination checkpoint, and the *zip1* checkpoint.

The Meiotic DNA-Damage Checkpoint

Broken DNA ends, and in particular the resulting ssDNA (coated with the ssDNA-binding protein RPA), activate the DNA-damage checkpoint during the mitotic cell cycle [35–37]. The breaks activate the checkpoint kinase Mec1, which with the help of the adaptor protein Rad9 phosphorylates and activates the protein kinases Rad53 and Chk1 [38]. These secondary kinases then phosphorylate a variety of checkpoint targets. Independently of Mec1, the replication factor C-like protein Rad24 also recognizes ssDNA, and loads a PCNA-like clamp consisting of Rad17, Ddc1, and Mec3 onto broken ends. This is required for full activation of Mec1 [38,39].

Evidence that the DNA damage checkpoint is also active prior to the meiotic divisions comes from the study of budding yeast *cdc13* mutants. At the restrictive temperature, temperature-sensitive *cdc13* mutants accumulate large amounts of ssDNA at the telomeres [35]. During the mitotic division, this triggers the DNA-damage checkpoint and leads to a Rad9-dependent cell-cycle arrest at metaphase [36]. Inactivation of *CDC13* prior to the meiotic divisions leads to an arrest in G2/prophase that also depends on *RAD9* [40]. Disruption of the RecQ-family helicase Sgs1 likely also triggers the meiotic DNA damage checkpoint. *sgs1* mutants exhibit chromosome instability and a Rad24-, Ddc1-, and Mec3-dependent delay in meiotic G2/prophase. Importantly, this delay occurs even in the absence of Spo11-induced DSBs, suggesting a general defect in DNA metabolism that is sensed by the checkpoint (Figure 3A) [41].

Mec1, Rad24, Rad17, Ddc1, and Mec3 appear to be involved in all meiotic (and mitotic) checkpoints sensing chromosomal integrity (see below). However, the meiotic DNA damage checkpoint stands apart from the other meiotic checkpoints in two ways. First, unlike the recombination checkpoint and the *zip1* checkpoint, it exhibits a functional requirement for Rad9 (and presumably Rad53) [34,42]. Second, the chromosome structure proteins Red1 and Mek1, which play an important role in the *rad50S* checkpoint, recombination checkpoint, and *zip1* checkpoint, are dispensable for the meiotic DNA damage checkpoint [41,43] (Figure 3). Thus, even though both meiotic recombination and DNA damage (or stalled replication forks) lead to the formation of DSBs that are repaired through ssDNA intermediates, different surveillance

mechanisms are responsible for detecting these DNA lesions and halting cell-cycle progression.

A role for the meiotic DNA-damage checkpoint in detecting non-recombination-induced DNA lesions appears to be conserved across species. Radiation-induced DNA damage triggers programmed cell death in mouse spermatocytes and in *C. elegans* oocytes. In both cases, germ-cell apoptosis depends on p53, a key regulator of DNA-damage-dependent apoptosis in mitotic cells [31,44], suggesting that a meiotic DNA-damage checkpoint is also active in mice and worms.

The *rad50S* Checkpoint

Unlike the DNA-damage checkpoint described above, the checkpoints described in the following sections appear to respond to particular meiosis-specific recombination intermediates. *rad50S*-like mutations, a set of non-null alleles of *RAD50*, as well as null mutations in *SAE2/COM1*, result in a repair defect early during recombination (refer to Table 1, in which the mutants are grouped according to which checkpoint they activate). In these mutants, Spo11 remains covalently attached to the ends of DSBs, and breaks are not resected [45]. *rad50S*-like mutants delay in G2/prophase for several hours. (Note, however, that eventually these cells enter meiosis despite the persistence of breaks, which may be a form of adaptation — see below). A *rad50S* checkpoint may also be active in mice. Although spermatocytes of *Rad50*$^{S/S}$ mice do not enter a permanent meiotic block, they exhibit increased apoptosis, resulting in testes that are progressively depleted of mature spermatocytes [46].

Like all other checkpoints, the *rad50S* checkpoint requires the DNA damage sensors Mec1 and Rad24 [47]. However, because ssDNA does not appear to be exposed in *rad50S*-like mutants, it is unclear how the damage-sensing proteins recognize the recombination intermediates. Based on the observations that neither *rad50S* mutants lacking the protein kinase Tel1, nor *mre11-58* mutants (which also accumulate Spo11-linked DSBs) exhibit a delay, it has been suggested that the Mre11/Rad50/Xrs2 (MRX) complex and Tel1 are the primary sensors of protein-linked DSBs [47]. Consistent with this idea, Tel1 and the MRX complex appear to be exclusively required for the *rad50S* checkpoint [47].

Once damage is sensed, the checkpoint signal is then relayed through Rad9 (and presumably Rad53) — this is similar to the meiotic DNA-damage checkpoint, but further distinguishes the *rad50S* checkpoint from the recombination checkpoint and the *zip1* checkpoint. Unlike the meiotic DNA-damage checkpoint, however, the chromosomal structure proteins Mek1, Red1 and Hop1 are also required for *rad50S* checkpoint function [43,47,48] (Figure 3B). Mek1 is a meiosis-specific paralogue of the protein kinase Rad53 and also exhibits Mec1-dependent phosphorylation [49]. It is possible that Mek1 substitutes for some functions of Rad53 in the context of meiotic recombination intermediates. In the mitotic DNA-damage checkpoint, Rad9 is phosphorylated by Mec1, which allows Rad53 to bind to Rad9 through its phospho-specific FHA domain. This recruitment by phospho-Rad9 then allows Mec1 to phosphorylate Rad53 [38,50]. In this context it is interesting to note that Mek1 binds to phosphorylated Red1 with its phospho-specific FHA domain [6] and that Red1 is required for the phosphorylation of Mek1 [49]. In this way, Red1 may act as an adaptor between Mec1 and Mek1, similar to role of Rad9 in the activation of Rad53.

Table 1. Speculative classification of budding yeast mutants exhibiting a checkpoint-dependent G2/prophase delay[1].

Meiotic DNA-damage checkpoint	*rad50S* checkpoint	Recombination checkpoint	*zip1* checkpoint
cdc13	*rad50S*	*dmc1*	*mms4*
sgs1	*com1/sae2*	*sae3*	*zmm* mutants
rad51?		*mei5*	(23°C and 33°C)[2]
		mnd1	
		hop2	
		rec8	
		zmm mutants (33°C)[2]	

[1] It is possible that some of the indicated mutants activate more than one checkpoint.
[2] *zmm* mutants are *zip1*, *zip2*, *zip3*, *mer3*, and *msh5* [13].

The kinase activity of Mek1 is necessary to maintain the checkpoint-dependent arrest of recombination mutants [6,51,52], and both Ddc1 and Red1 have been reported to exhibit Mek1-dependent phosphorylation [51–53]. However, the question whether Red1 is a substrate of Mek1 has been controversial. Indeed, recent experiments using kinase-specific ATP analogues indicate that Red1 is not a direct substrate of Mek1 [6], and that the phosphorylation of Red1 is not in fact Mek1-dependent, but rather depends on Clb5/Clb6-CDK and a novel meiotic protein kinase (T.-F. Wang, personal communication).

Aside from their checkpoint roles, Mek1, Red1 and Hop1 are central components of meiotic chromosomes and are involved in several aspects of meiotic recombination [5–7,48,52]. This raises the possibility that the meiotic chromosomal context is important for sensing unprocessed DSBs and/or relaying the checkpoint signal. It is also possible that structural defects of chromosome axes are sensed by the checkpoints. Which aspect of chromosome structure, if any, is involved in checkpoint signaling is an important question to be addressed.

The Recombination Checkpoint

The recombination checkpoint has been investigated mostly in mutants lacking factors required for the initial strand-invasion step of meiotic recombination, such as *DMC1*, *HOP2*, and others (Figure 1B, Table 1); these mutants, unlike *rad50S*-like mutants, are competent to remove Spo11 from the ends of DSBs. However, due to a failure to engage in interhomolog repair, these mutants accumulate large amounts of hyperresected DSBs and exhibit a delay in G2/prophase that is substantially more pronounced than that caused by activation of the *rad50S* checkpoint [11,54,55].

The hyperresection of DSBs observed in homology-search mutants leads to large amounts of Rad51-coated ssDNA, and it has been suggested that the Rad51 nucleoprotein filament may constitute a signal

recognized by the recombination checkpoint [42,56]. Consistent with this interpretation, a *rad50S* mutation (which prevents formation of the Rad51 filament) strongly reduces the delay of *dmc1* mutants [54]. Furthermore, in the absence of Rad51, the delay exhibited by *dmc1* mutants is substantially reduced [56]. Indeed, *rad51* mutants, which also accumulate large amounts of ssDNA, exhibit only a modest delay in meiotic G2/prophase [56] (this delay is presumably dependent on the meiotic DNA-damage checkpoint). Similar arguments can also be made for a signaling role for the Dmc1 nucleoprotein filament. *hop2* and *mnd1* mutants, which accumulate both Rad51 and Dmc1 filaments, exhibit a more pronounced cell cycle arrest than *dmc1* mutants [11]. In support of the notion that Dmc1 and Rad51 filaments constitute additive signals, lack of *DMC1* reduces the G2/prophase delay of *hop2* mutants to the level of *dmc1* single mutants [57]. However, lack of *RAD51* does not alleviate the arrest of *hop2* mutants [57]. It is therefore also possible that the absence of *RAD51* and *DMC1* prevents the recombination intermediates of *dmc1* and *hop2* mutants, respectively, from being processed into structures that are detected by the checkpoint.

The recombination checkpoint shares components with the *rad50S* checkpoint and the DNA-damage checkpoint, including Mec1, Rad24, Rad17, Mec3 and Ddc1 [34,42,53] (Figure 3C). In their absence, *dmc1* mutants do not experience a G2/prophase delay, and initiate the first meiotic division despite a large number of unrepaired DSBs [42,53,58]. In contrast to the *rad50S* checkpoint and the meiotic DNA damage checkpoint, however, neither Rad9 nor Tel1 play a role in the recombination checkpoint [42,47].

In a scenario similar to the *rad50S* checkpoint, a macromolecular assembly of the meiotic chromosomal proteins Hop1, Red1 and Mek1 is thought to provide a framework for the activation of the recombination checkpoint [43,48,52,59,60]. The correct localization of these proteins to chromosomes appears to depend in part on the histone methyltransferase Dot1 [61]. The recombination checkpoint response of *dmc1* mutants is completely eliminated in cells lacking *HOP1*, *RED1*, or *MEK1*, and is much reduced in the absence of *DOT1* [19,43,61].

The recombination checkpoint is widely conserved. Mice lacking *Dmc1*, *Hop2*, or *Msh5* (and a growing list of other factors) experience a block in gametogenesis followed by widespread apoptosis of germ cells [62]. Also, inactivation of *Spo11* or *Mei1* (another factor likely required for DSB formation) in a $Dmc1^{-/-}$ or $Msh5^{-/-}$ mutant background results in the bypass of the cell-cycle arrest [63–65], suggesting that, like in yeast, a checkpoint in mouse detects DSBs and/or subsequent repair intermediates. To date, however, no components of the mouse recombination checkpoint have been identified. $Atm^{-/-}$ mutants, which show a profound defect in the somatic DNA-damage checkpoint, exhibit a meiotic arrest very similar to $Dmc1^{-/-}$ mutants [66,67]. This suggests that *Atm* has a direct role in DSB repair. *Atm* may still be involved in the checkpoint, but given that $Atm^{-/-}$ mutants arrest, other aspects of the checkpoint are clearly intact. The analysis of another likely checkpoint component, *Atr*, has been precluded by the fact that loss of *Atr* is embryonic-lethal [68,69]. Nevertheless, cytological evidence is consistent with a role for *Atr* in the recombination checkpoint [70,71]. A number of other somatic checkpoint factors have been implicated in the recombination checkpoint based on cytological data, including TopBP1 [64,72] and Rad1 [73].

As observed in mouse gametogenesis, cells with meiotic DSB repair defects are removed by apoptosis in the female germline of *C. elegans* hermaphrodites [31,74]. The damage-dependent programmed cell death is induced in the pachytene stage of meiotic G2/prophase and requires the checkpoint factors MRT-2, HUS-1, HPR-9 and RAD-5 [31,75] (Table 2). MRT-2, HUS-1, and HPR-9 likely act as a complex in parallel with RAD-5 [76]. It is unclear whether the checkpoint kinase CHK-2 has a role in the worm recombination checkpoint. A mutation in *chk-2* does prevent apoptosis in oocytes lacking *rad-51*. However, this may be due to a defect in DSB formation rather than inactivation of the checkpoint [77,78]. Not all worm repair mutants trigger checkpoint-dependent apoptosis. No programmed cell death is elicited in oocytes lacking the SC components HIM-3 or REC-8, despite defects in synapsis and an accumulation of RAD-51 foci (a cytological marker for unrepaired DSBs) [77]. Given that *him-3* is related to *HOP1* (Table 2), this may also indicate a checkpoint role for HIM-3.

The recombination checkpoint of *S.pombe* has long eluded detection, because most *S. pombe* repair mutants do not exhibit dramatic cell-cycle delays, and even mutants completely deficient in DSB repair progress through meiosis [79]. Careful analysis of meiotic cell-cycle kinetics, however, indicated that repair-deficient *meu13* (*hop2*) mutants delay entry into meiosis I by approximately 30 minutes [33,80]. The *meu13* delay depends on the formation of DSBs and requires a set of conserved checkpoint factors, including Rad17, Rad9, Rad1, Rad3, Mek1, Cds1, and Cut5 [33,72,80], most of which are also involved in the recombination checkpoint in other organisms (Table 2).

Evidence for a recombination checkpoint in *Drosophila* oocytes comes from the analysis of *spnA*, *spnB*, *spnD*, and *okra* mutations, which disrupt several Rad51-like factors [30,81,82]. These mutants exhibit defects in the formation of the karyosome, a chromosome structure specific for meiotic G2/prophase. Furthermore, the subsequent patterning of the eggshell is abnormal in these mutants due to a failure to accumulate wild-type levels of the patterning protein Gurken [83]. Both defects are suppressed in mutants disrupting the *SPO11* homolog *Mei-W68*, suggesting that they result from a defect in DSB repair. Furthermore, both karyosome and egg-patterning defects depend on the checkpoint factors *Mei-41* and *Chk2*, and Chk2 is phosphorylated in a Mei-41-dependent manner in *spnB*, *spnD* and *okra* mutants [30,84]. Several other DNA damage checkpoint factors including the Chk1-homolog *grapes*, and the *Mei-41* interacting factor *Mus304* are likely not involved in the recombination checkpoint [84,85].

The *zip1* Checkpoint

The stable invasion of the homolog by a subset of DSBs that will later be repaired as crossovers requires the SC

Table 2. Meiotic checkpoint proteins and their homologues.

S. cerevisiae	*S. pombe*	*C. elegans*	*Drosophila*	Mouse	Function
Checkpoint Factors					
Rad24	**Rad17p**	HPR-17	Rad17	Rad17	RFC-like clamp loading factor
Rad17	**Rad1p**	**MRT-2**	Rad1	Rad1	PCNA-like clamp (Rad17/Mec3/Ddc1)
Mec3	Hus1p	**HUS-1**	Hus1-like	Hus1	PCNA-like clamp
Ddc1	**Rad9p**	**HPR-9**	Rad9	Rad9	PCNA-like clamp
Mec1	**Rad3p**	ATL-1	**Mei-41**	Atr	PI3kinase-like kinase
Mek1	**Mek1p**	-	-	-	Meiotic kinase (Rad53 paralogue)
Red1	Rec10p	-	-	-	Meiotic chromosomal protein
Hop1	Hop1p	HIM-3	-	-	Meiotic chromosomal protein
Dot1	-	-	Gpp	Dot1L	Histone methyltransferase
Rad53	**Cds1p**	(CHK-2)	**Chk2**	Chk2	Kinase with FHA domain
Tel1	Tel1p	ATM-1	Tefu	Atm	PI3kinase-like kinase
Rad9	Crb2p	BRC-1?	-	Brca1?	Adaptor protein with BRCT domain
Mre11	Rad32p	MRE-11	Mre11	Mre11	Nuclease, MRX complex component
Xrs2	Nbs1p	-	Nbs	Nbs1	MRX complex component
Rad50	Rad50p	RAD-50	Rad50	Rad50	MRX complex component
Sir2	Sir2p	several	Sir2	several	Histone deacetylase
Pch2	-	**PCH-2**	-	-	ATPase
Dpb11	**Cut5p**	-	Mus101	TopBP1	Protein with BRCT domain
Tel2	-	**RAD-5**	-	-	DNA binding protein
(Chk1)	Chk1p	CHK-1	(Grp)	Chk1	Protein kinase
Targets					
Cdc28	**Cdc2p**	CDK-1	Cdc2	Cdc2	Cyclin-dependent kinase
Swe1	(Wee1p)	several	**Wee1**	Wee1	Tyrosine kinase of Cdc28
(Mih1)	**Cdc25p**	CDC-25	Twe	several	Tyrosine phosphatase of Cdc28
Ndt80	-	-	-	-	Transcription factor
Sum1	-	-	-	-	Transcriptional repressor
-	-	**CED-1**	(p53)	**p53**	Transcription factor
several	several	several	**Vas**	several	Translation initiation factor
Adaptation					
Glc7	several	several	several	several	Protein phosphatase 1
Fpr3	Fkbp39p	several	several	several	FK506-binding protein

Protein names in bold indicate factors whose meiotic checkpoint role has been demonstrated experimentally. Names in parentheses indicate factors for which experiments did not identify a meiotic checkpoint role. RFC – replication factor C, PCNA – proliferating cell nuclear antigen, PI3kinase – 3-phospho inositol kinase, FHA domain – forkhead associated domain, BRCT domain – Brca1 carboxy terminal domain, MRX complex – Mre11/Rad50/Xrs2 complex, Gpp – Grappa, Tefu – Telomere fusion, Grp – Grapes, Twe – Twine, Vas – Vasa.

components Zip1, Zip2, and Zip3, as well as a set of other recombination factors (Figure 1B). In their absence, cells undergo a temperature-dependent delay in G2/prophase [13,86–88]. The best-analyzed checkpoint response is the delay of *zip1* mutants, which requires Rad24, Rad17, Ddc1, Mec3, and Mec1, as well as Red1, Hop1 and Mek1 [34]. The nature of the checkpoint signal in these mutants is unclear. However, in contrast to the other checkpoints, lesion detection requires the ATPase Pch2 [89]. Pch2 is specifically required for the *zip1* checkpoint, because inactivation of *PCH2* eliminates the cell-cycle delay of *zip1*, *zip2*, and *mms4* mutants [89,90], but does not impair the arrest of *hop2*, *mnd1* and *sgs1* mutants [34,41,91]. The bypass of the *dmc1* arrest in the absence of *PCH2* appears to depend on the strain background [19,89]. Pch2 localizes to the nucleolus; this localization appears to be important for Pch2 function and depends both on Dot1 and the histone deacetylase Sir2 [61,89]. The exact role of Pch2 in the *zip1* checkpoint is, however, unclear. Pch2 may be involved in the production or accumulation of the recombination intermediate detected by the *zip1* checkpoint, because *PCH2* also plays a direct role in recombination (V. Börner, personal communication) [19].

A Synapsis Checkpoint?

Not all meiotic checkpoints respond to DSB-derived recombination intermediates. Some mutant mice, such as *Spo11*$^{-/-}$ or *Mei1*$^{-/-}$ mice, also exhibit meiotic blocks in the absence of DSBs [92–94], suggesting that some aspect of synapsis, or lack thereof, may constitute another checkpoint signal. The block in *Spo11*$^{-/-}$ and *Mei1*$^{-/-}$ spermatogenesis and oogenesis occurs at a later stage than the block in *Dmc1*$^{-/-}$ or *Msh5*$^{-/-}$ meiocytes [63–65,95], supporting the notion that the defects of *Spo11*$^{-/-}$ and *Mei1*$^{-/-}$ germ cells are potentially detected by a distinct checkpoint. In *C. elegans*, mutations in the SC component SYP-1, or deletions of the *cis*-acting chromosome segments required for synapsis (so-called pairing centers), cause checkpoint-dependent apoptosis of germ cells. Germ cell loss is only partially rescued if DSB formation is eliminated, suggesting the possibility of a DSB-independent synapsis checkpoint [96]. Interestingly, DSB-independent apoptosis in worm synapsis mutants requires the activity of PCH-2 [96], suggesting a conserved role for Pch2 in checkpoint signaling. However, it is unclear whether a similar synapsis checkpoint also exists in budding yeast, because the absence of DSBs does not cause a checkpoint response in yeast and may in fact accelerate

meiotic progression [97]. Either the absence of synapsis is not detected in budding yeast, or in this organism the intermediates sensed by the synapsis checkpoint cannot be formed in the absence of DSBs.

Signal Integration

Some recombination mutants may activate more than one checkpoint. A striking example of additive checkpoint activation comes from the analysis of *zmm* mutants, a class of mutants in budding yeast that includes *zip1*, *zip2*, *zip3*, *mer3*, and *msh5*. These mutants are proficient in strand invasion at 23ºC, albeit with a delay, but fail to form single-end invasion intermediates at 33ºC. Concomitantly, *zmm* mutants only delay in G2/prophase at 23ºC, but completely arrest at 33ºC [13], presumably because the failure to process Rad51 and Dmc1 filaments at 33ºC activates the recombination checkpoint in addition to the *zip1* checkpoint. Given that several checkpoint components (e.g. Mec1) are shared between different checkpoints, we speculate that these factors may serve as signal integrators that translate the inputs of the various checkpoints into a corresponding cell-cycle delay.

Checkpoint Targets

The activated checkpoint factors transmit their signal to downstream targets that control cell-cycle progression, DNA repair, programmed cell death and, in some cases, development. Most studies concerning checkpoint targets have been conducted in the context of the recombination checkpoint and the *zip1* checkpoint. Whether the different checkpoints activate distinct targets has thus far not been investigated.

Cell-Cycle Progression

The major cell-cycle targets of the recombination checkpoint and *zip1* checkpoint are cyclin-dependent kinases, protein kinases composed of a catalytic kinase subunit (CDK) and a regulatory cyclin subunit. CDKs, when associated with cyclin A or B in higher eukaryotes, or Clb1, 3, or 4 in budding yeast, drive cells into meiosis (reviewed in [98]). Both the CDK subunit and the cyclin subunits are subject to inhibitory regulation in response to checkpoint activation. CDKs are inhibited in a checkpoint-dependent manner by the dual specificity protein kinase Wee1, which phosphorylates the CDK on a crucial threonine and tyrosine (T14, Y15). In budding yeast *hop2* mutants, Swe1 (budding yeast Wee1, Table 2) is hyperphosphorylated and stabilized, and inactivation of *SWE1* allows the partial bypass of checkpoint-dependent delay [99,100]. In *Drosophila spnB* (*rad51*-like) mutants, Wee1 is modified in a Chk2-dependent manner [84] indicating that similar to the case in budding yeast, cell-cycle arrest also occurs by modulating Wee1 activity. The *S. pombe* recombination checkpoint, on the other hand, does not regulate CDKs through Wee1. Rather, CDKs remain phosphorylated on Y15 during the *hop2* delay, owing to Mek1-dependent inhibition of Cdc25, a CDK-Y15 phosphatase [33,80]. In contrast, Cdc25 (Mih1) does not play a checkpoint role in *S. cerevisiae* [100]. Despite subtle differences in regulation, it appears that CDK is a conserved meiotic checkpoint target.

In budding yeast, checkpoint activation also keeps the transcript (and protein) levels of the B-type cyclins low [101,102]. The promoters of meiotically expressed B-type cyclins contain a short DNA element called the middle sporulation element (MSE) that is found in many other so-called 'middle genes' whose expression is induced once cells exit from meiotic G2/prophase and enter meiosis I. Meiotic cyclin expression is controlled by two transcription factors, Ndt80 and Sum1. Ndt80 is a transcriptional activator that binds to the MSE and induces middle gene expression [101,102]. Sum1 is a transcriptional repressor that recognizes a DNA element that overlaps with the MSE, and thereby competes with Ndt80 for MSE binding at a subset of middle genes [103–105]. Both Ndt80 and Sum1 are under checkpoint control. *NDT80* expression levels are kept low during checkpoint activation, and overexpression of *NDT80* allows a partial bypass of the *dmc1* G2/prophase delay [99,106]. Furthermore, the extensive phosphorylation of Ndt80 is reduced, albeit not eliminated, in a checkpoint-dependent manner in *dmc1* or *zip1* cells [101,106,107]. Ndt80 phosphorylation has been shown to depend in part on the meiotic kinase Ime2 and the Polo kinase Cdc5 [108,109], but it is unclear whether these kinases are involved in the checkpoint-dependent phosphorylation changes of Ndt80. Sum1, on the other hand, appears to be regulated at the level of protein stability. The level of Sum1 protein transiently drops as meiotic cells progress from G2/prophase into meiosis I, despite increasing levels of *SUM1* mRNA [104]. Moreover, Sum1 protein remains at high levels while cells are delayed in G2/prophase, and *SUM1* is required for the checkpoint arrest of *dmc1* mutants [99,104]. The checkpoint factors controlling Ndt80 phosphorylation and the drop in Sum1 protein levels remain to be identified.

DSB Repair

At least in budding yeast, the meiotic checkpoints also induce DSB repair. For example, Rfa2, a subunit of the ssDNA-binding protein complex RPA, is hyperphosphorylated in *dmc1* mutants. This phosphorylation is dependent on *MEC1* and DSBs, and is thought to be required for DSB repair [110,111]. Furthermore, Rad24 interacts with the repair protein Rad57 specifically during meiosis, suggesting another link between checkpoint surveillance and repair [53].

Apoptosis

In multicellular organisms, programmed cell death frequently eliminates repair-defective meiocytes, and the apoptotic machinery appears to be an important checkpoint target in both mouse and *C. elegans*. Reports differ as to whether *p53* is required for the induction of apoptosis in mouse repair mutants. The finding that inactivation of *p53* (or the CDK inhibitor $p21^{Cip1}$) allows $Atm^{-/-}$ mutant spermatocytes to partially overcome the G2/prophase arrest [32] has been confirmed by some, albeit not all, subsequent reports [112,113]. *p53*-independent apoptosis has been observed in spermatocytes harboring certain chromosomal translocations [44], while both *p53*-dependent and *p53*-independent apoptosis of spermatocytes occurs in several other mouse meiotic mutants [67,114]. These findings suggest that only a subset of the checkpoint pathways that are active during mouse spermatogenesis trigger *p53*-dependent apoptosis.

In *C. elegans*, apoptosis of *rad-51* mutant oocytes is induced through the action of the *p53*-homolog *ced-1* [77]. Prior to the pachytene stage of meiotic G2/prophase, translation of *ced-1*/*p53* mRNA is inhibited by the RNA-binding protein GLD-1 [115]. GLD-1 levels drop during pachytene, leading to an increase in CED-1 protein levels in pachytene oocytes, which in *rad-51* mutant oocytes allows the recombination checkpoint signal to be translated into a proapoptotic signal [115].

Development

In budding yeast, checkpoint activation inhibits spore development concomitantly with cell-cycle progression as a consequence of the inhibition of the transcription factor Ndt80, which controls the expression of genes required for both processes [101,102]. Curiously, the *Drosophila* recombination checkpoint affects the patterning of the embryo. The recombination defective *spn* mutants exhibit defects in karyosome formation and Gurken accumulation similar to that of mutants lacking the translation initiation factor *vasa*. However, unlike the *spn* mutants, the *vasa* mutant phenotype is not *mei-41*-dependent, suggesting that *vasa* acts downstream of the *Drosophila* recombination checkpoint. Consistent with this, Vasa is modified in a Chk2-dependent manner in *spnB* mutants [30,84].

Adaptation

The meiotic checkpoints, at least in budding yeast, appear to be less responsive to DNA damage than the mitotic DNA-damage checkpoint. In mitotic cells, a single irreparable DSB can trigger an extended checkpoint delay [116,117]. Meiotic cells, on the other hand, are able to progress through meiosis and form spores even if a DSB remains unrepaired [118]. Moreover, despite the large number of DSBs typically introduced during meiosis, the cell-cycle block of many repair mutants is transient. As indicated above, exogenous DNA damage may be sensed differently than recombination intermediates, which may partially explain the less dramatic response. An additional, non-exclusive possibility is that meiotic cells adapt more easily to damage than do mitotic cells. Adaptation is known to occur in mitotic cells and allows cells with very limited DNA damage to overcome the checkpoint-dependent block and progress through the cell cycle [117,119].

Adaptation has also been demonstrated for the recombination checkpoint in budding yeast. A factor likely involved in this process is protein phosphatase 1 (PP1). Overexpression of the catalytic subunit of PP1, Glc7, shortens the G2/prophase delay of many meiotic repair mutants and can alleviate the arrest caused by constitutively active *MEK1* [19,49]. Glc7 associates with a variety of targeting factors that provide substrate-specificity. In one strain background, inactivation of *GIP1*, which encodes a meiosis-specific substrate-targeting factor of Glc7, causes a block in meiotic G2/prophase [49]. However, *gip1* mutants do not arrest in other strain backgrounds [120], suggesting that there may be other specificity factors acting redundantly with Gip1. Glc7 is inhibited by the FK506-binding protein Fpr3 [19]. Fpr3 interacts with Glc7 through its proline isomerase (PPIase) domain, and the PPIase domain of Fpr3, though not its catalytic activity, is required to prevent premature adaptation. Mutations affecting the Fpr3 PPIase domain, as well as inactivation of Fpr3 using the small-molecule inhibitor rapamycin, cause a reduced checkpoint delay in many repair mutants, similar to the overexpression of *GLC7*. Furthermore, co-overexpression of *GLC7* and *FPR3* re-establishes the checkpoint delay [19]. Thus, adaptation to persistent recombination intermediates depends on the modulation of PP1 activity. Glc7 may allow adaptation by dephosphorylating Red1 or Red1-dependent targets. Indeed, Glc7 interacts with Red1, and Red1 can be dephosphorylated by Glc7 *in vitro* [49,121]. Moreover, a mutant of Glc7 that fails to interact with Red1 (*glc7-T152K*) exhibits a DSB-dependent cell-cycle arrest in meiotic G2/prophase that is bypassed by the inactivation of *RED1* [49].

Conclusion and Future Directions

Much progress has been made in recent years towards a molecular dissection of checkpoint mechanisms monitoring meiotic recombination. However, much work still needs to be done, especially in multicellular organisms, where the molecular details of the various checkpoints monitoring meiotic recombination need to be elucidated. Particular attention should also be given to the relationship between sexual dimorphism and checkpoint control. In mouse, it has been repeatedly observed that DSB repair defects cause much stronger arrests in males than in females [122]. Perhaps different repair capacities or different checkpoint stringencies underlie these apparent sex differences, although it has recently been suggested that the different speeds with which male and female meiocytes progress through meiosis, as well as failures to correctly associate X and Y chromosomes, may in part be to blame for the observed differences in meiotic arrest [123].

One general problem that has hampered analysis of the recombination checkpoint thus far is that the majority of checkpoint factors are also directly involved in meiotic DSB repair [5,124,125]. In budding yeast, the choice of repair template in particular appears to be affected in many checkpoint mutants. Cells lacking *HOP1*, *RED1*, *MEK1,* or *DOT1* can repair the majority of DSBs in a *DMC1*-independent manner [6,7,43,61], employing an alternative sister-directed repair pathway that requires the recombination factor Rad54 [7,43,126]. Similarly, mutations in *MEC1*, *RAD17*, *RAD24* and *MEC3* cause increased levels of illegitimate repair from the sister chromatid or from ectopic positions [58,127], although how these factors function to direct template choice is at present not understood. These additional roles in template choice have made it difficult to clearly define checkpoint functions for most factors. However, *dmc1 red1* double mutants do not delay meiotic cell-cycle progression, even if *DMC1*-independent repair is eliminated by mutation of *RAD54* (cited in [43]), supporting a checkpoint role for Red1. Furthermore, several cytological [42,60] and genetic assays [19] are now available that should help to determine whether the bypass of a meiotic G2/prophase arrest is in fact the consequence of an inactivated checkpoint or rather the consequence of accelerated repair. In the context of template choice, it would also be interesting to investigate whether mitotic

DNA-damage checkpoint factors have a related role in rendering the sister chromatid the preferred DSB-repair template during mitotic growth.

What other frontiers can be defined for the recombination checkpoint? Apart from the identification of additional checkpoint factors to fill the gaps in our understanding of the checkpoint pathways, an important open question is the identity of the lesions that trigger a checkpoint response. We postulate here that several intermediates in the recombination pathway serve as signals to activate different checkpoint pathways. Given the plethora of highly efficient DNA-repair pathways that are active in the cell at any point, it will require some very clever approaches to delineate which repair intermediate activates which pathway. Furthermore, many of the checkpoint factors are members of multiple checkpoint-signaling cascades, and all pathways ultimately lead to cell-cycle arrest in meiotic G2/prophase, and/or apoptosis. Whether this means that the signals converge into one single pathway, or whether the checkpoint components required for more than one checkpoint are assembled into distinct signaling modules by checkpoint-specific factors, remains to be determined.

In summary, research conducted in recent years on the checkpoint regulation of meiotic recombination has substantially increased our understanding of the molecular nature of these surveillance mechanisms. These insights also raised many more questions, and we are looking forward to new discoveries that will shed further light on these important guardians of genomic integrity.

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