

Molecular Mechanisms of Recombination

Recombination occurs during the prophase of the first meiotic division - which can be divided cytologically into four stages: leptotene (chromosome condensation), zygotene (synapsis of homologous chromosomes), pachynema (full synapsis), and diplotene (viable chromosomes) (Zickler and Kleckner 1999).

“Indeed, it appears that proteins involved in meiotic recombination are generally among the more rapidly diverging of all cellular proteins (Ramesh, Malik, and Logsdon Jr 2005, Richard et al. (2005), Keeney (2007)).”

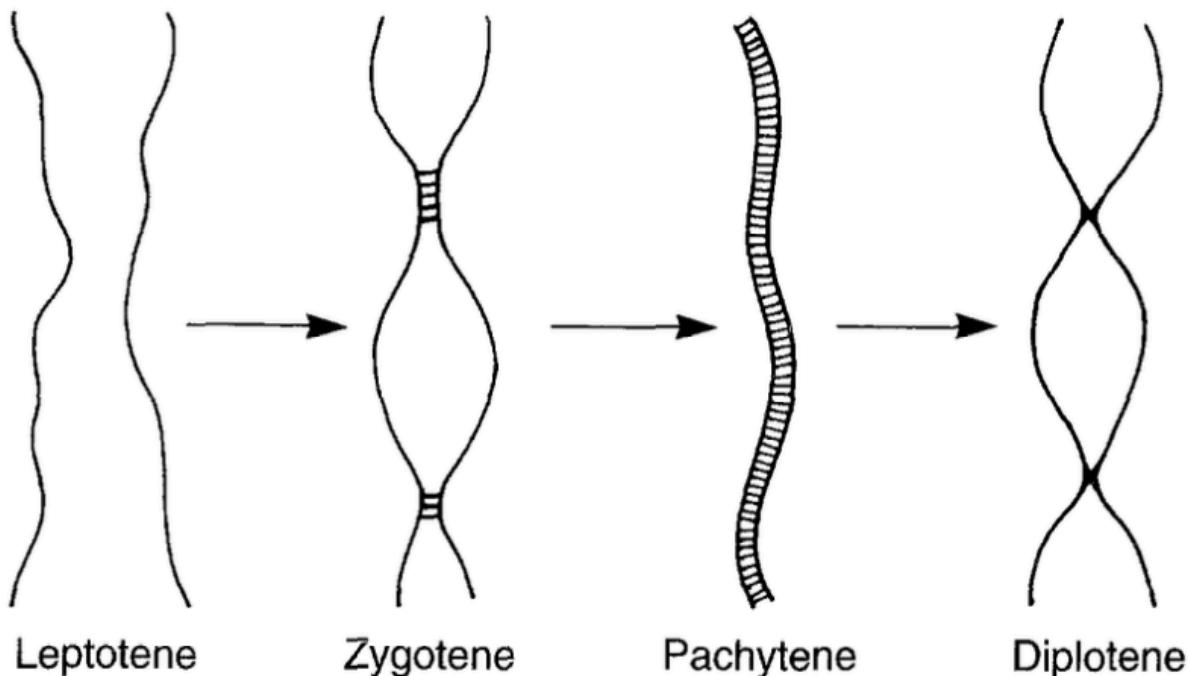


Figure 1.1 - Simple representation of the four cytological stages of recombination (Schmekel and Daneholt 1995)

In-depth reviews on the molecular biology of recombination: (Zickler and Kleckner 1999), (Petronczki, Siomos, and Nasmyth 2003), (S. L. Page and Hawley 2004).

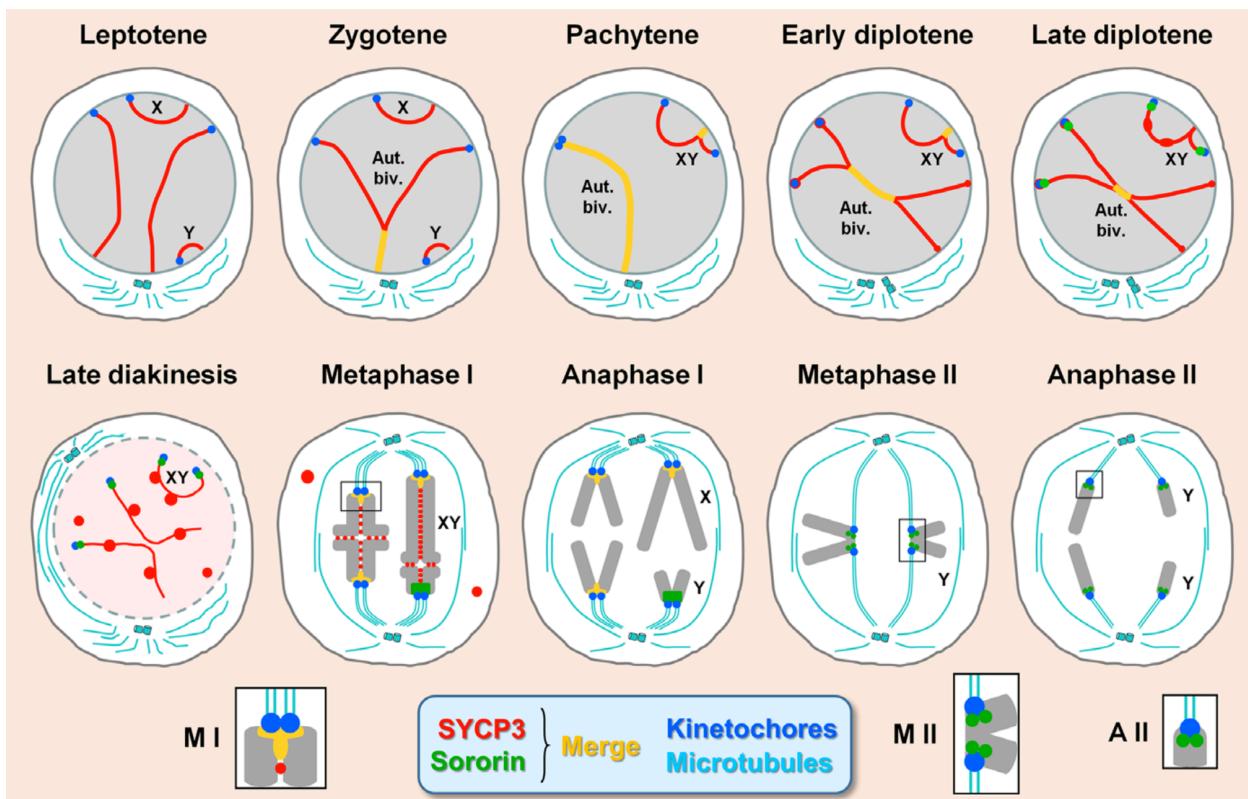


Figure 1.2 - Cartoon depiction of the stages of meiosis in mice (Gómez et al. 2016)

Double Strand Break (DSB) Formation

“At fine scale, we reveal a stereotyped hotspot structure—DSBs occur within narrow zones between methylated nucleosomes—and identify relationships between SPO11, chromatin, and the histone methyltransferase PRDM9 (Lange et al. 2016).”

“Resection lengths (per DSB end) ranged 300–1,800 nt (mean = 894 nt, median = 870 nt) (Lange et al. 2016).” mice

- “80% of crossover breakpoints fell within a zone <1 kb wide centered on the DSB hotspots’ centers (Lange et al. 2016).” mice
- “noncrossovers did not cluster close to DSB positions but instead spread across much of the resection zone (Lange et al. 2016).” mice
- “nearly all recombination events were entirely within the extent of SSDS coverage (Lange et al. 2016).” - mice

“hotspots are just one organizational level among many. More than a third of DSBs apparently occur outside of hotspots, and even in hotspots, H3K4me3 signal (a proxy for PRDM9 activity) explains only 40% of the variation in DSB frequency (Lange et al. 2016).”

“Beyond the hotspot scale, we find differences between sub-chromosomal domains, variation between autosomes correlated with chromosome length, and exceptionally high PAR DSB activity (Lange et al. 2016).”

“DSB formation is inhibited once chromosomes successfully engage their homologs (Thacker et al. 2014,Lange et al. (2016)).”

“Meiotic recombination initiates with the programmed generation of large numbers of DNA double-strand breaks (DSBs) (200–400 per cell in mice and humans) by the SPO11 enzyme [3–7] (Keeney, Giroux, and Kleckner 1997, Bergerat et al. (1997), Baudat et al. (2000), Romanienko and Camerini-Otero (2000), Baudat and Massy (2007), Finsterbusch et al. (2016))”

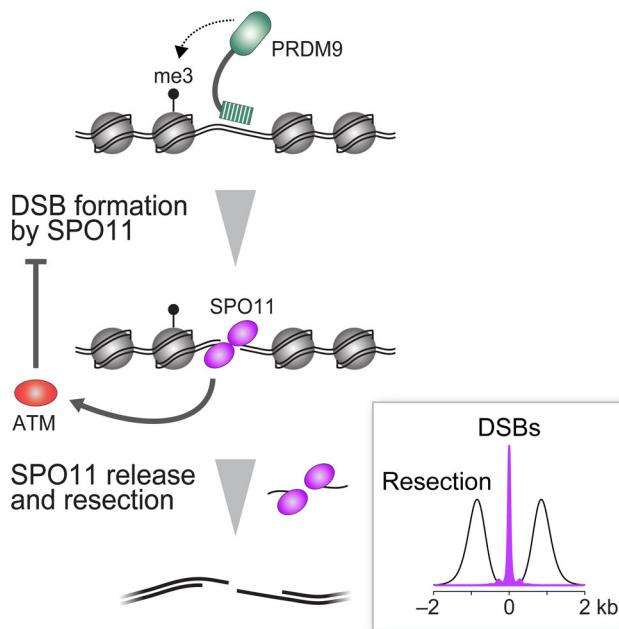


Figure 1.X - (Lange et al. 2016)

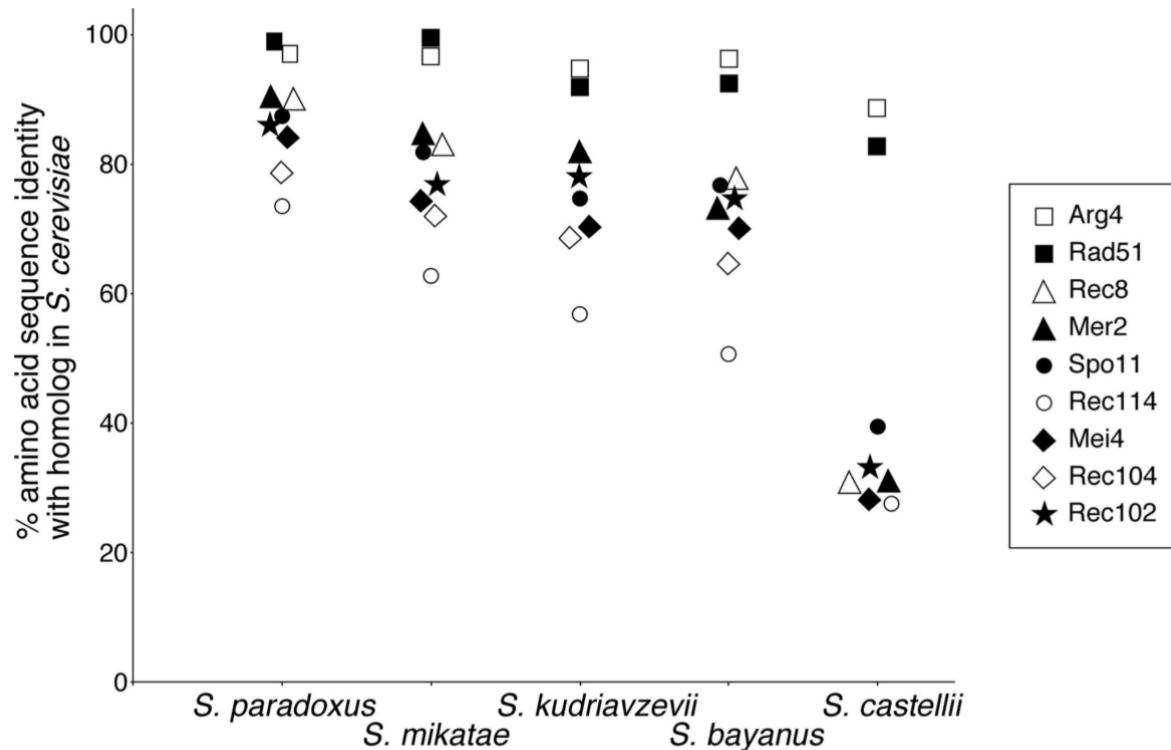


Figure 5. Rapid divergence of DSB proteins

Figure 1.X - (Keeney 2007)

PRDM9

histone methyltransferase w/ sequence-specific DNA binding (Brick et al. 2012, Smagulova et al. (2016))

"We favor that PRDM9 chromatin modification provides a landmark to attract SPO11 to locations at sub-kilobase scale, but that other features including nucleosome occupancy (but not H3K4me3) and PRDM9 itself then shape the DSB distribution within the hotspot. (Massy 2013, Lange et al. (2016))"

See : (Parvanov et al. 2017)

ATM

ATM regulates SPO11 activity - role for variation in DSB formation across multiple genomic scales? (Lange et al. 2016). "Our findings support this hypothesis by demonstrating that ATM not only controls DSB numbers but also molds the DSB landscape (Lange et al. 2016)." (Lange et al. 2011)

Should have been included????

SPO11

Summary: SPO11 is a type-II topoisomerase-like catalytic enzyme, with origins in Archaea, that generates single-strand breaks in DNA. There is a single conserved tyrosine residue that is required for its catalytic activity. There is also evidence that in some species, including mice, it has a second role during synapsis.

In-depth review: (Keeney 2007).

“Spo11 mRNA has been detected in nonmeiotic cells, although no function for the gene has been demonstrated in these cases (Keeney 2007).

One of the very first meiotic recombination genes to be identified (M. S. Esposito and Esposito 1969, Klapholz, Waddell, and Esposito (1985)). First identified & function characterized in yeast (*S. cerevisiae*) - meiosis-specific (Cao, Alani, and Kleckner 1990, Keeney, Giroux, and Kleckner (1997)).

“It is likely that a pair of Spo11 monomers acts in concert to cut both DNA strands. While DSBs are abundant in meiotic DNA, single-strand nicks are not detected, even at very strong DSB hot spots (Keeney, Giroux, and Kleckner 1997).”

Type II Topoisomerase-like, with origins in Archaea (Keeney, Giroux, and Kleckner 1997, Bergerat et al. (1997)).

“site-directed mutagenesis of a conserved tyrosine (Y135F) abolishes meiotic recombination (Bergerat et al. 1997).”

“Spo11 localizes to discrete foci early in meiosis and later to regions of homologous chromosome synapsis. We speculate that there is an additional role for Spo11, after it generates DSBs, in synapsis (Romanienko and Camerini-Otero 2000).”

“SPO11 makes DSBs through a topoisomerase-like reaction linking a SPO11 molecule to each 5’ DNA end (Figure 1A). DNA nicks nearby release SPO11 covalently bound to short oligonucleotides (SPO11 oligos), and 5’ -> 3’ exonuclease resection generates single-stranded DNA (ssDNA) that is bound by strand-exchange proteins DMC1 and RAD51 and engages in homology search (Hunter 2015, Lange et al. (2016)).”

“Spo11 orthologs are readily identifiable in widely diverged species because of conservation of core structural domains essential for catalytic activity, but the protein sequence overall is not very well conserved (Keeney 2001, D. Gadelle et al. (2003), Keeney (2007)).”

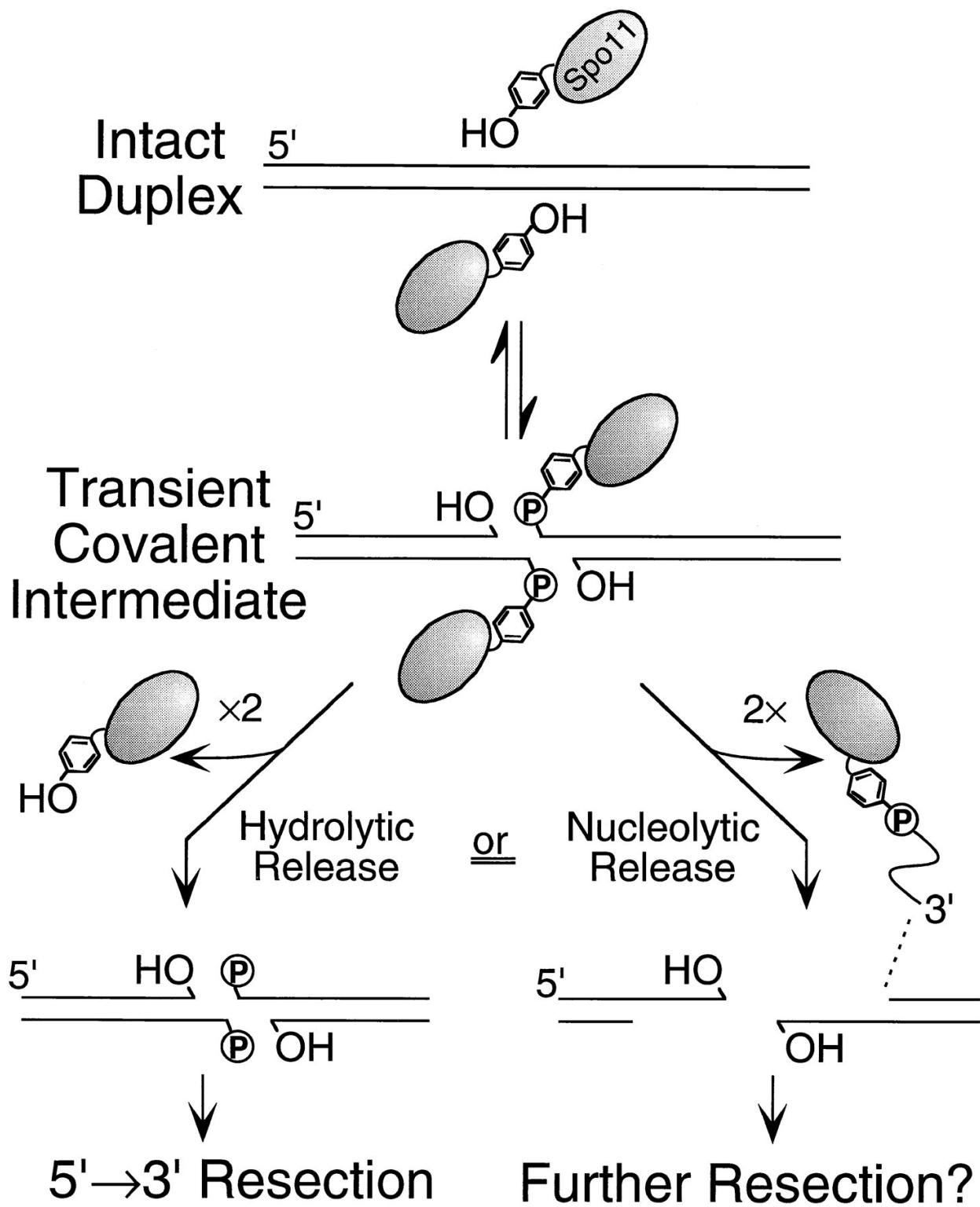


Figure 1.X - “we propose that a tyrosine side chain on Spo11 attacks the DNA phosphodiester backbone, generating a phosphodiester linkage between the protein and the 5' terminal strand and releasing a free 3' OH-terminus (Keeney, Giroux, and Kleckner 1997).”

MCD Recombinosome

“MEI4, REC114 and IHO1 form chromatin-bound complexes that appear crucial for DSB formation (Stanzione et al. 2016).”

“Pairwise interactions between IHO1-REC114 and REC114-MEI4 assemble chromatin-bound recombiosomes that promote DSB formation by activating SPO11 through an as yet unidentified mechanism (Stanzione et al. 2016).”

“This complex interacts with Spo11 through intermediary proteins (Stanzione et al. 2016).”

MEI4

Meiosis-specific (Menees, Ross-MacDonald, and Roeder 1992) Required for chromosome synapsis (Menees, Ross-MacDonald, and Roeder 1992).

“Cytological analyses reveal that, in mice, MEI4 is localized in discrete foci on the axes of meiotic chromosomes that do not overlap with DMC1 and RPA foci (Kumar, Bourbon, and Massy 2010).”

“Relatively little is known about the behaviors and functions of the meiosis-specific Rec114 and Mei4 proteins (Keeney 2007).”

REC114

Meiosis-specific (Bullard et al. 1996)

“Rec114 overexpression suppresses DSB formation, suggesting that the balance of the amount of Rec114 relative to other factors is critical (Bishop et al. 1999, Keeney (2007)).”

IHO1

“Curiously, although there are no clear IHO1 orthologues beyond vertebrates, IHO1 is also a coiled-coil protein. Thus, we hypothesize that IHO1 is a functional equivalent of Mer2/Rec15 and that SPO11 activity depends on a conserved MCD recombiosome in mice as in yeasts (Stanzione et al. 2016).”

Interacts with HORMAD1 (Stanzione et al. 2016).

HORMAD1/2

“Meiosis-specific HORMA-domain proteins are axis components that mediate key functions in control of DSB formation and repair and/or in the quality control of recombination in diverse taxa (Stanzione et al. 2016)”

“HORMA-domain proteins are needed for robust accumulation of MCD recombiosome components on chromatin and axes in mice (Stanzione et al. 2016)”

“In mammals, the HORMA-domain protein HORMAD1 preferentially associates with unsynapsed axes and is thought to have three main functions (Wojtasz et al. 2009, Fukuda et al. (2010), Shin et al. (2010), Daniel et al. (2011), Kogo et al. (2012), Shin, McGuire, and Rajkovic (2013), Stanzione et al. (2016))”

- promotes DSB break formation
- supports SC formation
- checkpoint for synapsis formation

“HORMAD1 may induce conformational changes in IHO1 via direct binding, or HORMAD1-mediated recruitment of unidentified enzymatic activities may lead to activating modifications of MCD recombiosome components. HORMAD1 is required for ‘spread out’ IHO1 localization along unsynapsed axes, but MEI4,

REC114 and IHO1 form foci along unsynapsed axes even in the absence of HORMAD1, so IHO1–HORMAD1 interaction is not the sole link between MCD recombinosomes and axes (Stanzione et al. 2016)”

(Wojtasz et al. 2009)

MRN Complex

Summary: The MRN complex is necessary for the removal of SPO11 from the DNA backbone post DSB formation. MRE11 trims off SPO11, RAD50 holds the broken DNA ends together, NBS1 is responsible for nuclear localization of the complex. The complex has important functions in DNA repair and telomere homostasis and is thus, not meiosis-specific.

MRE11-RAD50-NBS1 = MRN complex.

“Mre11-Rad50-Xrs2 (MRX)—These proteins form an evolutionarily conserved complex with multiple roles in many different aspects of DNA metabolism, including DNA repair, telomere maintenance, and checkpoint signaling. Mre11 has single-strand endonuclease and 3’→5’ exonuclease activities and Rad50 is an ATP-binding protein structurally related to SMC proteins (Keeney 2007).”

“Mre11 and Rad50 are evolutionarily conserved and form an ATP-regulated nuclease involved in processing hairpin-capped and protein-bound DNA ends (Oh et al. 2016).”

“it is not yet clear why MRX is required for formation of DSBs and not just for DSB processing (Keeney 2007).”

RAD50

“Rad50, as a member of the SMC family, has N- and C-terminal globular domains that come together to form a module for ATP-dependent dimerization and DNA binding (Hopfner 2005, Keeney (2007)).”

“These domains are separated by stretches of heptad repeat sequence that fold back to form a long alpha-helical coiled coil. One end of this coiled coil lies at the ATP binding domain, while the other end has a zinc-hook structure that allows multimerization of MRX complexes (Hopfner et al. 2002, Keeney (2007)).”

“Both ATP binding and zinc-hook driven multimerization are essential for DSB formation (Alani, Padmore, and Kleckner 1990, Wiltzius et al. (2005), Keeney (2007)).”

NOT MEIOSIS-SPECIFIC - Involved in repair of DSB in nonmeiotic cells (Johzuka and Ogawa 1995)

MRE11

“Mre11 nuclease activity is required for Spoll to be removed from DSB ends (Keeney 2007).”

“the C-terminal region of *S. cerevisiae* Mre11 is required for DSB formation and interacts with as-yet-unknown meiosis-specific proteins (Usui et al. 1998, Keeney (2007)).” However: “mutations that affect the C terminus of mouse MRE11 do not block meiotic DSB formation (Theunissen et al. 2003, Keeney (2007)).”

NOT MEIOSIS-SPECIFIC - Involved in repair of DSB in nonmeiotic cells (Johzuka and Ogawa 1995)

NBS1/NBN

“Xrs2/Nbs1 is less conserved than Mre11 and Rad50 and has only been identified in eukaryotes (Stracker and Petrini 2011, Oh et al. (2016)).”

“Xrs2/Nbs1 is required for nuclear localization of Mre11 and has a number of protein-protein interaction motifs, suggesting it functions as a chaperone and scaffold (Carney 1998, Tsukamoto et al. 2005, Oh et al. (2016)).”

"Xrs2 and its human equivalent NBS1 have N-terminal FHA and tandem BRCT domains, which are motifs often involved in binding to phosphopeptides (Durocher and Jackson 2002, Chahwan et al. (2003), Glover, Williams, and Lee (2004), Becker et al. (2006), Keeney (2007))."

"*S. cerevisiae* Xrs2 also has conserved C-terminal domains required for interaction with Mre11 and with the kinase Tel1. The Mre11-interaction domain is required for DSB formation, but the Tel1-interaction domain is not (Shima et al. 2005; Tsukamoto et al. 2005) (Shima, Suzuki, and Shinohara 2005, Tsukamoto et al. (2005), Keeney (2007))."

NOT MEIOSIS-SPECIFIC - Involved in repair of DSB in nonmeiotic cells (XRS2 in yeast) (Ivanov, Korolev, and Fabre 1992)

(Start with (Oh et al. 2016))

Strand Invasion

"Rad51 is a multifunctional protein that catalyzes recombination directly in mitosis and indirectly, via Dmc1, during meiosis (Cloud et al. 2012)"

DMC1 and RAD51 are eukaryotic recombinases that mediate/catalyze homologous chromosome pairing during homologous recombination (Kobayashi et al. 2016).

DMC1 and RAD51 have high sequence similarity in mammals (>50%). (Kobayashi et al. 2016)

RAD51 -/- knockout is embryonic lethal and DMC1 -/- knockout results in sterilization. (Kobayashi et al. 2016)

RAD51 is expressed in both mitotic and meiotic cells. DMC1 is only expressed in meiotic cells. (Kobayashi et al. 2016)

"The eukaryotic RecA homolog Rad51 mediates DNA strand exchange in vitro by forming a helical protein filament on ssDNA, the so-called presynaptic filament (Ishishita, Matsuda, and Kitada 2014)."

"Human BRCA2 facilitates RAD51 nucleofilament formation in vitro by localising RAD51 to ssDNA (Ishishita, Matsuda, and Kitada 2014)."

"RAD51 and DMC1 initiate the 3' single-strand invasion into the DNA duplex of the homologous chromosome (M. S. Brown and Bishop 2014, Y. Xu et al. (2017))."

"To promote homologous pairing, DMC1 and RAD51 first bind to the ssDNA region, and form filamentous nucleoprotein complexes. The DMC1-ssDNA or RAD51-ssDNA complex is then bound to the dsDNA target, and the homologous DNA sequences are aligned within the ternary complex containing ssDNA, dsDNA, and DMC1 or RAD51 (Kobayashi et al. 2016)"

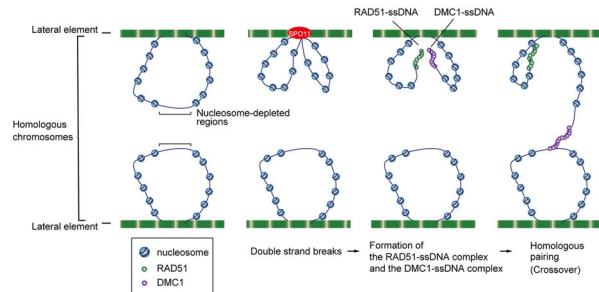


Figure 1.3 - Cartoon depiction of the stages of meiosis in mice (Gómez et al. 2016)

SPATA22

“SPATA22 co-localizes with a number of proteins involved in meiotic recombination, including RAD51, DMC1, and MLH1, and is present until mid-pachynema, suggesting a role in resolution of recombination intermediates (Hays et al. 2017)

“spermatogenesis associated 22 (Spata22), a previously uncharacterized vertebrate-specific gene of unknown function (La Salle et al. 2012).”

“Synapsis and DNA double-strand break (DSB) repair are both severely impaired in mutant oocytes and spermatocytes, suggesting that SPATA22 is a novel germ cell-specific factor required for progression of meiotic prophase in mice (La Salle et al. 2012).”

“both formation and maintenance of Rpa foci are independent of Spata22, but Spata22 is required for the maintenance, but not the formation, of Rad51 foci in mammalian meiosis (Ishishita, Matsuda, and Kitada 2014).”

“the overall conclusion that Rad51 foci disappear prematurely from meiotic chromatin in the absence of Spata22 function (Ishishita, Matsuda, and Kitada 2014).”

MEIOB

“MEIOB (meiosis specific with OB domains), a meiosis-specific single-stranded DNA-binding homolog of replication protein A1 (RPA1), is essential for meiotic recombination (Y. Xu et al. 2017).”

“MEIOB and SPATA22 form an obligate complex and contain defined interaction domains. The interaction between these two proteins is unusual in that nearly any deletion in the binding domains abolishes the interaction. Strikingly, a single residue D383 in MEIOB is indispensable for the interaction (Y. Xu et al. 2017).”

“We have identified the discrete interaction domains in both proteins. Unusually, a series of small deletions within the interaction domains of either protein abolished their interaction, suggesting that their binding is synergistic and that disruption anywhere along the binding interface may lead to the collapse of the complex. In support of this notion, strikingly, a single amino acid D383 in the SPATA22-binding domain of MEIOB is essential for the interaction. Mutation studies showed that both charge and structure at residue D383 are important (Y. Xu et al. 2017).”

“MEIOB and SPATA22 interact with the RPA complex in a cooperative manner (Y. Xu et al. 2017).”

“Both MEIOB and RPA1 bind to ssDNA. We find that the RPA1-binding domain and ssDNA-binding domain in MEIOB overlap with each other. This raises the possibility that binding of RPA with the MEIOB/SPATA22 complex may dislodge the complex from ssDNA or vice versa (Y. Xu et al. 2017).”

“Our results demonstrate that MEIOB and SPATA22, two meiosis-specific proteins, strongly interact with each other, suggesting that they form a heterodimer or a hetero-oligomer (Y. Xu et al. 2017).”

“Recent studies identified a novel protein, Meiob, which associates with Spata22 and Rpa, and showed that Meiob is required for meiotic progression, chromosome synapsis, and meiotic DSB repair (Souquet et al. 2013, Luo et al. (2013), Ishishita, Matsuda, and Kitada (2014)).”

“Meiob was identified as a protein that associates with Spata22 and with Rpa during prophase I (Souquet et al. 2013, Luo et al. (2013), Ishishita, Matsuda, and Kitada (2014)).”

“Meiob and Spata22 are localised to meiotic chromosomes interdependently (Luo et al. 2013, Ishishita, Matsuda, and Kitada (2014)).”

MCMDC2

“our work suggests that MCMDC2 plays an important role in either the formation, or the stabilization, of DNA strand invasion events that promote homologue alignment and provide the basis for inter-homologue crossover formation during meiotic recombination (Finsterbusch et al. 2016)”

Synaptonemal Complex (SC)

“*During the leptotene stage of prophase I, axial elements (AE) are formed along chromosomal cores between sister chromatids. During the subsequent zygotene stage, the AEs of two homologous chromosomes become connected by transverse filaments (TF) in a process referred to as synapsis. Because TFs overlap in the center to form a CE, AEs, TFs, and the CE constitute the tripartite SC (Yang et al. 2006).*”

“*The synaptonemal complex is a large zipper-like protein that connects one pair of sister chromatids to the homologous pair (Hamer et al. 2006).*”

“The SC is a zipper-like structure composed of two lateral elements (LEs) that are joined together by transverse filaments (Costa et al. 2005).” Reviewed in: (S. L. Page and Hawley 2004).

“*The synaptonemal complex formation starts during leptotene when the synaptonemal complex proteins 2 and 3 (SYCP2 and SYCP3) begin to form the axial elements (Hamer et al. 2006).*”

“Protein components SYCP1, [SYCP2,] SYCP3, SYCE2, and TEX12 were identified in basal-branching metazoans, while other components (SYCE1 and SYCE3) are more recent elements (Fraune et al. 2014).”

“*Later, when the homologous chromosomes become synapsed during the zygotene stage, the axial elements (now referred to as lateral elements) are joined by the transverse filaments formed by the synaptonemal complex protein 1 (SYCP1) (Hamer et al. 2006).*”

“*It has been estimated that the synaptonemal complex as a whole consists of more than ten meiosis-specific proteins (C. Heyting et al. 1989; Hamer et al. 2006).*”

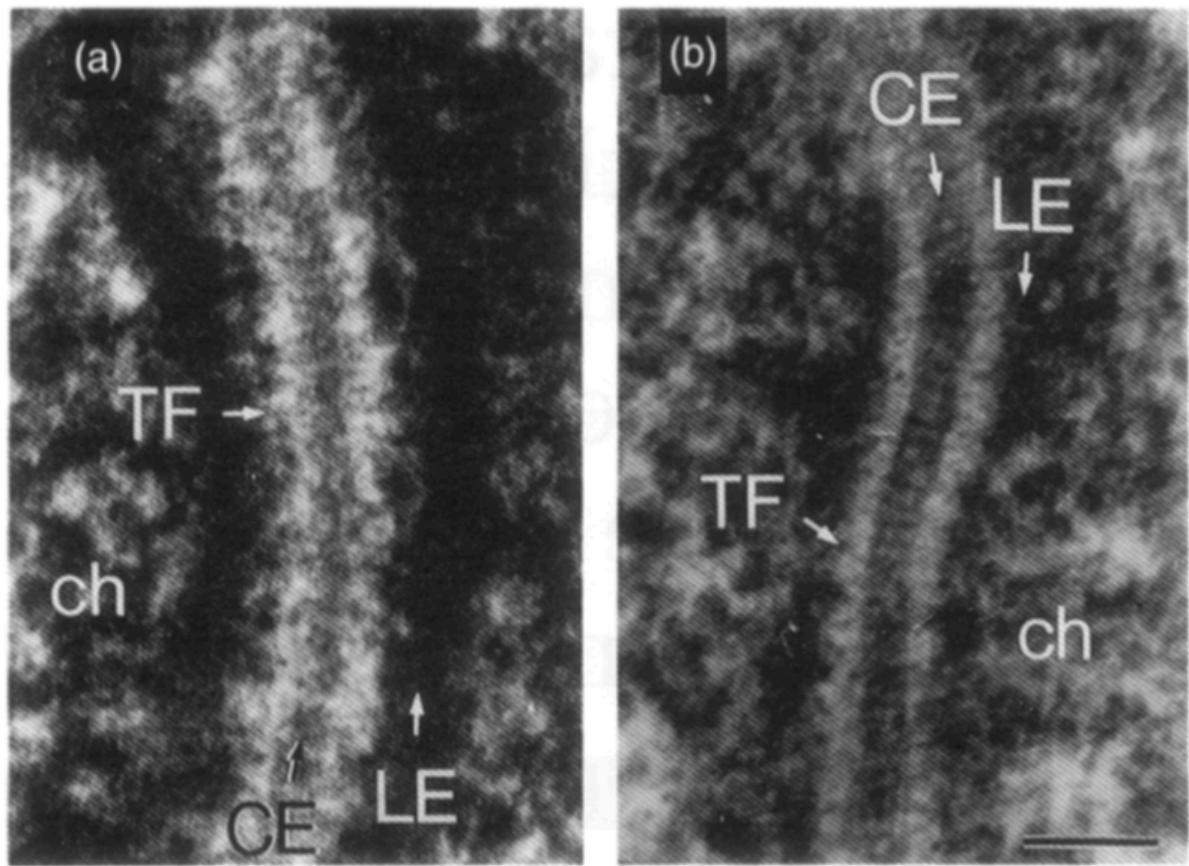


Figure 2.1 - Electron microscopy of the synaptonemal complex in spermatocytes of (a) rats and (b) a beetle (*Blaps cibrosa*) (Schmekel and Daneholt 1995).

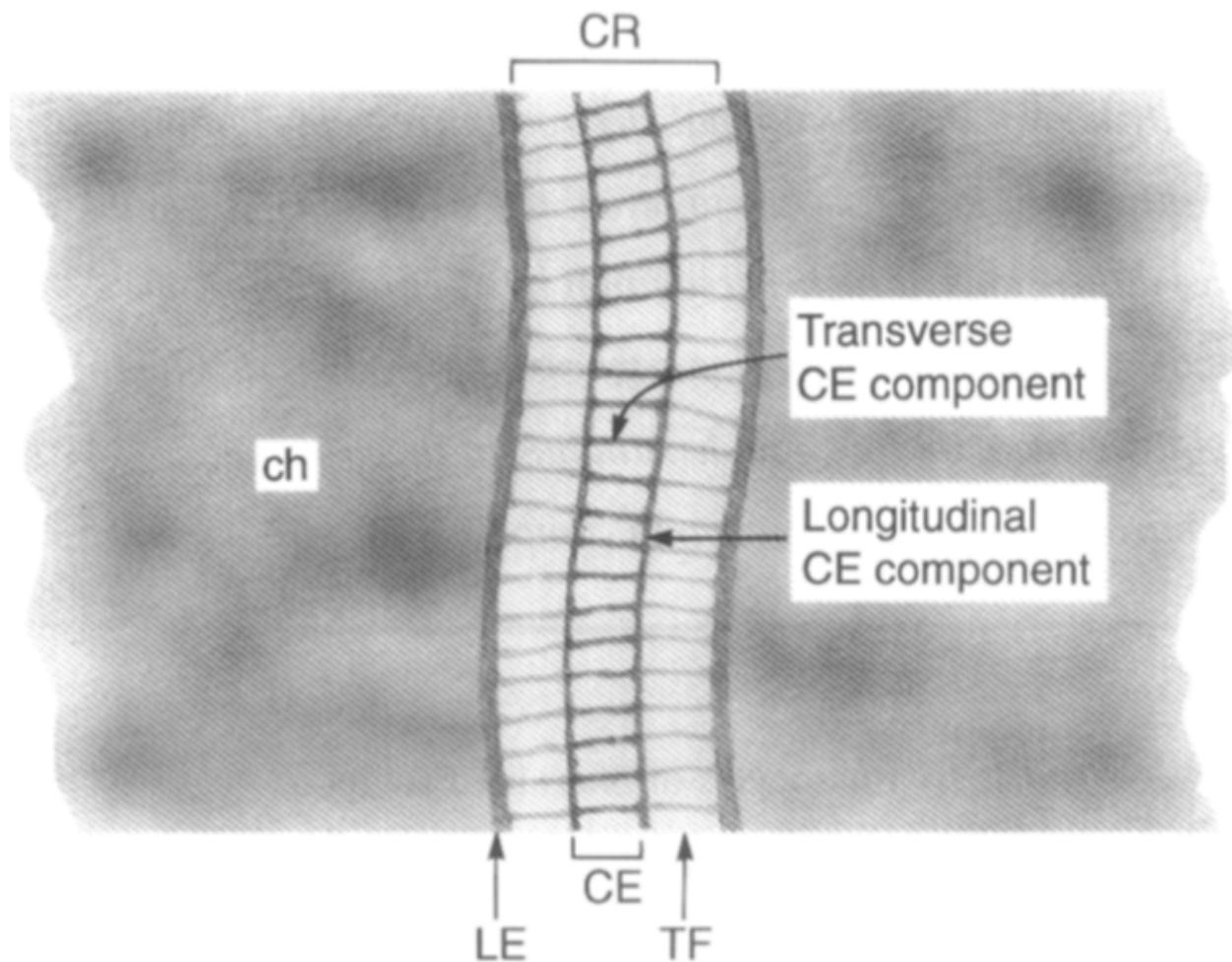


Figure 2.2 - Illustration of the structure of the synaptonemal complex: CR - central region, CE - central element, LE - lateral elements, TF - transverse filaments, ch - surrounding chromatin (Schmekel and Daneholt 1995).

Images: (Schmekel and Daneholt 1995)

REC8

“Rec8 (and Rec11) are meiosis-specific cohesin components that assemble on chromosomes around the time of premeiotic DNA replication (Watanabe and Nurse 1999, Kitajima et al. (2003), Keeney (2007)).”

“DSB formation and meiotic recombination are greatly reduced in the absence However, the magnitude of the recombination decrease varies substantially depending on the genomic region assayed, ranging from ~4-fold to >100-fold (DeVeaux and Smith 1994, Krawchuk, DeVeaux, and Wahls (1999), Parisi et al. (1999), Ellermeier and Smith (2005), Keeney (2007)).”

RAD21L

Central Element (CE) of the Synaptonemal Complex

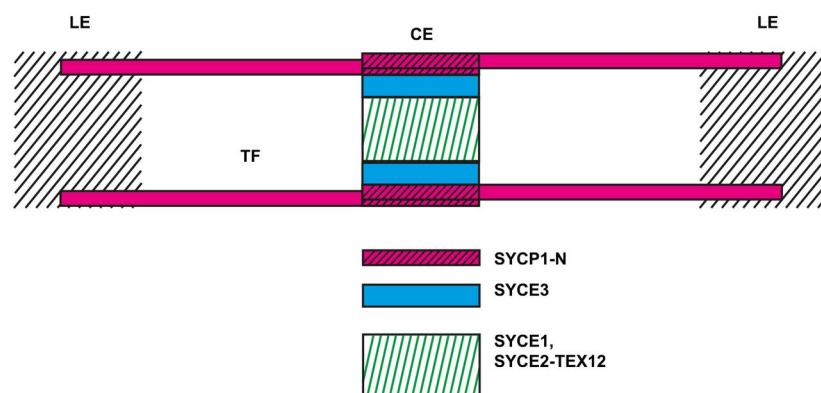


Figure 3.1 - Model for the organization of the central element (Hernández-Hernández et al. 2016).

SYCE1, SYCE2, & SYCE3 - *Synaptonemal Central Elements*

Identification: SYCE1 & SYCE2 (Costa et al. 2005), SYCE3 (Schramm et al. 2011)

Evolution of CE proteins in *Metazoa*: (Fraune et al. 2013)

TEX12 - *Testis-expressed sequence 12 protein*

TEX12 is a component of the central structure of the synaptonemal complex (Hamer et al. 2006).

TEX12, SYCE1 and SYCE2 depend on the synaptonemal transverse filament protein SYCP1 for localization (Hamer et al. 2006).

TEX12 exactly co-localizes with the central element protein SYCE2 - with the same, often punctate, localization pattern (Hamer et al. 2006). This was confirmed by a co-immunoprecipitation experiment (See Figure 6) (Hamer et al. 2006).

TEX12 is “required for propagation of synapsis along the paired homologous chromosomes and maturation of early recombination events into crossovers (Hamer et al. 2008).”

The TEX12 protein is small (14 kDa) (Hamer et al. 2006).

Functional domain - “The regions located from aa 49 to 123 of human Tex12 were defined as essential for the capability to polymerize (Davies, Maman, and Pellegrini 2012) and nicely correspond to the most conserved parts of the proteins in our analysis (Fraune et al. 2013).”

TEX12 can be traced back to the ancestor of *Eumetazoans* - traced back all the way to *Hydra* (with same function), very ancient (Fraune et al. 2013).

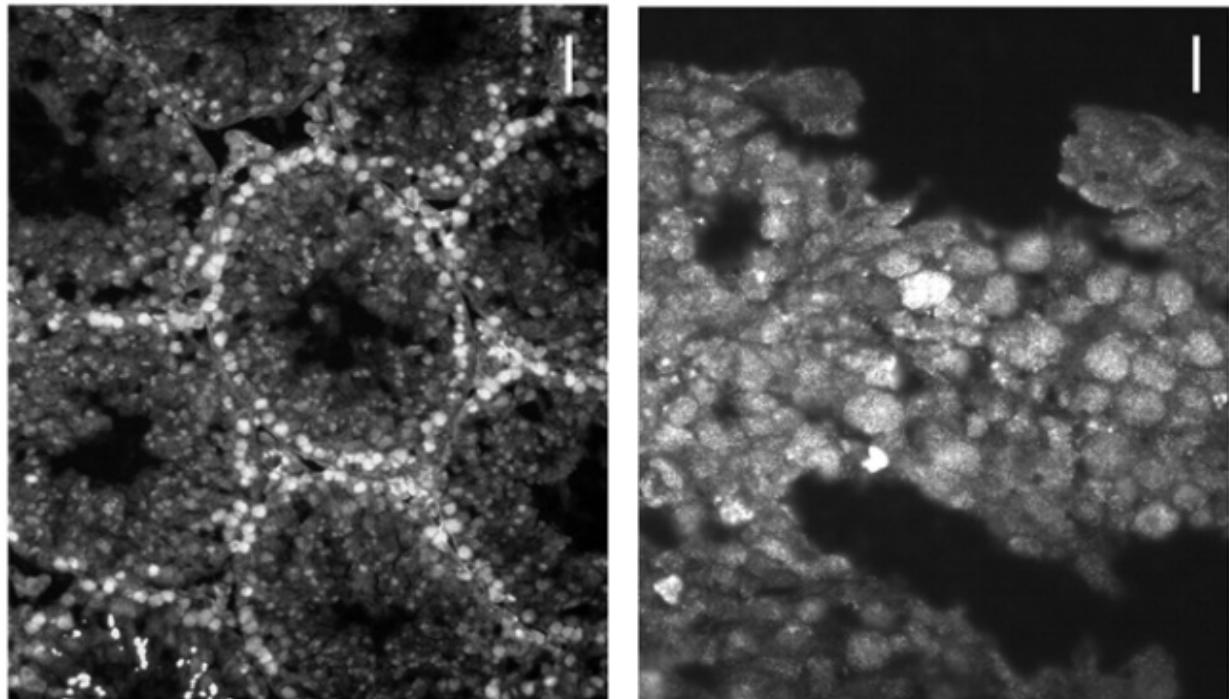


Figure 3.2 - TEX12 is expressed in both testes (left) and ovaries (right) in mice (in situ hybridization)(Hamer et al. 2006).

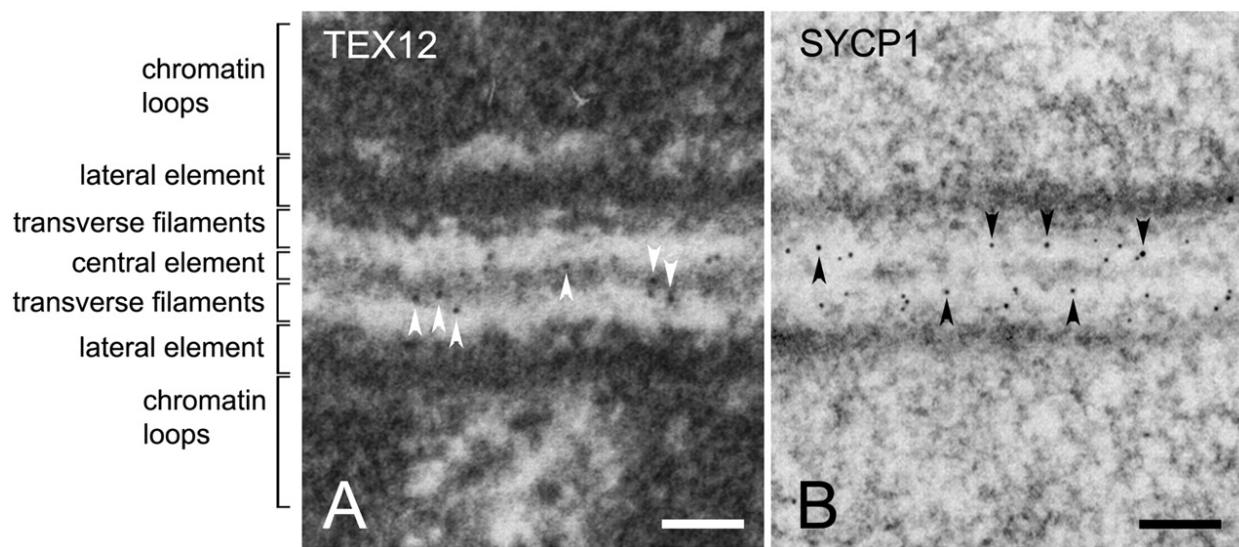


Figure 3.3 - TEX12 localizes to the central element of the synaptonemal complex (immunogold labeling & electron microscopy) (Hamer et al. 2006).

SYCP1 - Synaptonemal Complex Protein 1

Major component of the transverse filaments in the synaptonemal complex - bridges the gap between lateral elements (LEs) and central element (CE) (R. Meuwissen et al. 1992). Review of the functions of the TF: (Boer and Heyting 2006).

Required for normal assembly of the central element of the synaptonemal complex and normal centromere pairing.

SYCP1 is required for the formation of the XY body in pachytene spermatocytes (Vries et al. 2005).

"In addition to their roles as synaptonemal complex components, SYCP1 and SYCP3 act at the centromeres to promote the establishment and/or maintenance of centromere pairing and, by doing so, improve the segregation fidelity of mammalian meiotic chromosomes (Bisig et al. 2012)."

"The transcription of the gene encoding SCP1 is restricted to zygotene-diplotene spermatocytes (R. Meuwissen et al. 1992)." They did not look at ovarian tissues - so, this doesn't mean it exhibits sex-specific expression.

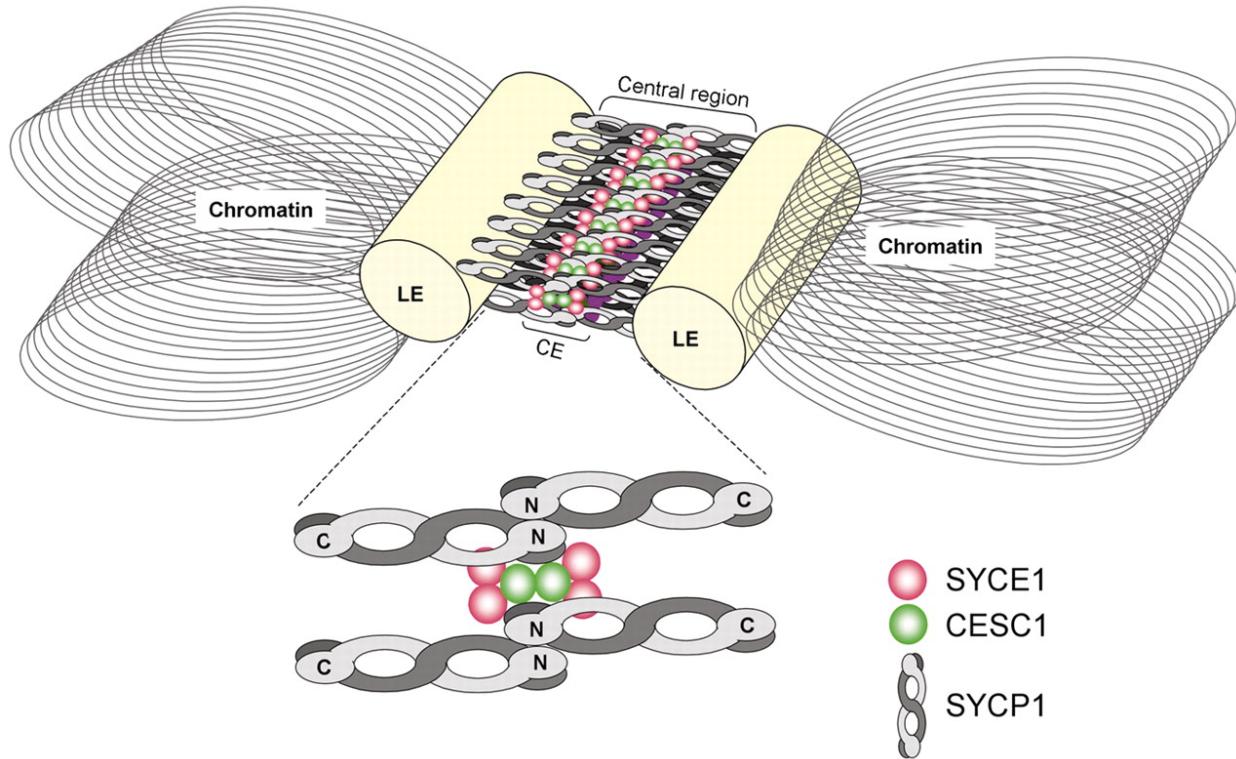


Figure 4.1 - Model of interactions between SYCP1, SYCE1 and SYCE2 (CESC1) (Costa et al. 2005).

"It is believed that, the increased electron-density observed in the CE compared with the adjacent rest of the central region is owing to the arrangement of the N-terminal region of dimers of SYCP1 that interact in a head-to-head fashion, while forming an interdigitating array of dimers (Costa et al. 2005)." See: (Schmekel et al. 1996), (Öllinger, Alschheimer, and Benavente 2005)

"It shares several features with nuclear lamins and some recently identified nuclear matrix proteins." Speculations that SYCP1 evolved via specialization of a nuclear matrix protein (R. Meuwissen et al. 1992).

"All of these proteins are (predicted to be) capable of forming long coiled-coil dimers consisting of two amphipathic α -helices which associate through hydrophobic interaction (R. Meuwissen et al. 1992)."

Three domains:

1. Central Domain capable of forming an α -helical coiled-coil: “The major part is similar to proteins that are capable of forming (amphipathic) α -helical coiled-coil dimers, such as the S2 domain of myosin heavy chain, or tropomyosin. This region shows amino acid sequence similarity to the coiled-coil region of myosin heavychain. A leucine zipper is included in this region (positions 341-369). (R. Meuwissen et al. 1992).” - 700 AAs long from residue 52 - 752.

2. Amino-terminal domain: The amino-terminus is 52 AAs long (R. Meuwissen et al. 1992).

3. Carboxy-terminal domain: “The carboxy-terminus is enriched in the S/T-P-X-X-motif, which is characteristic of DNA-binding proteins, and has two small basic domains (R. Meuwissen et al. 1992).” - 194 AAs long.

“The protein has several potential phosphorylation sites (potentially p34Cdc2 protein kinase) that could play a role in SC assembly and disassembly(R. Meuwissen et al. 1992).”

SYCP1 recruits SYCE1 (Costa et al. 2005).

Evidence that SYCP1 associates with PRDM9-bound complexes (and SYCP3 & REC8) (Parvanov et al. 2017).

The loading of regulatory factor Sororin (and: SMC5,SMC6) depends on SYCP1 (Gómez et al. 2016).

SYCP1 in monotremes: (Casey, Daish, and Grutzner 2015); In chickens: (Zheng et al. 2009)

First described: (R. Meuwissen et al. 1992)

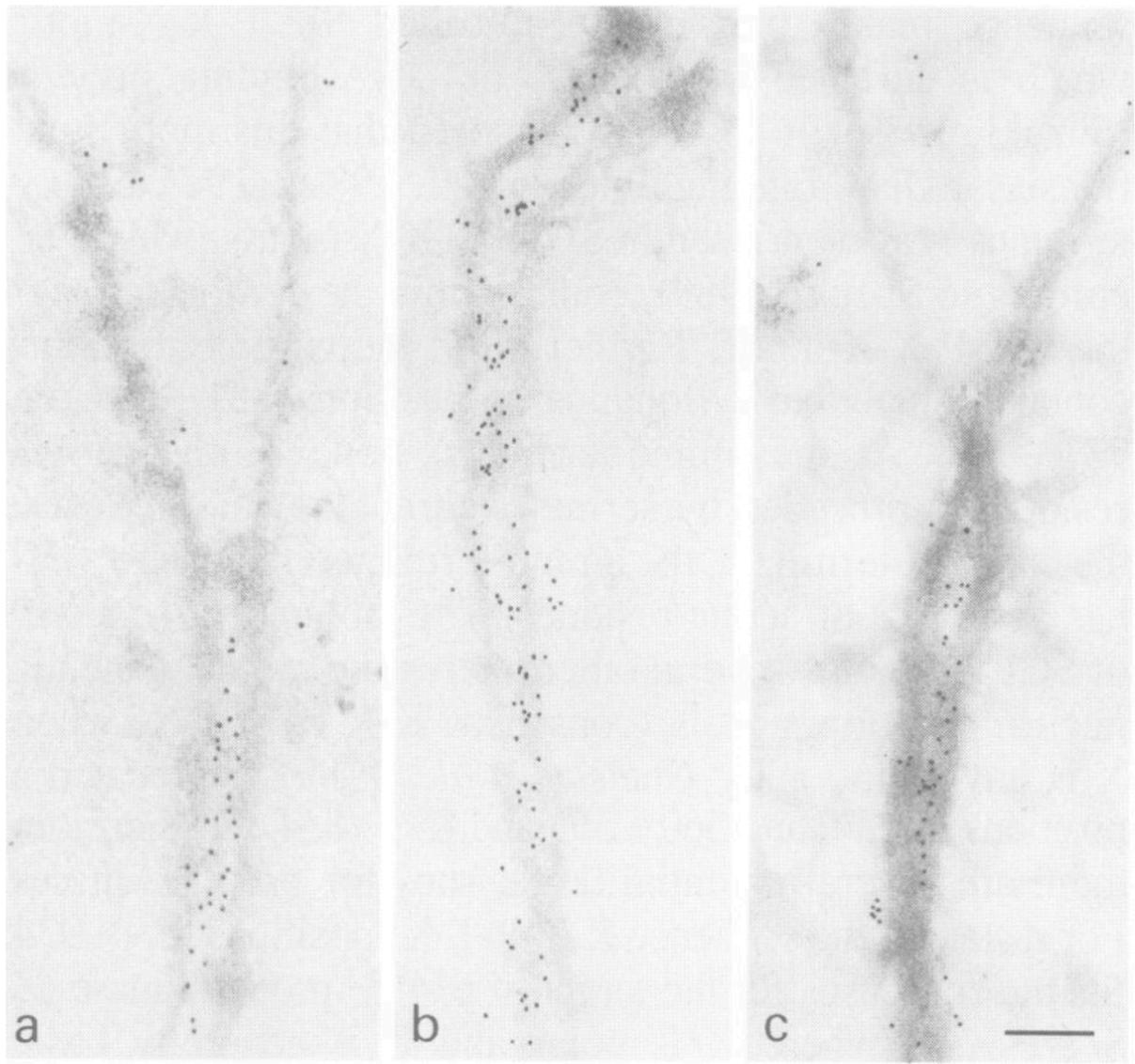


Figure 4.2 - SYCP1 localizes to the transverse filaments of the synaptonemal complex (immunogold labeling & electron microscopy) (R. Meuwissen et al. 1992).

SYCP2 - *Synaptonemal Complex Protein 1*

SYCP2 & SYCP4 are major/integral components of the two axial/lateral elements (AEs) of the synaptonemal complex.

SYCP2 & SYCP3 form heterodimers - SYCP2 is required for the localization of SYCP3 to the AE/LEs (Yang et al. 2006)

‘An evolutionarily conserved coiled coil domain in SYCP2 is required for binding to SYCP3 (Yang et al. 2006).’

May bind DNA at scaffold attachment regions.

“The phenotype of Sycp2 mutant mice is sexually dimorphic; males are sterile because of the absence of AE formation and the subsequent disruption of chromosome synapsis in prophase I spermatocytes, and females are subfertile (Yang et al. 2006).”

“Both Sycp2 and -3 mutant oocytes exhibit a type of chromosome synapsis, in which SYCP1 localizes to long fibers that are interrupted by some axial gaps (Yang et al. 2006).”

“SYCP2 is the largest SC protein yet described and in the mouse consists of 1,500 amino acids (Fraune et al. 2014).”

“It appears to be involved in LE assembly as well as linking LEs and TFs [Offenberg et al., 1998] (Yang et al. 2006; Winkel et al. 2009, Fraune et al. (2014)).”

“We conclude that SYCP2 belongs to the group of ancient SC proteins that was already present in the common ancestor of metazoans more than 500 million years ago (Fraune et al. 2014).”

See: (Winkel et al. 2009)

Crossover vs. Non-Crossover Decision

TEX11

(Yang et al. 2008)

MutS MSH4-MSH5

(Kneitz et al. 2000, Snowden et al. (2004), Kolas et al. (2005))

CNTD1

(Holloway et al. 2014)

HEI10

(Ward et al. 2007, Qiao et al. (2014))

MutL MLH1-MLH3

“MLH1/MLH3 are endonucleases responsible for the formation of the majority of crossovers (Baker et al. 1996, Edelmann et al. (1996), Lipkin et al. (2002), Rogacheva et al. (2014), Y. Xu et al. (2017))”

Mus81

“MUS81 produces a subset of MLH1/MLH3-independent crossovers (De los Santos et al. 2003, Holloway et al. (2008), Y. Xu et al. (2017))”

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