The Meiotic Checkpoint Network: Step-by-Step through Meiotic Prophase

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The generation of haploid gametes by meiosis is a highly conserved process for sexually reproducing organisms that, in almost all cases, involves the extensive breakage of chromosomes. These chromosome breaks occur during meiotic prophase and are essential for meiotic recombination as well as the subsequent segregation of homologous chromosomes. However, their formation and repair must be carefully monitored and choreographed with nuclear dynamics and the cell division program to avoid the creation of aberrant chromosomes and defective gametes. It is becoming increasingly clear that an intricate checkpoint-signaling network related to the canonical DNA damage response is deeply interwoven with the meiotic program and preserves order during meiotic prophase. This meiotic checkpoint network (MCN) creates a wide range of dependent relationships controlling chromosome movement, chromosome pairing, chromatin structure, and double-strand break (DSB) repair. In this review, we summarize our current understanding of the MCN. We discuss commonalities and differences in different experimental systems, with a particular emphasis on the emerging design principles that control and limit cross talk between signals to ultimately ensure the faithful inheritance of chromosomes by the next generation.

Meiosis is a specialized chromosome segregation process, wherein a diploid parent cell gives rise to haploid gametes (Kleckner 1996; Petronczki et al. 2003; Gerton and Hawley 2005). The reduction in ploidy is essential for gametogenesis in all sexually reproducing organisms and is achieved by a single round of DNA replication followed by two chromosome segregation events that uniquely segregate not only sister chromatids but also homologous chromosomes. Separation of homologous chromosomes occurs during the first meiotic division (meiosis I), followed by the separation of sister chromatids during meiosis II.

The mechanics of chromosome segregation require that chromosome pairs that are to be segregated must first be connected to each other to ensure their proper orientation on the spindle (Miller et al. 2013). Just like during mitosis, meiotic sister chromatids are held together by sister chromatid cohesion that is established when the diploid genome is duplicated during premeiotic S phase (Fig. 1A). However, no such a priori linkage exists for homologous chromosomes. Consequently, a major mechanistic challenge of meiosis is to identify homologous chromosome pairs and establish connections between them. Much of meiotic prophase, the extended

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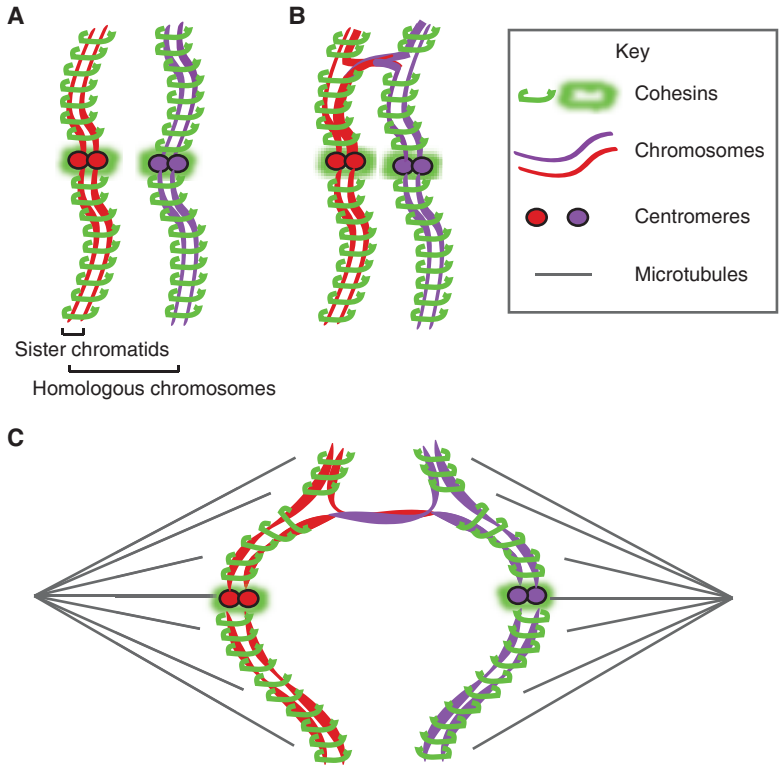

Figure 1. A crossover establishes a physical link between homologous chromosomes. (*A*) Schematic of a pair of homologous chromosomes (red and purple). The replicated sister chromatids are held together by cohesion (green rings). (*B*) A crossover between homologous chromosomes, in conjunction with cohesion distal to the crossover site, establishes a physical connection between them. (*C*) A crossover allows homologous chromosomes to orient properly on the meiotic spindle (gray lines).

G_2 phase preceding meiosis I, is dedicated to achieving this goal.

In most organisms, the connections between homologous chromosomes are established by crossover recombination (Fig. 1B). Crossovers exchange covalent links between sequences of homologous chromosomes, and in conjunction with crossover-distal sister chromatid cohesion, provide the physical connections necessary for homologous chromosome segregation during meiosis I (Fig. 1C) (van Heemst and Heyting 2000; Lee and Orr-Weaver 2001). Crossover recombination is initiated after premeiotic DNA replication with the programmed introduction of numerous DNA DSBs by the conserved SPO11 enzyme (Fig. 2A) (Keeney 2001). Removal of SPO11 and 5′ resection of DSB ends produces 3′ single-stranded DNA (ssDNA) ends that are used by the strand-invasion proteins RAD51 and DMC1 to search for homologous repair templates (Neale and Keeney 2006). In meiosis, a distinct interhomolog (IH) bias is generated to promote crossover recombination between homologous chromosomes rather than sister chromatids (Hollingsworth 2010; Lao and Hunter 2010). Moreover, a process known as crossover interference ensures an even distribution of crossovers before stable strand-invasion interactions with the homolog (Carpenter and Sandler 1974; Bishop and Zickler 2004; Berchowitz and Copenhaver 2010). Only stabilized strand-invasion intermediates are processed into double-Holliday junctions and ultimately resolved as crossovers, whereas the remaining intermediates are displaced from the homolog to be repaired as non-

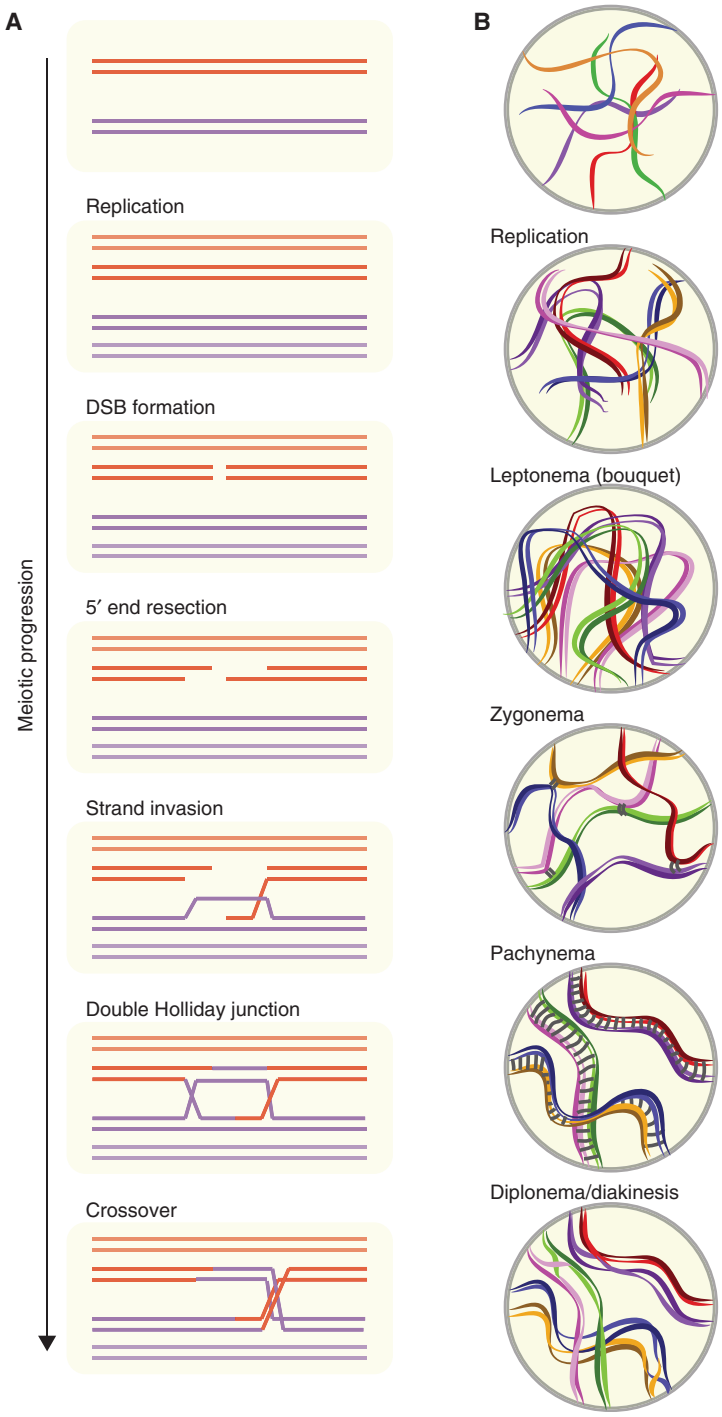

Figure 2. Meiotic DNA replication and DSB repair events occur concomitantly with chromosome structural morphogenes. Schematic of DNA metabolism (*A*), and chromosomal organization events (*B*) during meiotic prophase. The homologous chromosomes replicate during premeiotic S phase. At leptonema, the DSBs are initiated, whereas telomeres of the chromosomes become tethered to the nuclear envelope and the meiotic chromosomes assume a bouquet conformation (in most organisms). Synapsis (depicted by gray lines) between homologous chromosome pairs is thought to initiate at sites of crossover repair in zygonema. By pachynema the homologous chromosomes are fully synapsed and the crossover-designated repair is at the double-Holliday junction intermediate stage. The synaptonemal complex disassembles at diplonema to reveal the crossover sites between the homologous chromosomes.

crossovers (Allers and Lichten 2001; Hunter and Kleckner 2001).

DSB formation and repair are facilitated by chromosome structure transitions that are easily observable by cytology and underlie the cytologically defined stages of meiotic prophase—leptonema, zygonema, pachynema, and diplonema (Fig. 2B) (Baarends and Grootegoed 2003; Storlazzi et al. 2003). Meiotic chromosome morphogenesis initiates concomitantly with DNA replication with the assembly of proteinaceous chromosome axes that give each chromosome a rod-like center with emanating chromatin loops (Klein et al. 1999; Blat et al. 2002; Panizza et al. 2011; Borde and de Massy 2013). The loop-axis organization is completed in leptonema and is important for DSB formation as well as for establishing IH bias (Blat et al. 2002; Storlazzi et al. 2003; Carballo et al. 2008; Kim et al. 2010; Hong et al. 2013). As cells progress through zygonema, homologous chromosomes pair, their axes align, and in many organisms, the chromosomes progressively synapse. Synapsis refers to the assembly of a tripartite proteinaceous scaffold called the synaptonemal complex (SC) that is formed by central transverse filaments laid down between the paired axes of the homologous chromosomes (Page and Hawley 2004; Fraune et al. 2012). DSBs that have been designated to become crossovers are suggested to be the sites of synapsis initiation, in addition to synapsis initiation at the centromeres in some organisms (Klein et al. 1999; Henderson and Keeney 2004; Tsubouchi and Roeder 2005; Obeso and Dawson 2010; Subramanian and Hochwagen 2011). The final stages of crossover recombination occur in the context of the SC. When all chromosomes achieve full-length synapsis, the cells are in pachynema. By the subsequent diplonema, the cells have completed repair and disassemble their SC as they prepare to segregate the homologous chromosomes.

Alongside these chromosomal transitions, nuclear organization is often found to undergo remarkable changes (Fig. 2B). The specific nuclear restructuring varies between organisms and can take the form of telomere clustering in the nuclear envelope (the "bouquet" stage observed in many organisms), the subnuclear congression of chromosomes, as observed in *Caenorhabditis elegans* and *Drosophila melanogaster*, or a dramatic elongation of the nucleus, as seen in *Tetrahymena thermophila* (Scherthan 2001; Sheehan and Pawlowski 2009; Takeo et al. 2011; Tanneti et al. 2011; Loidl et al. 2012; Woglar and Jantsch 2013). In addition, chromosomes often undergo periods of extraordinary dynamicity, exemplified by the "horsetail movement" in *Schizosaccharomyces pombe* and the rapid pachytene movements in *Saccharomyces cerevisiae* or maize (Ding et al. 1998; Tomita and Cooper 2006; Koszul et al. 2009; Sheehan and Pawlowski 2009; Sonntag Brown et al. 2011; Lee et al. 2012). These processes typically occur in a stage-specific manner and, in most instances, are thought to either help chromosome pairing or resolve unproductive chromosomal interactions (Koszul and Kleckner 2009).

Work over the past several years has revealed that meiotic cells rely on an intricate network of signaling mechanisms to coordinate this complex program and create dependencies between different processes (Roeder and Bailis 2000; Hochwagen and Amon 2006; Longhese et al. 2009; MacQueen and Hochwagen 2011). These dependencies are necessary to establish the correct timing of meiotic prophase events and to avoid deleterious interactions between different processes. They also provide an opportunity to delay or even cull meiotic cells if meiotic processes go awry. Here, we attempt to summarize our current understanding of this network of dependencies. In an effort to simplify, we will refer to the checkpoint components by their human homologs wherever possible and indicate the organism-specific nomenclature in superscript when referencing the function in an organism-specific context.

A WEB OF DEPENDENCIES CREATES ORDER IN MEIOTIC PROPHASE

Throughout this review, we refer to the overall signaling network comprising these mechanisms as the meiotic checkpoint network (MCN). In line with the original definition of cell cycle checkpoints (Hartwell and Weinert 1989), we use the term "checkpoint mechanism"

to describe any signaling mechanism that creates a dependent relationship between metabolically independent meiotic processes (e.g., DSB formation and SC assembly). This broad definition is intended to emphasize that checkpoints are not primarily surveillance mechanisms that respond to abnormal events. Although meiotic DSBs are a form of genome damage, their formation is an inherent part of every meiotic prophase, and thus per se not abnormal. Consequently, we view the MCN not simply a damage response network, but as an integral coordinating mechanism that is central to the ordered execution of meiotic prophase.

Figure 3 provides a broad overview of our current understanding of the MCN. By far, the most dependencies arise from the formation of DSBs, presumably reflecting the inherent dangers associated with chromosome breakage. However, some processes are also linked to the completion of DNA replication or the proper pairing and synapsis of chromosomes. Remarkably, almost all currently known dependencies in meiotic prophase involve the activities of the conserved PI3-like kinases ATM and ATR. This means that the MCN must have mechanisms to differentiate between signals to elicit the appropriate responses. We discuss this important feature of the MCN in a later part of this review, but first focus on the general architecture of the MCN.

THE MAIN PLAYERS

The core signaling machinery of the MCN uses many of the players of the canonical DNA damage response (DDR) network (Table 1), including the conserved checkpoint sensor kinases ATM and ATR (MacQueen and Hochwagen 2011). ATM and ATR are evolutionarily related serine/threonine kinases that become activated by distinct forms of DNA damage as well as by asynapsis during meiosis (Carballo and Cha 2007; Burgoyne et al. 2009). ATM responds primarily to blunt and protein-conjugated DSB ends, whereas ATR is activated by RPA-coated ssDNA resulting from DSB processing, as well as ssDNA/dsDNA junctions (Harrison and Haber 2006; Lovejoy and Cortez 2009). Both kinases rely on the activity of cofactors for damage recognition. ATM detects blunt ends with the help of the MRN complex (MRE11-RAD50-NBS1) (Usui et al. 2001; Nakada et al. 2003; You et al. 2005). ATR detects ssDNA through its activator ATRIP, and ssDNA/dsDNA junctions through the PCNA-like 9-1-1 complex (RAD9-RAD1-HUS1) (Zou and Elledge 2003; Harrison and Haber 2006; Refolio et al. 2011). In addition, the cofactors BRCA1 and TOPBP1 promote ATR activity in response to unsynapsed meiotic chromatin (Refolio et al. 2011; Royo et al. 2013). ATM and ATR phosphorylate large and often overlapping sets of substrates on serine-glutamine (SQ) or threonine-glutamine (TQ) dipeptides. Many of the known effectors of the MCN are direct targets of ATM/ATR (Table 2), creating immediate links between signal and outcome. In addition, ATM/ATR activate the CHK1 and CHK2 effector kinases, which further relay checkpoint signals but typically control a more restricted set of processes.

CONTROL OF DSB FORMATION

Ongoing Replication Blocks DSB Formation

The first known checkpoint mechanism in meiotic prophase is the meiotic replication checkpoint. As in mitotic cells, a primary function of the meiotic replication checkpoint is the maintenance of replication potential, which occurs through ATR- and CHK2-dependent stabilization of replication forks (Branzei and Foiani 2010; Blitzblau and Hochwagen 2013). However, in addition, the meiotic replication checkpoint also prevents DSB formation as long as replication is ongoing (Figs. 3 and 4A) (Tonami et al. 2005; Ogino and Masai 2006; Blitzblau and Hochwagen 2013). The enforced temporal separation of replication and DSB formation is important because it ensures that crossovers only form between replicated chromosomes (see Fig. 1). Moreover, it prevents lethal conflicts between DSB formation and DNA replication (Blitzblau and Hochwagen 2013). The replication checkpoints of *S. pombe* and *S. cerevisiae* suppress DSBs through transcriptional repression of essential regulators of DSB formation, although the identity of the ultimate checkpoint

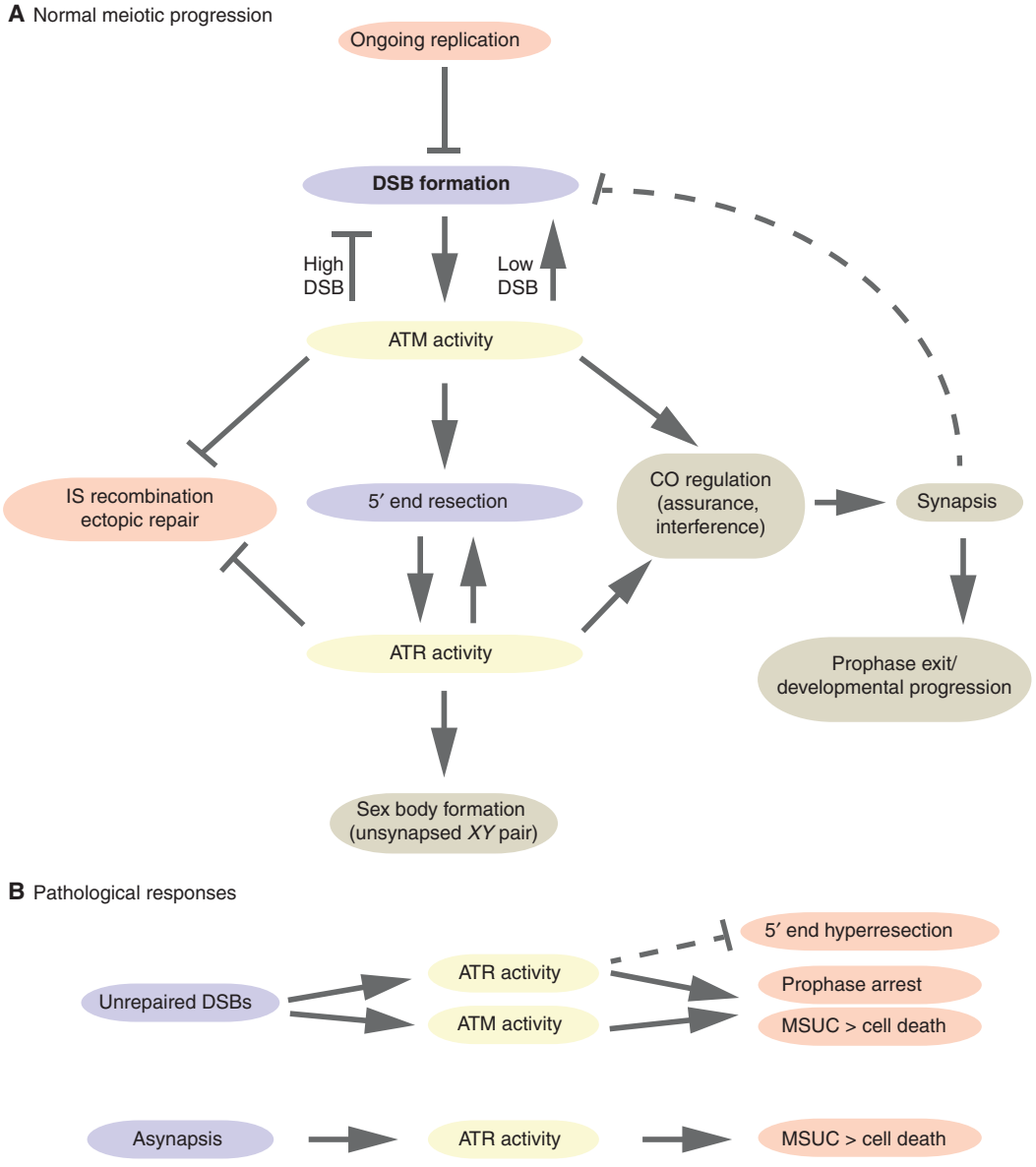

Figure 3. Dependent relationships established by the MCN. The meiotic checkpoint network creates a web of dependencies to promote sequential progression of meiotic events (*A*), or prevent meiotic progression in the face of defective repair or synapsis (*B*). Dashed lines and arrows indicate a modulation in activity.

target differs between the two yeasts. In *S. pombe* expression of Mde2, an axis associated DSB regulator, is down-regulated by the checkpoint, whereas expression of SPO11 itself is under the control of the replication checkpoint in the budding yeast (Ogino and Masai 2006; Miyoshi et al. 2012; Blitzblau and Hochwagen 2013). In addition, the replication checkpoint of *S. cerevisiae* also directly controls the chromosomal localization and activation of other components of the DSB machinery (MER2 and REC114). Signaling in this case occurs both through $CHK2^{Rad53}$-dependent and independent mechanisms and involves regulation of the conserved

Table 1. MCN proteins and their homologs

Mammals	*S. cerevisiae*	*C. elegans*	*S. pombe*	*Drosophila*	*Arabidopsis*	Function
Signaling proteins						
ATR	**Mec1**	**ATL-1**	**Rad3p**	**Mei-41**	**ATR**	PI3[a] kinase-like kinase
ATM	**Tel1**	**ATM-1**	Tel1p	**Atm**	**ATM**	PI3 kinase-like kinase
RAD9A, RAD9B	**Ddc1**	**HPR-9**	**Rad9p**	**Rad9A**, Rad9B	–	PCNA[b]-like clamp (9-1-1 complex)
RAD1	**Rad17**	**MRT-2**	**Rad1p**	Rad1		PCNA-like clamp (9-1-1 complex)
HUS1 HUS1B	**Mec3**	**HUS-1**	Hus1p	**Hus1**	–	PCNA-like clamp (9-1-1 complex)
CHK1	(Chk1)	**CHK-1**	Chk1p	(Grp)	–	Protein kinase
CHK2	**Rad53** **Mek1**	**CHK-2**	**Cds1p** **Mek1p**	**Mnk**	–	Protein kinase with FHA[c] domain
Several	**Cdc5**	**PLK-2**	Plo1p	**Polo**	–	Protein kinase
HORMAD1 **HORMAD2**	**Hop1**	**HTP-1** **HTP-2** HIM-3	Hop1	–	ASY1	Chromosomal HORMA-domain proteins
SYCP3	**Red1?**	**HTP-3?**	Rec10?	C(2)M?	ASY3?	Chromosome axis component
Several	**Sir2**	**SIR-2**	Sir2p	**Sir2**	SRT1 SRT2	NAD-dependent deacetylase
TRIP13	**Pch2**	**PCH-2**	–	**Pch2**	–	AAA^{+}-ATPase[d]

Proteins shown to be involved in the MCN pathway are in bold. Proteins that were shown not to be part of the MCN function are in parentheses. Proteins that share functional homology but no obvious sequence homology are followed by "?".

[a]Phosphoinositide 3-kinase.

[b]Proliferating cell nuclear antigen.

[c]Fork-head associated domain.

[d]ATPases associated with diverse cellular ATPase.

cell cycle kinase DDK (Blitzblau and Hochwagen 2013). A role for CHK2 in coordinating premeiotic DNA replication and subsequent meiotic prophase entry was also suggested for *C. elegans* (MacQueen and Villeneuve 2001). A possibly even earlier meiotic role of ATR and CHK2 in DNA replication was recently suggested in *S. pombe*. In this organism, mutation of an ATR/ATM- and $SPO11^{Rec12}$-dependent phosphorylation site on $CHK2^{Mek1}$ resulted in a delay in DNA replication (Tougan et al. 2010). Although this phosphorylation event may represent feedback regulation of replication by DSBs, this possibility requires further study as deletion of ATR^{Rad3} or $CHK2^{Mek1}$ did not similarly affect S-phase progression (Ogino and Masai 2006).

DSB Levels—A Balancing Act

In addition to linking DSB formation to the sufficient completion of DNA replication, there is increasing evidence that the MCN also feeds back to modulate DSB levels once DSB formation has initiated. In mouse and *Drosophila*, loss of ATM leads to increased abundance of DSB markers, whereas loss of ATR causes similar phenotypes in *A. thaliana*, suggesting that DSB-dependent activation of these kinases down-regulates further DSB formation (Joyce et al. 2011; Lange et al. 2011; Kurzbauer et al. 2012). Meiotic DSB levels must be tightly controlled, as an excessive DSB load can lead to severe problems in DNA repair (Johnson et al. 2007). Indeed, a number of meiotic phenotypes of $Atm^{-/-}$ mice can be alleviated by reducing *SPO11* copy number (Bellani et al. 2005; Barchi et al. 2008). A particular function of ATM in this context may be to prevent repeated DSB formation at the same chromosomal locus (including the sister chromatid). Spatial proximity of DSBs could explain why $Atm^{-/-}$ mice display a strong increase in the amount of postcleavage SPO11-

Table 2. Phosphorylation events involved in creating dependencies

Modifying enzyme(s)	Target	Phosphorylated residue(s)	Organism	Effect(s)	References
ATR^{Mec1}/ATM^{Tel1}	$CtIP^{Sae2}$	(Ser73) (Thr90) Ser249 Ser279 Ser289	*S. cerevisiae*	Activation of DSB resection	Cartagena-Lirola et al. 2006; Terasawa et al. 2008
ATR^{Mec1}/ATM^{Tel1}	$HORMAD^{Hop1}$	Ser298 (Ser311) Thr318	*S. cerevisiae*	Inhibition of intersister repair	Carballo et al. 2008
ATR	HORMAD1	Ser375	Mouse	MSCI, signaling of asynapsis?	Fukuda et al. 2012; Royo et al. 2013
ATR	HORMAD2	Ser271	Mouse	MSCI?	Royo et al. 2013
ATR^{Mec1}/ATM^{Tel1}	$RPA2^{Rfa2}$	Ser122	*S. cerevisiae*	Altered crossover distribution in some intervals	Bartrand et al. 2006
ATR^{Mec1}/ATM^{Tel1}	$RNF212^{Zip3}$	Up to four residues	*S. cerevisiae*	Altered crossover levels in some intervals	Serrentino et al. 2013
ATR^{Mec1}/ATM^{Tel1}	$SCP1^{Zip1}$	Ser75	*S. cerevisiae*	Dissolution of centromere pairing	Falk et al. 2010
ATM	Histone H2AFX	Ser139	Mouse	Persistence of the bouquet	Fernandez-Capetillo et al. 2003
ATR	Histone H2AFX	Ser139	Mouse	MSCI	Royo et al. 2013
ATR^{Mec1}/ATM^{Tel1}	Rec114	Thr175 Ser187 (Ser256)	*S. cerevisiae*	Reduced DSB formation	Carballo et al. 2008
ATR^{Mec1}/ATM^{Tel1}	$CHK2^{Mek1}$	(Ser12) (Ser14) Thr15	*S. pombe*	Activation of $CHK2^{Mek1}$ kinase activity	Tougan et al. 2010
$CHK2^{Mek1}$	Rad54	Thr132	*S. cerevisiae*	Inhibition of intersister repair	Niu et al. 2009
$CHK2^{Mek1}$	Rdh54	Thr6 Thr673	*S. pombe*	Inhibition of intersister repair?	Tougan et al. 2010
$CHK2^{Mek1}$	Mus81	Thr281 Thr422	*S. pombe*	Inhibition of intersister repair?	Tougan et al. 2010
$CHK2^{Mek1}$	Histone H3	Thr11	*S. cerevisiae*	Inhibition of intersister repair?	Govin et al. 2010
$CHK2^{Mek1}$	Cdc25	Up to nine residues	*S. pombe*	DSB-dependent nuclear exclusion of Cdc25; cell cycle delay	Perez-Hidalgo et al. 2008
CHK2	SUN-1	Ser8 Ser12[a] Ser24 Ser35/Thr36 Ser43 Ser58 Ser62	*C. elegans*	Chromosome pairing and synapsis initiation	Penkner et al. 2009

[a]Ser12 phosphorylation is likely indirect because it also depends on PLK-2 (Labella et al. 2011).

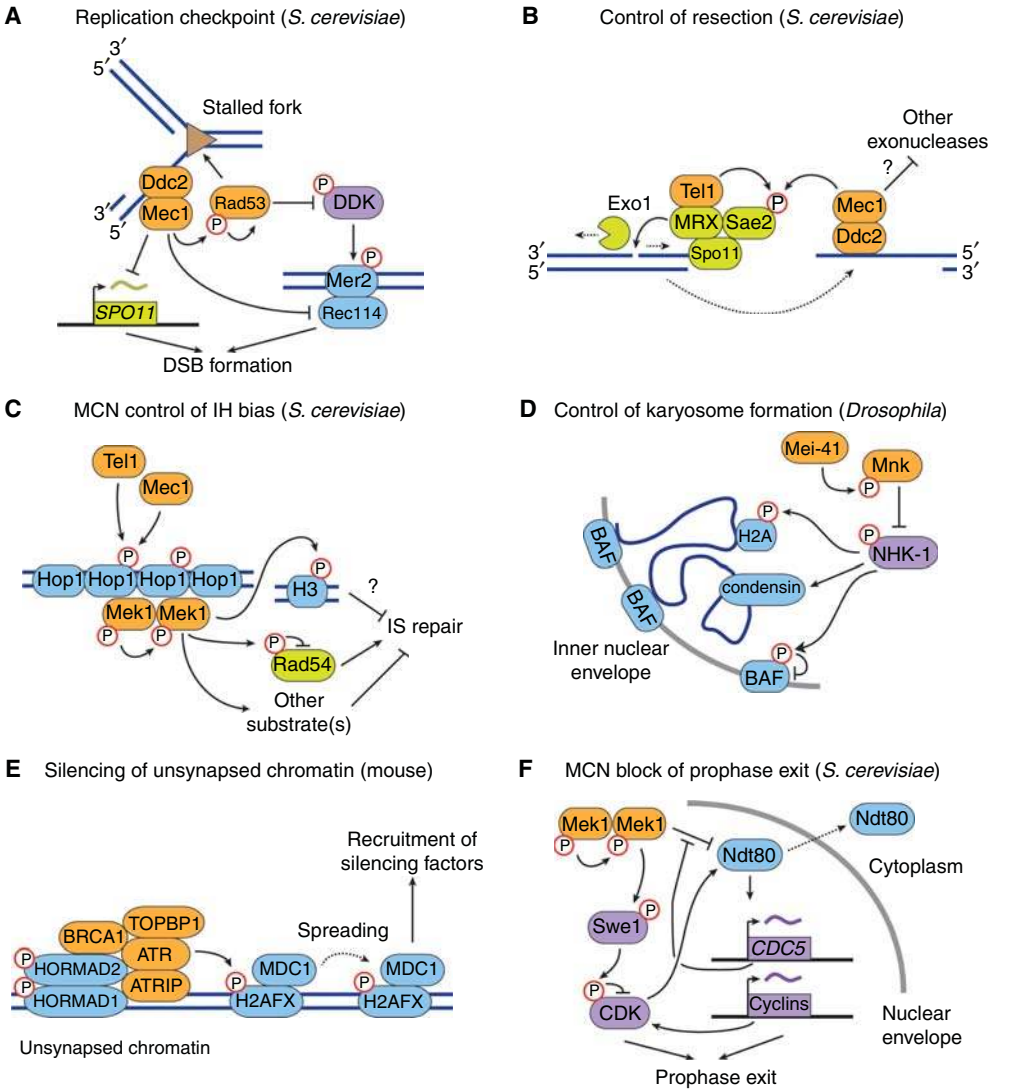

Figure 4. The meiotic checkpoint network integrates signal to the appropriate response. (*A*) Stalled replication forks prevent DSB formation via several mechanisms in *S. cerevisiae*. Mec1 regulates transcription of *SPO11* and recruitment of Rec114 to the meiotic chromosomes, whereas the downstream Rad53 kinase controls phosphorylation of Mer2 by regulating the activity of DDK kinase. (*B*) MCN regulates resection. Both Tel1 and Mec1 kinases activate Sae2 for DSB end resection to generate 3′ ssDNA overhangs. The MCN also prevents hyper-resection of break ends. (*C*) Mec1/Tel1 kinases promote IH bias via phosphorylation of Hop1, which in turn leads to recruitment, dimerization, and activation of Mek1 kinase. Regulation of Rad54 activity by Mek1 inhibits IS repair thus promoting IH bias. (*D*) In *Drosophila*, the MCN negatively regulates NHK-1 kinase. NHK-1 kinase controls condensation of the oocyte chromatin and also allows its release from the nuclear envelope on completion of DSB repair. (*E*) Unsynapsed chromatin in mouse recruits ATR via HORMAD1/2. ATR facilitates phosphorylation of H2AFX that spreads into the chromatin loops and recruits silencing factors. (*F*) MCN regulates exit from meiotic prophase by controlling the expression and localization of Ndt80 transcription factor as well as by inhibiting CDK kinase. Cdc5 kinase relieves inhibition of Ndt80 by the MCN in a feedforward loop to allow rapid exit from prophase.

oligonucleotide complexes, but only a mild increase in the number of cytologically discernable RAD51 foci (Barchi et al. 2008; Lange et al. 2011). Analyses of recombinant chromatids from *S. cerevisiae* tetrads at specific DSB sites in mutants lacking ATM^{Tel1} or ATR^{Mec1} also support this model (Zhang et al. 2011). Although the target of ATM in this context remains to be identified, recent experiments in *S. cerevisiae* suggest the conserved SPO11 accessory factor REC114 as a promising candidate. REC114 is a substrate of ATM^{Tel1} and ATR^{Mec1} and mutations mimicking constitutive ATM/ATR-dependent phosphorylation cause a notable decrease in DSB levels (Carballo et al. 2013). CHK2-dependent regulation of the DSB regulators DSB-1 and DSB-2 may have the equivalent function in *C. elegans* (Rosu et al. 2013; Stamper et al. 2013).

A number of recent studies in *S. cerevisiae* indicate that defects in DSB repair further modulate DSB levels. The effects are rather complex as the MCN shows both DSB-promoting and DSB-suppressing effects depending on the amount of DSBs formed, the type of repair defect, and whether cells are able to prematurely exit prophase (Argunhan et al. 2013; Blitzblau and Hochwagen 2013; Carballo et al. 2013; Gray et al. 2013; Lao et al. 2013; Rockmill et al. 2013). Finally, work in yeast and mice also suggests a feedback between DSB formation and homolog interactions, as DSB formation continues on unsynapsed chromosomes (Kauppi et al. 2013a,b; Thacker et al. 2014).

CONTROL OF DSB REPAIR

Activation of DSB End Processing

DSB formation itself triggers a major activation of the MCN (Fig. 3). One of the first events following meiotic DSB formation is MRN/CtIP-initiated end resection, which promotes homologous recombination and also creates a barrier to error-prone end-joining mechanisms of repair (Joyce et al. 2012; Yin and Smolikove 2013). Resection is initiated by MRE11-dependent endonucleolytic incisions near DSBs, followed by bidirectional resection that requires both MRN and EXO1 (Zakharyevich et al. 2010; Garcia et al. 2011). In *S. cerevisiae*, the MRN^{Xrs2} complex detects unprocessed meiotic DSB ends and activates ATM^{Tel1} kinase, which in turn phosphorylates the MRN interacting protein $CtIP^{Sae2}$ to initiate DSB resection (Fig. 4B) (Usui et al. 2001; Cartagena-Lirola et al. 2006; Terasawa et al. 2008). In a positive feedback loop, resected DNA ends lead to the activation of ATR^{Mec1}, which further contributes to $CtIP^{Sae2}$ activation. However, this dependency is not strictly linear because ATR^{Mec1} also becomes activated independently of ATM^{Tel1}, and is itself sufficient to phosphorylate $CtIP^{Sae2}$ and initiate resection (Cartagena-Lirola et al. 2008).

Meiotic resection initially is limited, but if DSB repair is blocked, meiotic cells enter a phase of DSB hyperresection. Intriguingly, ATR^{Mec1} and the 9-1-1 complex are also required to restrain hyperresection (Shinohara et al. 2003; Gray et al. 2013; Clerici et al. 2014). Given that a number of nucleases are involved in the resection process (Mimitou and Symington 2009; Zakharyevich et al. 2010; Garcia et al. 2011; Schaetzlein et al. 2013), an appealing model is that the MCN ensures appropriate resection rates by activating some nucleases, while (temporarily) inhibiting others (Segurado and Diffley 2008; Manfrini et al. 2010; Luo et al. 2013; Souquet et al. 2013). In *S. cerevisiae*, resection by BLM^{Sgs1}/DNA2, in particular, is likely only activated late in meiosis (Manfrini et al. 2010; Zakharyevich et al. 2010).

Suppression of Intersister Recombination

For meiotic DSBs to support crossover formation between homologous chromosomes, repair from the more readily available homologous sequences on the sister chromatid must be suppressed. Several mechanisms act in concert to achieve this goal, both by down-regulating sister-directed RAD51-recombinase activity and by promoting the homolog as the preferred repair template (Kim et al. 2010; Lao and Hunter 2010; Kurzbauer et al. 2012; Hong et al. 2013; Lao et al. 2013; Liu et al. 2014). Research in a number of organisms indicates a central role of the MCN in establishing meiotic homolog bias (Carballo et al. 2008; Latypov et al. 2010), al-

though the mechanistic details are best understood in *S. cerevisiae* (Fig. 4C). In this organism, ATM^{Tel1}/ATR^{Mec1} phosphorylate the HORMA-domain-containing chromosomal axis protein $HORMAD^{Hop1}$, the homolog of mammalian HORMAD1/2, on several clustered S/TQ sites (Table 1) (Carballo et al. 2008). This leads to the recruitment, dimerization, and activation of the CHK2-like effector kinase $CHK2^{Mek1}$ (Niu et al. 2005, 2007; Carballo et al. 2008; Wu et al. 2010) whose binding, in turn, stabilizes the phosphorylation mark on $HORMAD^{Hop1}$ (Chuang et al. 2012). Once activated, $CHK2^{Mek1}$ kinase promotes IH bias possibly in part by phosphorylating and inhibiting RAD54, a SWI/SNF-family ATPase that stimulates RAD51-recombinase activity for repair from the sister chromatid (Niu et al. 2009). However, genetic experiments suggest that other (currently unknown) targets of $CHK2^{Mek1}$ provide the primary mechanism to promote IH bias (Niu et al. 2009; Terentyev et al. 2010). Research in *S. cerevisiae* and *S. pombe* has identified several additional $CHK2^{Mek1}$ targets, including a chromatin mark (histone H3 T11), the RAD54-related yeast protein Rdh54, and the resolvase MUS81 (Govin et al. 2010; Tougan et al. 2010). So far, only Rdh54 has been excluded as a likely functional target of the MCN (Niu et al. 2009). Notably, Rdh54 phosphorylation during vegetative growth is implicated in checkpoint adaptation (Ferrari et al. 2013).

Suppression of Ectopic Recombination

There is evidence that the MCN also protects genome stability by preventing nonallelic (ectopic) recombination. Mutants of the plant *Arabidopsis thaliana* lacking both ATM and ATR display DSB-dependent associations between nonhomologous chromosomes that persist into metaphase I, suggestive of ectopic crossover recombination (Culligan and Britt 2008). Moreover, increased ectopic recombination is also observed in *S. cerevisiae* cells lacking a functional 9-1-1 complex and mice lacking the 9-1-1 component HUS1 (Grushcow et al. 1999; Thompson and Stahl 1999; Shinohara et al. 2003; Lyndaker et al. 2013a; Shinohara and Shinohara 2013). Although the relevant checkpoint targets remain unknown, the checkpoint network may restrain ectopic recombination by coordinating the two DSB ends (Shinohara and Shinohara 2013), a notion supported by the observation that RAD51 and DMC1 recombinases frequently appear in an abnormal side-by-side arrangement in 9-1-1 complex mutants of *S. cerevisiae* (Shinohara et al. 2003). The increased number of RAD51 and DMC1 foci in *ATR* mutants of *A. thaliana* may reflect a similar defect, although the geometry of recombinase loading appears to differ between the two organisms (Kurzbauer et al. 2012). It is possible that increased ectopic recombination is responsible for the decreased crossover levels observed in a number of checkpoint mutants (Shinohara et al. 2003). However, in many cases mutations in checkpoint factors also show a strong delay in DSB repair, which may argue for a more direct role of the meiotic checkpoint machinery in promoting meiotic recombination (Shimada et al. 2002; Shinohara et al. 2003; Peretz et al. 2009; Joyce and McKim 2010).

Obligate Crossover Formation and Crossover Interference

Finally, there is limited evidence that the MCN has a role in regulating crossover distribution. Several processes are at work to ensure that each homologous chromosome pair receives a crossover (the obligate crossover), and that neighboring crossovers do not occur too close to each other (crossover interference). In male mice, ATM activity is required for the obligate crossover in the small pseudoautosomal region of homology that allows pairing between X and Y chromosomes (Barchi et al. 2008). In addition, mice lacking ATM have increased autosomal crossover numbers accompanied by reduced crossover interference (Barchi et al. 2008). Similarly, in *S. cerevisiae*, ATM^{Tel1}/ATR^{Mec1}-dependent phosphorylation of the Rfa2 subunit of RPA, as well as of the SC component $RNF212^{Zip3}$, alters crossover distribution in some genetic intervals (Bartrand et al. 2006; Serrentino et al. 2013), although the generality of these effects remains to be determined. A crossover interference defect was also observed

in *S. cerevisiae* mutants lacking the phosphatase PP4, which is responsible for the dephosphorylation of several ATR/ATM substrates (Falk et al. 2010). However, the mechanism by which the MCN influences crossover distribution has so far remained elusive.

NUCLEAR ORGANIZATION, PAIRING, AND SYNAPSIS

Checkpoint Control of Nuclear Restructuring

In addition to coordinating DSB repair, the MCN links meiotic nuclear dynamics to both DNA replication and DSB metabolism. In *S. cerevisiae*, one of the first instances of nuclear restructuring, the dispersal of mitotic telomere clusters, is linked to S-phase completion (Trelles-Sticken et al. 2005a), and at least under some circumstances requires ATR^{Mec1} activity (Trelles-Sticken et al. 2005b). A related connection between S-phase and nuclear restructuring may exist in *C. elegans*. Following S phase in this organism, chromosomes aggregate in a polarized nuclear crescent with their telomeres anchored in clusters in the nuclear envelope, reminiscent of the bouquet stage seen in many organisms. This nuclear reorganization requires CHK2, although not ATM/ATR (MacQueen and Villeneuve 2001; Penkner et al. 2009). Thus, how CHK2 is activated in this case is unclear. CHK2 activity is required for multiple events in this context, including the enrichment of ZIM proteins at chromosomal pairing centers and the phosphorylation of the chromosome anchor SUN-1 at the nuclear envelope (Phillips and Dernburg 2006; Penkner et al. 2009). Dephosphorylation of SUN-1, in turn, is required for the dissolution of the polarized crescent as cells enter pachynema (Penkner et al. 2009; Woglar et al. 2013). A checkpoint-dependent restructuring of the nucleus into a bouquet-like state is also observed in *Tetrahymena*, although this process requires both DSB formation and ATR (Loidl and Mochizuki 2009; Loidl et al. 2012).

One of the best-understood mechanisms of MCN-dependent nuclear reorganization in this context is the release of chromosomes from the nuclear envelope in *Drosophila* (Fig. 4D). Chromosomal release occurs on completion of meiotic recombination and leads to the formation of a compact chromosome cluster called the karyosome. Before DSB repair, karyosome formation is prevented by the ATR^{Mei-41} and $CHK2^{Mnk}$-dependent inhibition of NHK-1 kinase (Ghabrial and Schupbach 1999; Abdu et al. 2002; Lancaster et al. 2010). One of the substrates of NHK-1 is the nuclear envelope protein BAF, which must be phosphorylated to release chromosomes into the nucleus (Lancaster et al. 2007). NHK-1 is also required for histone H2A Thr119 phosphorylation, SC disassembly, and condensin loading, which may further contribute to karyosome formation (Ivanovska et al. 2005; Lancaster et al. 2010).

Chromosome Pairing and the Bouquet

The bouquet stage coincides with the active pairing of homologous chromosomes, and a failure to properly pair is associated with delayed dispersal of the chromosomal bouquet in many organisms. For example, the presence of an extra chromosome extends the bouquet stage and alters repair dynamics in trisomic human oocytes (Roig et al. 2005; Robles et al. 2013). Similarly, telomere clusters persist in pairing-defective *spo11* mutants of *S. cerevisiae* and *Sordaria* (Trelles-Sticken et al. 1999; Storlazzi et al. 2003). DSB processing is also necessary for exit from the bouquet stage in *Tetrahymena* (Loidl et al. 2012). At least in some cases, these delays may depend on checkpoint regulation, as mouse mutants lacking ATM or its substrate histone H2AFX (formerly known as H2AX) fail to exit the bouquet stage (Fernandez-Capetillo et al. 2003; Liebe et al. 2006). Finally, in *S. cerevisiae*, the MCN also destabilizes the nonhomologous pairing of centromeres in response to DSBs through ATR^{Mec1}-dependent phosphorylation of the central SC component $SCP1^{Zip1}$ (Falk et al. 2010).

Control of Synapsis Initiation

An interesting case of meiotic checkpoint control is the initiation of chromosome synapsis,

which is coupled to chromosome pairing or DSB formation in a variety of organisms. In *C. elegans*, synapsis initiation is blocked by MCN-mediated Ser12-phosphorylation of SUN-1, the nuclear envelope protein that establishes connections between chromosome ends and the cytoskeleton during meiosis. Ser12-phosphorylation of SUN-1 depends on CHK2 and the Polo-like kinase PLK2, but is independent of ATM/ATR (Penkner et al. 2009; Labella et al. 2011; Woglar et al. 2013). Erasure of Ser12 phosphorylation, and thus synapsis initiation, requires appropriate DSB repair (Woglar et al. 2013) as well as appropriate pairing interactions between chromosomes, which appear to be monitored by a force-dependent checkpoint mechanism (Penkner et al. 2009; Wynne et al. 2012; Rog and Dernburg 2013). A different mechanism appears to link synapsis initiation to the onset of DSB formation in *S. cerevisiae*. In the absence of DSBs, synapsis initiation at centromeres is actively blocked by a mechanism involving the putative SUMO-ligase $RNF212^{Zip3}$ and the proline isomerase Fpr3 (MacQueen and Roeder 2009). How the DSB signal is transmitted to allow synapsis initiation at centromeres in this situation remains unknown, although $RNF212^{Zip3}$ has recently emerged as a promising MCN substrate (Serrentino et al. 2013).

ASYNAPSIS AND TRANSCRIPTIONAL SILENCING

It is now well established that unsynapsed chromosomes or chromosome segments elicit the activation of several branches of the MCN. Checkpoint signaling is apparent in meiocytes with partial asynapsis, including cells carrying extra chromosomes or chromosome translocations (Mahadevaiah et al. 2008; Burgoyne et al. 2009; Garcia-Cruz et al. 2009; Kouznetsova et al. 2009), and also occurs transiently on late-synapsing chromosomal regions (Blanco-Rodriguez 2012). In *C. elegans*, asynapsis is associated with a delayed exit from the bouquet state (Carlton et al. 2006; Colaiacovo 2006), and can trigger apoptosis (Bhalla and Dernburg 2005).

In mammals, sites of asynapsis are associated with the phosphorylation of several axis proteins including HORMAD1 and 2 (Fig. 4E) (Fukuda et al. 2012; Royo et al. 2013) and lead to the recruitment of BRCA1, ATRIP, TOPBP1, and ATR to the unsynapsed chromosome axes, followed by the ATR-dependent accumulation of γ-H2AFX (histone H2AFX phosphorylated on Ser139) (Perera et al. 2004; Turner et al. 2005; Burgoyne et al. 2009; Refolio et al. 2011). If asynapsis persists, γ-H2AFX and ATR spread over the entire chromatin with the help of the γ-H2AFX-binding factor MDC1 (Ichijima et al. 2011), and trigger the heterochromatinization and meiotic silencing of unsynapsed chromatin (MSUC). Transcriptional silencing as a consequence of asynapsis is also observed in a number of nonmammalian organisms, including *Neurospora* and *C. elegans* (Shiu et al. 2001; Bean et al. 2004; Checchi and Engebrecht 2011). Depending on which chromosomal regions are silenced, MSUC in mice frequently leads to the loss of spermatocytes, presumably as a result of the depletion of essential survival factors (Burgoyne et al. 2009; Manterola et al. 2009).

MSUC is closely related to the meiotic silencing of sex chromosomes within the sex body by meiotic sex chromosome inactivation (MSCI) (Fig. 5), a physiological process that responds to the unavoidable partial asynapsis of heteromorphic sex chromosomes, but does not lead to cell death (Turner et al. 2006). Sex body formation takes place in late zygonema and is associated with a second wave of γ-H2AFX formation. γ-H2AFX formation occurs in two waves in mouse meiocytes. The first wave coincides with the onset of recombination, is ATM-dependent, and forms foci that are thought to mark DSBs (Mahadevaiah et al. 2001; Barchi et al. 2005; Bellani et al. 2005). In contrast, the second wave of γ-H2AFX formation depends on ATR, marks the remaining unsynapsed chromosomes, and behaves like an MSUC response in that γ-H2AFX and ATR spread across the associated chromatin loops (Mahadevaiah et al. 2001; Turner et al. 2005; Royo et al. 2013). Curiously, although mediated by the DNA-damage sensor kinase ATR, the second wave is independent of SPO11 (Barchi et al. 2005; Bellani et al. 2005). We discuss potential alternative modes of ATR activation later in this review.

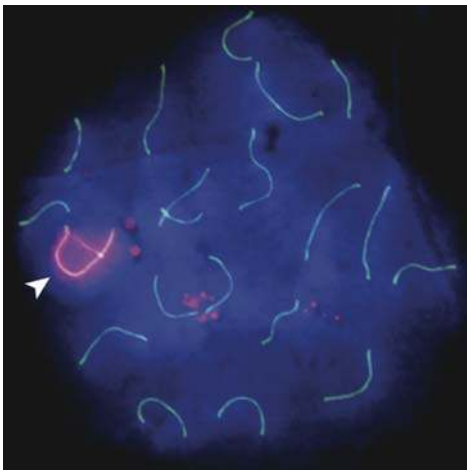

Figure 5. Meiotic chromosome spread from mouse spermatocyte in pachynema depicting MSCI. The *XY* pair manifests as the sex body (white arrowhead) and is enriched for ATR (red). SCP3 (green) marks the axes of synapsed and unsynapsed chromosomes, DNA is in blue. (Image courtesy of Sarai Pacheco and Ignasi Roig.)

CELL CYCLE PROGRESSION, CELL DEATH, AND LINKS TO DEVELOPMENT

Control of Prophase Exit

Similar to the mitotic DNA damage response, activation of the MCN also triggers a delay in meiotic prophase, presumably to provide sufficient time for the completion of meiotic recombination. A checkpoint-dependent prophase delay or arrest in response to defects in synapsis or DNA repair is apparent in many organisms (Lydall et al. 1996; Shimada et al. 2002; Hochwagen and Amon 2006; Joyce and McKim 2010; Lyndaker et al. 2013a; Woglar et al. 2013), although mechanistic details on how the MCN influences the cell cycle machinery are so far largely restricted to *S. cerevisiae* and *S. pombe*. In both yeasts, the meiotic cell cycle delay is mediated by ATR-dependent activation and dimerization of $CHK2^{Mek1}$ (Lydall et al. 1996; Xu et al. 1997; Shimada et al. 2002; Wu et al. 2010). $CHK2^{Mek1}$ acts in part through inhibition of cyclin-dependent kinase (CDK). In *S. cerevisiae*, $CHK\text{-}2^{Mek1}$ kinase phosphorylates and activates the CDK-inhibitory kinase $WEE1^{Swe1}$ (Fig. 4F) (Tung et al. 2000; Acosta et al. 2011), whereas in *S. pombe*, $CHK2^{Mek1}$ kinase promotes the nuclear exclusion (and thus inactivation) of the CDK-activating phosphatase CDC25 (Perez-Hidalgo et al. 2008). The outcome in both cases is persistent inhibitory tyrosine phosphorylation of CDK. In parallel, the MCN of *S. cerevisiae* also triggers the nuclear export of the Ndt80 (Hepworth et al. 1998; Wang et al. 2011), a key transcription factor that activates the transcription of a large set of genes including B-type cyclins as well as the prophase-exit promoting kinase PLK^{Cdc5} (Chu and Herskowitz 1998; Sourirajan and Lichten 2008). Tyrosine phosphorylation and repression of cyclins both keep CDK inactive and thus prevent precocious prophase exit while the MCN is active. Recent research and modeling has furthermore shown that Ndt80 and PLK^{Cdc5} are embedded in an intricate system of feedback and feedforward loops that creates a bistable switch for rapid exit from meiotic prophase once the checkpoint network is inactivated (Acosta et al. 2011; Okaz et al. 2012).

Persistent Defects and the Induction of Cell Death

If defects in repair or synapsis persist, the checkpoint networks of various organisms adopt different terminal strategies. *S. cerevisiae* cells enter a prolonged prophase arrest that can be exited by aborting meiosis should environmental conditions become favorable for mitotic growth (Simchen 2009). Alternatively, *S. cerevisiae* can adapt to the damage by inactivating the MCN, and attempt meiosis (Bailis et al. 2000; Hochwagen et al. 2005; Iacovella et al. 2010). In contrast, meiocytes in metazoans are frequently culled by checkpoint-dependent induction of the apoptotic cell death program (Gartner et al. 2000; Bhalla and Dernburg 2005; Di Giacomo et al. 2005), a process that also functions as a screening mechanism against germ cell precursors with chromosomal abnormalities (Ahmed et al. 2013; Stevens et al. 2013; Titen et al. 2014). As in the mitotic DNA damage response, the decision to enter the apoptotic program in response to repair defects requires CHK2-dependent ac-

tivation of the p53 family of proteins, and is generally restricted to specific stages in meiotic prophase (Derry et al. 2001; Barchi et al. 2005; Suh et al. 2006; Rutkowski et al. 2011; Bolcun-Filas et al. 2014; Kim and Suh 2014). The role of the MCN in this decision has been difficult to define because, in most cases, loss of MCN factors itself causes DSB repair defects, which in turn trigger germ cell death (Barchi et al. 2008; Burgoyne et al. 2009). Conversely, even a relatively downstream factor in the MCN, such as p53, not only regulates apoptosis but also leads to reduced crossover formation in *Drosophila* (Lu et al. 2010). However, disruption of the 9-1-1 complex component HUS1 was recently shown to bypass both pachynema arrest and apoptosis in mouse spermatocytes (Lyndaker et al. 2013a), and disruption of CHK2 has similar effects in mouse oocytes (Bolcun-Filas et al. 2014), supporting a role of the MCN in this decision.

Interestingly, in both mouse and *C. elegans*, the meiotic cell death response shows a profound sexual dimorphism. Mouse spermatocytes experiencing defects in DSB repair or synapsis typically undergo cell death in pachynema, usually in conjunction with defective sex body formation and the resulting aberrant gene expression. In contrast, defective oocytes often proceed through the meiotic divisions (Nagaoka et al. 2011, 2012). Although many are later removed by atresia, surviving oocytes have a substantially higher rate of chromosome abnormalities compared with mature sperm. The reason for this inefficiency in removing aberrant oocytes is unclear. A different sexual dimorphism is observed in worms. *C. elegans* hermaphrodites show a robust apoptotic response to persistent meiotic defects (Gartner et al. 2000; Bhalla and Dernburg 2005). In contrast, *C. elegans* males only initiate the early stages of the apoptotic program but prevent caspase activation (Jaramillo-Lambert et al. 2010). This signaling modification may be linked to the constitutively asynaptic single X chromosome in male worms. Unexpectedly, despite the apoptotic culling mechanism only being active in hermaphrodites, male worms with synapsis defects produce fewer aberrant gametes, indicating the existence of apoptosis-independent proofing mechanisms in the male (Jaramillo-Lambert et al. 2010).

Links to Development

An alternative to triggering cell death in the face of persistent defects is to prevent the formation of mature gametes. Accordingly, in several organisms, the MCN creates dependencies between DSB repair and subsequent developmental events. One well-studied example occurs in *Drosophila*, in which DSB repair is linked to the developmental patterning of the oocyte. In this organism, persistent DSBs lead to ATR^{mei-41} and $CHK2^{Mnk}$-dependent modification of Vasa, an RNA helicase required for the translation of *gurken* mRNA and the dorsoventral patterning of the eggshell (Ghabrial et al. 1998; Staeva-Vieira et al. 2003). As a result, the MCN can block oocyte development. Analogously, the presence of persistent DSBs or defective synapsis also leads to an MCN-dependent block of the developmental program for spore formation in several fungi (Tung et al. 2000; Anderson et al. 2012; Guo and King 2013), ultimately preventing chromosomal defects from being passed on to the next generation.

ARCHITECTURAL FEATURES OF THE MCN

From this overview of the different checkpoint branches in meiotic prophase, it is apparent that the MCN is highly interconnected but uses a surprisingly small number of signaling molecules. This raises a number of questions, including how some of the signals are generated in the first place, how an appropriately modulated response is elicited, and how individual dependencies are separated and integrated.

The Context Matters

Increasing evidence suggests that the specialized architecture of meiotic chromosomes plays a fundamental role in shaping the response of the MCN. In many organisms, disruption of components of the meiotic chromosome axes, including SYCP3 and cohesins, leads to a defect in MCN signaling (Wang and Hoog 2006; Kouz-

netsova et al. 2009; Callender and Hollingsworth 2010; Lightfoot et al. 2011), although in some cases the loss of signal has been attributed to reduced DSB formation (Callender and Hollingsworth 2010). Perhaps not surprisingly, MCN roles have also been reported for several histone methyltransferases (San-Segundo and Roeder 2000; Checchi and Engebrecht 2011; Lamelza and Bhalla 2012; Ontoso et al. 2013a,b), which presumably promote chromosome axis assembly or contribute to the structural environment of MCN signaling. Further supporting an instructive role of the chromatin environment, differential chromatin marks on sex chromosomes and autosomes are associated with the differential response to asynapsis in *C. elegans* (Checchi and Engebrecht 2011; Lamelza and Bhalla 2012).

The chromosome axes likely have multiple functions in the context of the MCN. They form the platform for the binding and phosphorylation of HORMAD proteins, which form a key part of the chromosomal environment for the MCN in many organisms (Xu et al. 1997; Martinez-Perez and Villeneuve 2005; Carballo et al. 2008; Lin et al. 2010; Shin et al. 2010, 2013; Daniel et al. 2011; Kogo et al. 2012a,b; Wojtasz et al. 2012; Cheng et al. 2013). In addition, chromosome axis components also interact directly with components of MCN. For example, the *S. cerevisiae* axis protein Red1 physically associates with the 9-1-1 complex, an interaction required for MCN activity (Eichinger and Jentsch 2010). Cohesin is similarly required for the recruitment of the 9-1-1 complex in *C. elegans* (Lightfoot et al. 2011). Furthermore, because the activation of CHK2 kinases by ATM/ATR typically requires the presence of adaptor proteins, it has been suggested that chromosome axis proteins may provide such an adaptor function for the activation of the MCN (Niu et al. 2005; Carballo et al. 2008; Hunter 2008; Eichinger and Jentsch 2010; Tougan et al. 2010).

There is also increasing evidence that the sequential dynamic changes of meiotic chromosome axes play a significant role in the activation and modulation of the MCN. Most of this evidence stems from the functional analysis of $TRIP13^{Pch2}$, a widely conserved AAA^{+}-ATPase. $TRIP13^{Pch2}$ modulates meiotic chromosome structure in a variety of contexts, in many cases by controlling the chromosomal depletion or phosphorylation of HORMAD proteins (San-Segundo and Roeder 1999; Borner et al. 2008; Wojtasz et al. 2009; Roig et al. 2010; Vader et al. 2011; Miao et al. 2013; Chen et al. 2014; Lo et al. 2014). Mutants lacking $TRIP13^{Pch2}$ share a number of phenotypic features with mutants lacking ATM or ATR, consistent with the model that $TRIP13^{Pch2}$ is required for full activation of the MCN (San-Segundo and Roeder 1999; Borner et al. 2008; Joshi et al. 2009; Joyce and McKim 2009, 2010; Wojtasz et al. 2009; Zanders and Alani 2009; Roig et al. 2010; Zanders et al. 2011; Farmer et al. 2012). These effects are likely to a large extent a secondary consequence of disrupting HORMAD function, although in *S. cerevisiae*, $TRIP13^{Pch2}$ also directly modulates ATM^{Tel1} by interacting with the MRN^{Xrs2} complex (Ho and Burgess 2011).

Signal Generation

Chromosomal architecture may also lie at the root of one of the more perplexing aspects of meiotic checkpoint regulation, the ability of the MCN to respond to synapsis defects independently of SPO11-induced DSBs (Barchi et al. 2005; Bellani et al. 2005; Bhalla and Dernburg 2005; Barbosa et al. 2007; Joyce and McKim 2009; Lu et al. 2010). Available evidence suggests that features of the meiosis-specific chromosome structure itself may be able to activate the MCN. In most cases, checkpoint activity in response to asynapsis requires the activity of $TRIP13^{Pch2}$ on HORMAD proteins (Bhalla and Dernburg 2005; Joyce and McKim 2009, 2010; Kogo et al. 2012a; Wojtasz et al. 2012), and in several cases it also requires the activity of the histone deacetylase Sir2 (San-Segundo and Roeder 1999; Joyce and McKim 2010; Pek et al. 2012).

What DSB-independent feature of chromosome structure ultimately initiates the MCN signal remains unclear. The small ubiquitin-like protein modifier SUMO may be involved in signal formation, as it is one of the earliest

marks distinguishing the unsynapsed sex chromosomes for MSCI (Vigodner 2009), and is involved in MCN activation in *S. cerevisiae* (Eichinger and Jentsch 2010). However, SUMO accumulation on sex chromosomes depends on ATR (Royo et al. 2013), indicating that another aspect of asynapsis serves as a signal in this case. It is possible that the presence of HORMADs on unsynapsed chromosomes is itself the signal activating the MCN. In mouse, HORMAD1 has multiple roles in meiotic prophase (Shin et al. 2010, 2013; Daniel et al. 2011), whereas HORMAD2 is selectively required for SPO11-independent spreading of γ-H2AFX and MSUC/MSCI (Wojtasz et al. 2012). Because HORMAD2 directly binds to HORMAD1 (Wojtasz et al. 2012), an intriguing possibility is that HORMAD1/2 colocalization creates a SPO11-independent signal to activate the MCN. A direct checkpoint-activating function of HORMADs is also suggested by the observation that *C. elegans* mutants precociously expressing the HORMAD protein HTP-3 arrest at meiotic entry in an ATM^{ATL-1}-dependent manner without apparent DNA damage (Burger et al. 2013). Alternatively, there may be a SPO11-independent source of DSB formation and MCN activation, as indicated by the recent observation of SPO11-independent DNA repair foci on unsynapsed chromosomal regions of mouse meiocytes as well as SPO11-independent crossovers in *Coprinus cinereus* (Carofiglio et al. 2013; Crown et al. 2013).

Response Modulation

Another interesting feature of the MCN is the relative insensitivity to damage that is observed in several branches of this network. For example, whereas mitotic *S. cerevisiae* cells arrest in response to a single induced DSB (Lee et al. 2000), the same lesion elicits no comparable response in meiotic prophase (Malkova et al. 1996). A similar insensitivity to damage is also observed in mouse oocytes (Marangos and Carroll 2012). Intriguingly, the canonical *S. cerevisiae* $CHK2^{Rad53}$ checkpoint kinase, which would launch the arrest response in mitotic cells, is prevented from accessing meiotic chromosomes in most circumstances (Cartagena-Lirola et al. 2008) and is maintained in an inactive state by protein phosphatase 4 (Falk et al. 2010). Indeed, overexpression of the $CHK2^{Rad53}$ kinase delays meiotic progression (Usui and Kanehara 2013). Conversely, there also exist titration effects, whereby too many aberrant structures impair the normal checkpoint response. In particular, the MSUC response in mouse breaks down in the presence of too many unsynapsed chromosomes (Mahadevaiah et al. 2008; Kouznetsova et al. 2009). This may indicate a signaling limit for the MSUC response, and may also provide a safeguard against initiating MSUC in the early stages of meiotic prophase when most chromosomes are unsynapsed.

Signal Integration and Separation

The complexity of the meiotic checkpoint network raises the question how signals are integrated or separated. ATM and ATR achieve signal integration simply by phosphorylating many of the same target sites. Thus, the presence of blunt DNA ends and ssDNA can both elicit a delay in meiotic progression (Hochwagen and Amon 2006; Wu and Burgess 2006), and both kinases can stimulate DNA resection and regulate repair partner choice (Cartagena-Lirola et al. 2006; Carballo et al. 2008).

In other cases, it likely is necessary to avoid cross talk between signals. For example, ATR^{Mec1} regulates DSB formation differently in response to stalled replication during premeiotic S phase compared with leptonema when DSB formation has initiated (Argunhan et al. 2013; Blitzblau and Hochwagen 2013; Carballo et al. 2013; Cheng et al. 2013; Gray et al. 2013). Similarly, axis proteins (e.g., HORMAD1) assemble onto chromosomes concurrently with DNA replication but only become ATR substrates on DSB formation (Carballo et al. 2008; Wojtasz et al. 2009; Blitzblau et al. 2012; Cheng et al. 2013). One way to achieve signal separation is through alternative signaling complexes, such as the use of different CHK2 kinases (Blitzblau and Hochwagen 2013), or different signaling platforms, as has recently been suggested for the alternative

9-1-1 complexes active during mouse meiotic prophase (Lyndaker et al. 2013a,b; Vasileva et al. 2013). The decision for which signaling complex will ultimately be activated is likely driven by the distinct spectrum of MCN interactions that are possible at replication forks, DSBs, or unsynapsed regions, and will therefore again be strongly context dependent.

Finally, there is now substantial evidence that the signaling environment of the MCN evolves over the course of meiotic prophase. In *S. cerevisiae* and mouse there are clear differences in the timing by which specific MCN-mediated phosphorylation events appear and disappear (Barchi et al. 2005; Bellani et al. 2005; Fukuda et al. 2012; Cheng et al. 2013). Of particular interest here is the entry into pachynema, which is associated with an apparent switch in the signaling and response properties of the MCN. For example, the phosphorylated forms of HORMADs and $CHK2^{Mek1}$ specifically disappear in pachynema (Cartagena-Lirola et al. 2008; Fukuda et al. 2012; Cheng et al. 2013). In *C. elegans*, exogenous DSBs can trigger nuclear reorganization and persistent SUN-1 phosphorylation in leptonema/zygonema but not in pachynema (Woglar and Jantsch 2013). Moreover, repair pathway choice for exogenous DSBs also changes at later stages in meiotic prophase (Rosu et al. 2011; Libuda et al. 2013). Temporal evolution of MCN activity may in some cases be the result of stage-specific activation of phosphatases that remove MCN-dependent signals (Bailis et al. 2000; Hochwagen and Amon 2006; Falk et al. 2010; Cheng et al. 2013). In addition, in the spatially structured gonads of metazoans, temporal differentiation of the checkpoint response can also be imparted by external signals. For example, in *C. elegans* hermaphrodites, checkpoint-induced apoptosis is restricted by Ras/MAP kinase signaling to late pachynema, perhaps to avoid inappropriate cell death induction at earlier stages when SPO11-induced DSBs are prevalent (Rutkowski et al. 2011). The MCN therefore integrates both spatial and temporal information to yield a highly context-dependent coordination hub for the step-by-step progression through meiotic prophase.

CONCLUDING REMARKS

Our understanding of the MCN has progressed by leaps and bounds over the past several years, although with new insights, new experimental challenges have emerged. The increasingly evident interconnectedness of the MCN means that signaling outputs must be understood as the summation of signaling branches that modulate and feed back on each other. Dissecting this network will require more precisely regulatable genetic tools, new modeling approaches, as well as a better description of meiotic chromosome structure. Encouragingly, with the accelerating rate of discovery of direct MCN targets in multiple organisms as well as the first applications of systems-level analyses, the study of the MCN has clearly reached a new stage, and a comprehensive understanding of the MCN is starting to be within reach. Ultimately, of course, a major goal of this research is to use the emerging knowledge of the MCN for a better understanding of human chromosome inheritance and fertility. Because the MCN modulates the timing and activity of meiotic processes, partial loss-of-function mutations of MCN components are expected to have a major impact on gamete quality. The increasing abundance of whole-genome patient data holds big promise in this respect. In the coming years, informed by the research conducted in model organisms, we expect that these data will provide major insights into the high incidence of spontaneous abortions and chromosomal birth defects in humans.

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