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Meiotic Chromosome Synapsis and the Synaptonemal Complex: From Mechanistic Insights to Disease Associations

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Abstract: ***The synaptonemal complex (SC) is a highly conserved proteinaceous structure that physically links homologous chromosomes during meiosis, thereby orchestrating chromosome pairing, recombination, and segregation. Recent advances in super-resolution microscopy, cryo-electron microscopy, and multi-omics approaches have substantially deepened our understanding of the SC's molecular architecture, dynamic assembly–disassembly process, and its pivotal roles in reproductive biology. In this review, we synthesize current knowledge on the structural organization of the SC, elucidate how mutations in SC-associated genes perturb meiosis and contribute to reproductive disorders, and summarize recent progress in methodological innovations that facilitate SC research. We further highlight unresolved questions and propose future research directions, aiming to bridge basic mechanistic insights with potential clinical applications in the diagnosis and management of infertility.***

Keywords: Synaptonemal complex, Meiosis, Reproductive disorders, Gene mutations, Infertility.

1. Overview of Meiosis

Meiosis is an essential cell division process in sexually reproducing organisms, serving to generate haploid gametes (sperm and oocytes). Defects in this process lead to significant human infertility pathologies, including non-obstructive azoospermia (NOA) in males and premature ovarian insufficiency (POI) in females [1, 2]. During meiosis, DNA replicates once but undergoes two consecutive divisions: Meiosis I, which separates homologous chromosomes, and Meiosis II, which separates sister chromatids [3].

The complex process of meiotic prophase I unfolds through five morphologically distinct substages, each marked by specific chromosomal events. It begins with leptotene, where chromosome condensation initiates, followed by zygotene, characterized by homologous pairing and the initiation of synaptonemal complex (SC) formation. The process culminates in pachytene, where SC assembly completes and crossing over occurs. This is followed by diplotene, where the SC disassembles and chiasmata become visible, and finally diakinesis, where chromosome terminalization occurs [4].

Several critical events during prophase I ensure accurate chromosome segregation. These include the formation of double-strand breaks (DSBs), homologous chromosome pairing, synapsis (mediated by the synaptonemal complex, SC), and homologous recombination culminating in crossover formation [5]. The SC—a elaborate proteinaceous structure that assembles between paired homologous chromosomes—is fully established by the pachytene stage and disassembles during diplotene, a process essential for enabling accurate chromosomal disjunction.

2. The Composition and Discovery of the Synaptonemal Complex

The synaptonemal complex (SC) is a meiotic scaffold structure comprising two lateral elements bound to homologous chromosomes, interconnected by a central element through transverse filaments. Functionally essential during prophase I, it tightly couples homologs while recruiting critical meiotic proteins, with its assembly/ disassembly cycle regulating chromosome dynamics [6]. Cut Early studies using electron microscopy, conventional light microscopy, and genetic analyses established this foundational model but provided limited spatial resolution of protein arrangements [5]. Recent super-resolution techniques like STORM (Stochastic Optical Reconstruction Microscopy) have overcome historical limitations, enabling clear differentiation of lateral/central elements [7, 8] and allowing 3D molecular reconstruction via fluorescent antibody labeling, multi-planar imaging, and computational integration of 2D datasets [9].

3. SC Structure and Dynamic Assembly

3.1 Ultrastructure of SC

Discovered in 1956 by Fawcett and Moses [10, 11], the synaptonemal complex (SC) is a transient, zipper-like structure that assembles between homologous chromosomes during meiotic prophase I. Its ultrastructure comprises three distinct components: (1) two parallel lateral elements (LEs) that anchor the looped chromatin of homologous chromosomes; (2) a central region (CR) spanning approximately 90–150 nm between the LEs; and (3) numerous transverse filaments (TFs) that traverse the CR and connect the LEs to a central element (CE) within this region [12, 13]. As illustrated in Figure 1, the SC serves as a structural bridge that closely juxtaposes homologous chromosomes, providing the essential platform for homologous recombination and crossover formation.

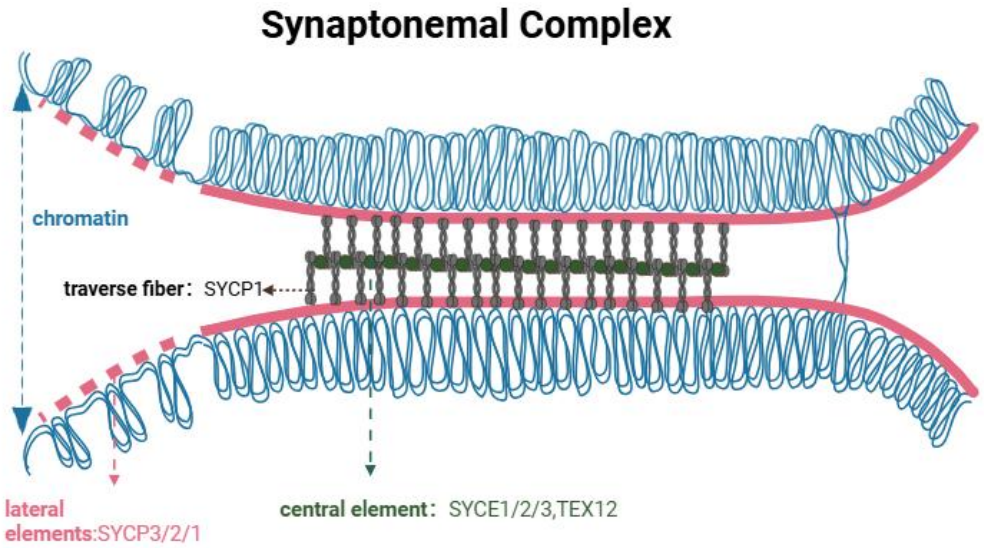

Figure 1: Schematic of the synaptonemal complex (SC). The lateral elements (LEs), associated with chromatin, are primarily composed of SYCP2 and SYCP3. Transverse filaments (e.g., SYCP1) extend from the LEs and connect to the central element (CE), which contains SYCE1, SYCE2, SYCE3, and TEX12. This structure ensures accurate homologous pairing and recombination.

3.2 Molecular Organization

Eight synaptonemal complex (SC) proteins have been identified in mammals: SYCP2 and SYCP3 localizing to axial/lateral elements (AE/LE); SYCP1 within transverse filaments (TF); and SYCE1-3, TEX12 (testis-expressed protein 12), and SIX6OS1 forming the central element (CE) (14-20)

3.3 Dynamic Assembly Process

3.3.1 Phosphorylation regulation

Phosphorylation dynamics critically regulate synaptonemal complex (SC) assembly, stabilization, and disassembly during meiotic prophase across species. In yeast, Zip1 phosphorylation (by Mec1/ATR) and dephosphorylation (by PP4) control its N-terminal dimerization to mediate centromere pairing [21], while C. elegans SYP-1 phosphorylation at polo-box domains promotes timely synapsis [22]. Crossovers trigger SC stabilization via component phosphorylation [23, 24], with ATM/ATR-mediated SYP-1 C-terminal phosphorylation redirecting DNA repair to sister chromatids, preventing excessive DSB damage [25]. Phosphorylation extends to lateral elements: ERK-mediated HTP-1 phosphorylation at Ser325 enhances SC extension/maintenance in C. elegans [26], while CDKA-1 phosphorylates ASY1 for chromosomal recruitment in Arabidopsis [27, 28]. Crucially, phosphorylation governs SC disassembly—Ipl1/Aurora B coordinates disassembly with cell-cycle progression in yeast [29]; DDK-Polo-CDK1 complexes drive meiotic dissolution [28]; PLK1 phosphorylates SYCP1/TEX12 to disrupt the central element in mice [30]; and AURKB/C inhibition impairs lateral element disassembly in human/mouse spermatocytes [31]. MAPK inactivation enables timely disassembly in C. elegans [32], whereas PP2A-B56 overexpression causes delayed assembly/premature disassembly in Drosophila [33], collectively underscoring phosphorylation's essential yet incompletely characterized role in SC dynamics.

3.3.2 Ubiquitination and the proteasome pathway

Ubiquitin-proteasome regulation of the synaptonemal complex (SC) is evolutionarily conserved, as demonstrated across diverse species. In yeast, Zip3 (ortholog of mammalian RNF212) and Zip1 recruit proteasomal core/regulatory particles to chromosomes, with functional proteasomes being essential for axial SC assembly [34]; Cdc53 knockout induces polycomplex formation [35], while STUbL complexes target SUMOylated Ecm11/Zip1 for degradation [36]. Similarly, C. elegans CRL4 components prevent polycomplex formation though likely not through direct SC ubiquitination [37], with ubiquitin also mediating pre-meiotic SC component degradation [38]. COP9 signalosome mutations cause SC assembly defects and polycomplexes via neddylation-dependent pathways [39] — a mechanism paralleled in plants where neddylation enables proper SC assembly and crossover positioning [39]. Drosophila studies reveal Sina inhibits polycomplex aggregation indirectly through unknown regulators [40], while SCF ubiquitin ligases maintain SC integrity by downregulating PP2A-B56 [33]. In mice, SKP1 localizes to SC lateral elements and its deletion triggers premature desynapsis through HORMAD accumulation [41], whereas testis-specific PSMA8 promotes SYCP3 degradation during meiosis II without affecting synapsis [42]. Despite this conserved regulatory requirement, specific ubiquitination substrates in SC dynamics remain largely unidentified.

3.3.3 Regulation of non-structural components

The conserved AAA+ ATPase TRIP13/PCH2 remodels HORMAD proteins bound to meiotic axes, with its recruitment to the synaptonemal complex (SC) regulating chromosome association—studies in yeast, mammals, and plants demonstrate that TRIP13/PCH2 remodels HORMAD domains (comprising a core region and C-terminal "safety belt" adopting variable conformations) to control SC assembly [43-45]. Supporting this, *pch-2* deletion

accelerates synapsis in C. elegans, *pch2/cdc53* double mutants suppress SC defects in budding yeast, Brassica rapa pch2 mutants exhibit partial synapsis [8], and Trip13 mutations cause synaptic defects in mice. Complementarily, non-remodeling proteins regulate murine synapsis: SC-interacting protein SCRE stabilizes the central element for homologous synapsis [8] (though functional homologs outside mammals remain unconfirmed), while testis-enriched HSPA2 localizes to SCs and is essential for proper disassembly and meiotic completion, potentially acting as a CDC2A (CDK1)-activating chaperone though CDC2A-independent SC regulation requires further validation [46, 47].

4. Consequences of SC malfunction

4.1 Pathogenic Mutation

Pathogenic mutation analysis reveals that SYCE1 deficiency manifests as large chromosomal deletions—exemplified by heterozygous loss at chr10:g.135111754_135427143del (with concomitant loss-of-function in the other allele) and homozygous deletion at chr10:g.135340247_135379115del in GRCh37, both causing meiotic arrest via complete loss-of-function [48] —while all reported SYCP3 mutations occur heterozygously (carrying one mutant and one wild-type allele) and associate with diverse infertility phenotypes: c.643delA in non-obstructive azoospermia [49], c.524_527delTTAA in severe oligospermia [50], and c.553-16_19del in recurrent miscarriage [51].

SYCE1 copy number variations (CNVs), including heterozygous deletions, lack functional validation but are predicted to cause meiotic arrest phenotypically equivalent to SYCE1-knockout mice [48]; critically, homozygous null mutations manifest clinically as non-obstructive azoospermia with confirmed meiotic arrest [48].

4.2 Pathogenic Mechanism and Characteristics

While both SYCP3 and SYCE1 disrupt synaptonemal complex (SC) function to cause meiotic arrest, their pathogenic mechanisms diverge fundamentally: SYCP3 exerts dominant-negative effects that impair lateral element assembly, manifesting as sex-specific infertility phenotypes, whereas SYCE1 loss-of-function mutations dismantle central element connectivity, invariably leading to absolute azoospermia—reflecting distinct genetic architectures, mutational spectra, and validation paradigms.

5. Diagnostic Markers for the Proteins of the Association Complex

5.1 Core Diagnostic Marker

For SYCP3 (axial element protein), diagnostic prioritization focuses on self-assembly domain point mutations (e.g., c.643delA/c.657T>C in exons 6-8) in males with non-obstructive azoospermia/severe oligospermia or ovarian-competent females with recurrent miscarriage, where heterozygous dominant-negative mutations confer >80% sensitivity for synapsis defects though negatives don't exclude other SC deficiencies; conversely, SYCE1 (central element protein) testing targets males with biopsy-confirmed meiotic arrest and absolute azoospermia through prioritized detection of 10q26.3 deletions (e.g., chr10: g.135340247_135379115del) or biallelic splice-site mutations (e.g., c.197-2A>G/c.271+2T>C), with confirmed biallelic pathogenic variants providing ≈95% specificity for central element disruption.

5.2 Auxiliary Diagnostic Markers

As auxiliary diagnostic biomarkers, SIX6OS1 (SYCE1-interacting protein) targets interaction-domain truncations (e.g., N-terminal deletions validated in murine models) to elucidate pathogenesis in SYCE1 mutation-negative cases with highly suggestive phenotypes, while CNV screening via MLPA or genome-wide CNV-seq—focusing on SYCE1/SYCP2 loci while excluding adjacent gene confounding—detects cryptic deletions (e.g., SYCE1 whole-gene deletions) in point mutation-negative patients.

5.3 Diagnosis Path Design

The flowchart summarizes the diagnostic approach for patients with infertility. Initial evaluation by semen analysis distinguishes oligospermia and azoospermia. In cases of oligospermia, SYCP3 point mutation analysis is indicated. Patients with azoospermia undergo testicular biopsy; if meiotic arrest is observed, SC protein gene testing is recommended. This testing can further identify SYCE1 deletions/biallelic mutations or pathogenic copy number variations (CNVs). Female patients with recurrent miscarriage are also directed toward SC protein gene testing, with subsequent analysis for SYCP3 mutations, SYCE1 variants, and CNV screening.

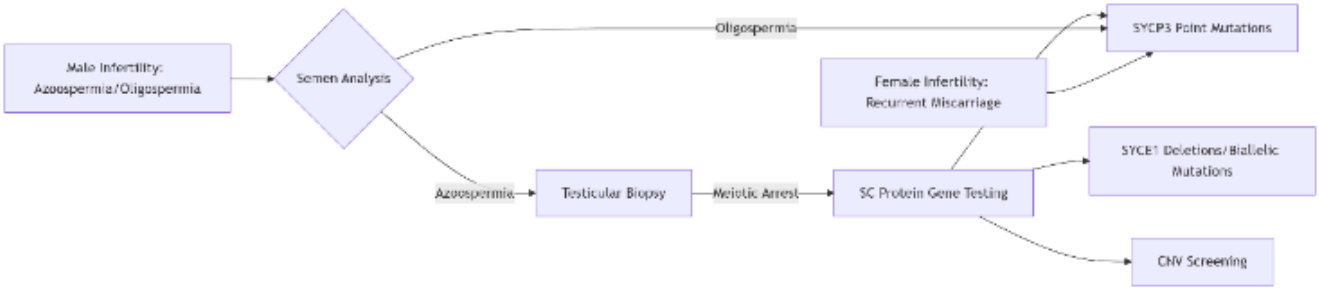

Figure 2: Diagnostic workflow for genetic evaluation in infertility.

5.4 Limitations of Markers

Notable gender disparity exists as SYCE1 mutations are exclusively reported in males, limiting diagnostic applicability; concurrently, technical bottlenecks necessitate long-read sequencing or optical mapping for SYCE1 large deletions due to routine whole-exome sequencing (WES) detection gaps, while false-negative risks persist—including SYCP3's ~30% incomplete penetrance (fertility in unaffected carriers) and unvalidated in silico predictions for SYCE1 splice variants' pathogenicity.

6. Conclusion

Mutations in synaptonemal complex proteins can serve as primary diagnostic biomarkers for meiotic origin-derived infertility. Specifically, the heterozygous point mutation in SYCP3 and the homozygous deletion in SYCE1 have clear clinical significance, necessitating the selection of detection strategies based on genetic patterns and phenotypic manifestations

7. Summary and Outlook

The synaptonemal complex (SC), serving as the core structure for homologous chromosome synapsis during meiosis, directly regulates chromosome pairing, recombination, and precise segregation through its dynamic assembly and disassembly, acting as a critical hub for germ cell quality control. However, genetic defects in SC components can trigger severe reproductive disorders. Specifically, heterozygous mutations in SYCP3 disrupt the assembly of lateral element fibers via a dominant-negative effect, leading to male non-obstructive azoospermia or severe oligozoospermia, as well as recurrent miscarriages in females. In contrast, homozygous/compound heterozygous mutations in SYCE1 result in complete loss of function, collapsing central element connections and causing absolute azoospermia, all accompanied by meiotic arrest.

Based on these findings, mutations in SC proteins have emerged as important clinical diagnostic biomarkers. SYCP3 point mutations (e.g., c.643delA in exons 6–8) demonstrate >80% sensitivity in detecting synapsis defects associated with male oligozoospermia and female miscarriages. Large-scale deletions in SYCE1 (e.g., chr10: g.135340247_135379115del) exhibit ~95% specificity in males diagnosed with meiotic arrest via testicular biopsy, while mutations in the SIX6OS1 interaction domain and copy number variation (CNV) screening can further elucidate cryptic etiologies. Notably, SC function is tightly regulated by phosphorylation (e.g., PLK1-mediated disassembly), the ubiquitin-proteasome system, and non-structural factors such as TRIP13/PCH2, which remodel HORMA protein conformations to influence assembly timing. These discoveries collectively underscore the complexity and conservation of the regulatory network.

Looking ahead, breakthroughs are concentrated in three areas: (1) applying cryo-electron microscopy combined with live-cell STORM imaging to resolve the three-dimensional dynamics of SC and pinpoint real-time disruption sites caused by pathogenic mutations; (2) establishing an oocyte SC analysis platform to unravel the rarity of female SYCE1 mutations and explore associations between meiotic errors and germ cell tumors; and (3) developing integrated multi-omics diagnostic pathways (whole-exome sequencing → long-read sequencing → interaction proteome validation) and targeted intervention strategies (e.g., SYCP3 small-molecule stabilizers or CRISPR-mediated regulation of phosphatase expression), thereby advancing translational research from cross-species findings to precision treatments for clinical infertility

References

[1] Veitia RA. Primary ovarian insufficiency, meiosis and DNA repair. Biomed J. 2020;43(2):115-23.

[2] Non-syndromic monogenic male infertility. Acta Biomed. 2019;90(10-s):62-7.

[3] Gottlieb SF, Gulani A, Tegay DH. Genetics, Meiosis. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Aaishwariya Gulani declares no relevant financial relationships with ineligible companies. Disclosure: David Tegay declares no relevant financial relationships with ineligible companies.: StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.; 2025.

[4] Vander Borght M, Wyns C. Fertility and infertility: Definition and epidemiology. Clin Biochem. 2018; 62: 2-10.

[5] Gao J, Colaiácovo MP. Zipping and Unzipping: Protein Modifications Regulating Synaptonemal Complex Dynamics. Trends Genet. 2018;34(3):232-45.

[6] Petronczki M, Siomos MF, Nasmyth K. Un ménage à quatre: the molecular biology of chromosome segregation in meiosis. Cell. 2003;112(4):423-40.

[7] Kaniecki K, De Tullio L, Greene EC. A change of view: homologous recombination at single-molecule resolution. Nat Rev Genet. 2018;19(4):191-207.

[8] Liu H, Huang T, Li M, Li M, Zhang C, Jiang J, et al. SCRE serves as a unique synaptonemal complex fastener and is essential for progression of meiosis prophase I in mice. Nucleic Acids Res. 2019; 47(11): 5670-83.

[9] Schücker K, Holm T, Franke C, Sauer M, Benavente R. Elucidation of synaptonemal complex organization by super-resolution imaging with isotropic resolution. Proc Natl Acad Sci U S A. 2015;112(7):2029-33.

[10] Fawcett DW. The fine structure of chromosomes in the meiotic prophase of vertebrate spermatocytes. J Biophys Biochem Cytol. 1956;2(4):403-6.

[11] Moses MJ. Chromosomal structures in crayfish spermatocytes. J Biophys Biochem Cytol. 1956; 2(2): 215-8.

[12] Cahoon CK, Hawley RS. Regulating the construction and demolition of the synaptonemal complex. Nat Struct Mol Biol. 2016;23(5):369-77.

[13] Jiang HW, Jiang XH, Ye JW, Shi Q. [Synaptonemal complex: the fundamental structure of meiosis]. Sheng Li Xue Bao. 2020;72(1):84-90.

[14] Gómez HL, Felipe-Medina N, Sánchez-Martín M, Davies OR, Ramos I, García-Tuñón I, et al. C14ORF39/SIX6OS1 is a constituent of the synaptonemal complex and is essential for mouse fertility. Nat Commun. 2016; 7: 13298.

[15] Hamer G, Gell K, Kouznetsova A, Novak I, Benavente R, Höög C. Characterization of a novel meiosis-specific protein within the central element of the synaptonemal complex. J Cell Sci. 2006;119(Pt 19):4025-32.
[16] Meuwissen RL, Offenberg HH, Dietrich AJ, Riesewijk A, van Iersel M, Heyting C. A coiled-coil related protein specific for synapsed regions of meiotic prophase chromosomes. Embo j. 1992;11(13):5091-100.
[17] Lammers JH, Offenberg HH, van Aalderen M, Vink AC, Dietrich AJ, Heyting C. The gene encoding a major component of the lateral elements of synaptonemal complexes of the rat is related to X-linked lymphocyte-regulated genes. Mol Cell Biol. 1994; 14(2): 1137-46.
[18] Schramm S, Fraune J, Naumann R, Hernandez - Hernandez A, Höög C, Cooke HJ, et al. A novel mouse synaptonemal complex protein is essential for loading of central element proteins, recombination, and fertility. PLoS Genet. 2011;7(5):e1002088.
[19] Offenberg HH, Schalk JA, Meuwissen RL, van Aalderen M, Kester HA, Dietrich AJ, et al. SCP2: a major protein component of the axial elements of synaptonemal complexes of the rat. Nucleic Acids Res. 1998; 26(11): 2572-9.
[20] Costa Y, Speed R, Ollinger R, Alsheimer M, Semple CA, Gautier P, et al. Two novel proteins recruited by synaptonemal complex protein 1 (SYCP1) are at the centre of meiosis. J Cell Sci. 2005;118(Pt 12):2755-62.
[21] Falk JE, Chan AC, Hoffmann E, Hochwagen A. A Mec1- and PP4-dependent checkpoint couples centromere pairing to meiotic recombination. Dev Cell. 2010;19(4):599-611.
[22] Sato-Carlton A, Nakamura-Tabuchi C, Chartrand SK, Uchino T, Carlton PM. Phosphorylation of the synaptonemal complex protein SYP-1 promotes meiotic chromosome segregation. J Cell Biol. 2018; 217(2): 555-70.
[23] Pattabiraman D, Roelens B, Woglar A, Villeneuve AM. Meiotic recombination modulates the structure and dynamics of the synaptonemal complex during C. elegans meiosis. PLoS Genet. 2017;13(3):e1006670.
[24] Nadarajan S, Lambert TJ, Altendorfer E, Gao J, Blower MD, Waters JC, et al. Polo-like kinase-dependent phosphorylation of the synaptonemal complex protein SYP-4 regulates double-strand break formation through a negative feedback loop. Elife. 2017;6.
[25] Garcia-Muse T, Galindo-Diaz U, Garcia-Rubio M, Martin JS, Polanowska J, O'Reilly N, et al. A Meiotic Checkpoint Alters Repair Partner Bias to Permit Inter-sister Repair of Persistent DSBs. Cell Rep. 2019; 26(3): 775-87.e5.
[26] Das D, Chen SY, Arur S. ERK phosphorylates chromosomal axis component HORMA domain protein HTP-1 to regulate oocyte numbers. Sci Adv. 2020;6(44).
[27] Yang C, Sofroni K, Wijnker E, Hamamura Y, Carstens L, Harashima H, et al. The Arabidopsis Cdk1/Cdk2 homolog CDKA;1 controls chromosome axis assembly during plant meiosis. Embo j. 2020;39(3):e101625.
[28] Argunhan B, Leung WK, Afshar N, Terentyev Y, Subramanian VV, Murayama Y, et al. Fundamental cell cycle kinases collaborate to ensure timely destruction of the synaptonemal complex during meiosis. Embo j. 2017;36(17):2488-509.
[29] Jordan P, Copsey A, Newnham L, Kolar E, Lichten M, Hoffmann E. Ipl1/Aurora B kinase coordinates synaptonemal complex disassembly with cell cycle progression and crossover formation in budding yeast meiosis. Genes Dev. 2009;23(18):2237-51.
[30] Jordan PW, Karppinen J, Handel MA. Polo-like kinase is required for synaptonemal complex disassembly and phosphorylation in mouse spermatocytes. J Cell Sci. 2012;125(Pt 21):5061-72.
[31] Wellard SR, Schindler K, Jordan PW. Aurora B and C kinases regulate chromosome desynapsis and segregation during mouse and human spermatogenesis. J Cell Sci. 2020;133(23).
[32] Nadarajan S, Mohideen F, Tzur YB, Ferrandiz N, Crawley O, Montoya A, et al. The MAP kinase pathway coordinates crossover designation with disassembly of synaptonemal complex proteins during meiosis. Elife. 2016;5:e12039.
[33] Barbosa P, Zhaunova L, Debilio S, Steccanella V, Kelly V, Ly T, et al. SCF-Fbxo42 promotes synaptonemal complex assembly by downregulating PP2A-B56. J Cell Biol. 2021;220(2).
[34] Ahuja JS, Sandhu R, Mainpal R, Lawson C, Henley H, Hunt PA, et al. Control of meiotic pairing and recombination by chromosomally tethered 26S proteasome. Science. 2017;355(6323):408-11.
[35] Zhu Z, Bani Ismail M, Shinohara M, Shinohara A. SCF(Cdc4) ubiquitin ligase regulates synaptonemal complex formation during meiosis. Life Sci Alliance. 2021;4(2).
[36] Liu C, Zhao H, Xiao S, Han T, Chen Y, Wang T, et al. Slx5p-Slx8p Promotes Accurate Chromosome Segregation by Mediating the Degradation of Synaptonemal Complex Components during Meiosis. Adv Sci (Weinh). 2020;7(4):1900739.
[37] Alleva B, Clausen S, Koury E, Hefel A, Smolikove S. CRL4 regulates recombination and synaptonemal complex aggregation in the Caenorhabditis elegans germline. PLoS Genet. 2019;15(11):e1008486.
[38] Burger J, Merlet J, Tavernier N, Richaudeau B, Arnold A, Ciosk R, et al. CRL2(LRR-1) E3-ligase regulates proliferation and progression through meiosis in the Caenorhabditis elegans germline. PLoS Genet. 2013; 9(3): e1003375.
[39] Jahns MT, Vezon D, Chambon A, Pereira L, Falque M, Martin OC, et al. Crossover localisation is regulated by the neddylation posttranslational regulatory pathway. PLoS Biol. 2014;12(8):e1001930.
[40] Hughes SE, Hemenway E, Guo F, Yi K, Yu Z, Hawley RS. The E3 ubiquitin ligase Sina regulates the assembly and disassembly of the synaptonemal complex in Drosophila females. PLoS Genet. 2019;15(5):e1008161.
[41] Guan Y, Leu NA, Ma J, Chmátal L, Ruthel G, Bloom JC, et al. SKP1 drives the prophase I to metaphase I transition during male meiosis. Sci Adv. 2020; 6(13): eaaz2129.
[42] Gómez HL, Felipe-Medina N, Condezo YB, Garcia-Valiente R, Ramos I, Suja JA, et al. The PSMA8 subunit of the spermatoproteasome is essential for proper meiotic exit and mouse fertility. PLoS Genet. 2019;15(8):e1008316.
[43] Ye Q, Kim DH, Dereli I, Rosenberg SC, Hagemann G, Herzog F, et al. The AAA+ ATPase TRIP13 remodels

HORMA domains through N-terminal engagement and unfolding. Embo j. 2017;36(16):2419-34.
[44] Yang C, Hu B, Portheine SM, Chuenban P, Schnittger A. State changes of the HORMA protein ASY1 are mediated by an interplay between its closure motif and PCH2. Nucleic Acids Res. 2020;48(20):11521-35.
[45] Deshong AJ, Ye AL, Lamelza P, Bhalla N. A quality control mechanism coordinates meiotic prophase events to promote crossover assurance. PLoS Genet. 2014; 10(4): e1004291.
[46] Allen JW, Dix DJ, Collins BW, Merrick BA, He C, Selkirk JK, et al. HSP70-2 is part of the synaptonemal complex in mouse and hamster spermatocytes. Chromosoma. 1996;104(6):414-21.
[47] Dix DJ, Allen JW, Collins BW, Poorman-Allen P, Mori C, Blizard DR, et al. HSP70-2 is required for desynapsis of synaptonemal complexes during meiotic prophase in juvenile and adult mouse spermatocytes. Development. 1997;124(22):4595-603.
[48] Huang Y, Tian R, Xu J, Ji Z, Zhang Y, Zhao L, et al. Novel copy number variations within SYCE1 caused meiotic arrest and non-obstructive azoospermia. BMC Med Genomics. 2022;15(1):137.
[49] Miyamoto T, Hasuike S, Yogev L, Maduro MR, Ishikawa M, Westphal H, et al. Azoospermia in patients heterozygous for a mutation in SYCP3. Lancet. 2003;362(9397):1714-9.
[50] Oud MS, Ramos L, O'Bryan MK, McLachlan RI, Okutman Ö, Viville S, et al. Validation and application of a novel integrated genetic screening method to a cohort of 1,112 men with idiopathic azoospermia or severe oligozoospermia. Hum Mutat. 2017; 38(11): 1592-605.
[51] Stouffs K, Vandermaelen D, Tournaye H, Liebaers I, Lissens W. Mutation analysis of three genes in patients with maturation arrest of spermatogenesis and couples with recurrent miscarriages. Reprod Biomed Online. 2011;22(1):65-71.