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Opinion

Meiosis in *Plasmodium*: how does it work?

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Meiosis is sexual cell division, a process in eukaryotes whereby haploid gametes are produced. Compared to canonical model eukaryotes, meiosis in apicomplexan parasites appears to diverge from the process with respect to the molecular mechanisms involved; the biology of *Plasmodium* meiosis, and its regulation by means of post-translational modification, are largely unexplored. Here, we discuss the impact of technological advances in cell biology, evolutionary bioinformatics, and genome-wide functional studies on our understanding of meiosis in the Apicomplexa. These parasites, including *Plasmodium falciparum, Toxoplasma gondii*, and *Eimeria* spp., have significant socioeconomic impact on human and animal health. Understanding this key stage during the parasite's life cycle may well reveal attractive targets for therapeutic intervention.

Highlights

Meiosis in *Plasmodium* is post-zygotic, unlike that in most model eukaryotes.

Key components involved in meiosis are either highly divergent or absent in *Plasmodium*.

There is DNA replication and recombination of homologous chromosomes without karyokinesis during meiosis in *Plasmodium*.

Meiosis is essential for malaria parasite transmission.

Ancestral and highly conserved: does meiosis differ in the malaria parasite *Plasmodium*?

Meiosis is ancient and indispensable in sexually reproducing organisms, a process to generate genetically diverse, haploid gametes from a single diploid cell [1,2]. Meiotic cell division has two **reductive divisions** (see Glossary), meiosis I and meiosis II; each is comprised of prophase, (pro)metaphase, anaphase, and telophase stages. Hallmarks of meiosis I include: (i) a prolonged prophase I period allowing mutual recognition and alignment of homologous chromosomes; (ii) formation of DNA **double-strand breaks** (**DSBs**); (iii) production and invasion of free, single-strand ends into double-stranded DNA; (iv) pairing and crossover between homologous chromosome regions facilitated by the **synaptonemal complex** (**SC**), a 'zipper-like' protein structure that stabilizes the connection between **sister chromatids** through structures known as '**chiasmata**' (Figure 1); and (v) alignment of homologous chromosomes in metaphase I along the metaphase plate. Separation (a reductive division) during anaphase I culminates in the chromosomes being pulled completely apart during telophase I. Meiosis II is more like mitosis, with a second **equational division** culminating in the formation of four individual haploid nuclei.

Extensive studies of meiosis have been performed in surprisingly few species: humans and mice, the metazoans *Drosophila melanogaster* and *Caenorhabditis elegans,* the plant *Arabidopsis thaliana*, several yeast species (e.g., *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*), and the ciliate *Tetrahymena thermophila* [1]. Although aspects of meiosis may be highly heterogeneous (e.g., an SC has not been identified in *S. pombe* or *Aspergillus*, although meiosis still occurs [3,4]), analysis of the expanding number of unicellular eukaryotes whose genome has been sequenced highlights the presence of a highly conserved 'meiotic toolkit' (Figure 2). This toolkit includes *SPO11*, encoding a topoisomerase of archaeal descent that induces DSBs; *HOP1,* which is part of the SC; *RAD50* and *MRE11,* which orchestrate DNA damage repair; *DMC1/RAD51, HOP2*, and *MND1*, which form a recombination complex; and *MSH4* and *MSH5*, which govern formation of **Holliday junctions** [5,6]. However, knowledge of meiotic

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cell division in apicomplexan parasites is extremely limited. This phylum is very diverse, and includes many important human and veterinary pathogens, such as the malaria parasite *Plasmodium* spp., *T. gondii*, and *Eimeria* spp. [7].

Plasmodium is a haploid organism, and meiosis differs substantially from that in diploid eukaryotes since it occurs post-fertilization in the developing zygote rather than to produce gametes (sex cells, Figure 1). This is not surprising as the meiotic process requires a diploid cell, and the zygote is the only diploid stage in the life cycle of these parasites and is essential for transmission through mosquitoes to vertebrate hosts [8]. Post-fertilization in the mosquito gut, the zygote differentiates (through six morphological stages – termed stages I–VI) into the motile **ookinete** (stage VI) over a period of 24 h, and during this time the DNA (2N) is duplicated (i.e., pre-meiotic replication) to form a tetraploid cell (4N), followed by two rounds of **chromosome segregation** to form four discrete haploid genomes, contained within a single nucleus in the fully mature ookinete (Figure 1). The ookinete invades the mosquito gut wall and develops into an oocyst where **endomitosis** (**sporogony**) results in the production of hundreds of haploid **sporozoites** that will migrate to the mosquito's salivary glands to infect the vertebrate host.

In this opinion article, we discuss the unique aspects of *Plasmodium* meiosis, highlighting several critical unanswered questions around the key stages and the molecular players involved. We focus on post-translational regulation through **reversible protein phosphorylation** (RPP) and the potential impacts state-of-the-art technological and bioinformatic advances can have on our understanding of *Plasmodium* meiosis.

Meiosis in *Plasmodium*: what do we know about the process, and how does it differ from that in other eukaryotes?

Cell biology of meiosis: the same, but in a different order?

Ultrastructural studies have identified hallmark stages of prophase I in the *Plasmodium* zygote, including **leptotene**, **zygotene**, and the clear presence of a long triple-banded SC [9,10]. However, unlike in the canonical model, the final stages of prophase I (**diplotene** and **diakinesis**) do not occur. The SC – each containing fully condensed chromosomes – persists until anaphase I rather than disassembling prior to metaphase I. The second reductive division (i.e., meiosis II) has not been observed, and the mature ookinete, despite containing four nuclear **kinetochore** clusters and having undergone two rounds of chromosome segregation, still contains a single nucleus [9–11].

Our recent studies on the spatiotemporal dynamics of the outer kinetochore marker NDC80 and microtubule plus-end tracker EB1 during zygote-stage development revealed key features of meiotic division in *Plasmodium* [11,12]. NDC80-GFP location in the zygote identifies a single cluster of kinetochores that disassembles to form two lateral clusters during stage I (Figure 3). The formation of two clustered kinetochore foci accompanies DNA replication producing a 4N nucleus, resembling premeiotic S phase of *S. pombe* and mammalian meiosis. During stage II of zygote development, the kinetochores start to move apart, marking the start of meiotic prophase I and the onset of chromosome segregation. The dispersed NDC80-GFP signal suggests that anaphase has not initiated, probably indicating synapsis formation and crossover during stages II–III. Chromosome segregation likely occurs in two rounds, which we infer from two rounds of kinetochore clustering and declustering, with four clustered NDC80-GFP foci in a single nucleus present at the end of zygote to ookinete differentiation (Figure 3). Nuclear division and cytokinesis begin only when the ookinete has converted to an oocyst.

Glossary

Centromere: a constricted region of DNA that links pairs of sister chromatids together during cell division.
Chiasmata: a structure or physical linkage that forms between a pair of homologous chromosomes by crossover recombination and physically connects them during meiosis.
Chromosome segregation: the process whereby paired homologous chromosomes are separated and migrate to opposite poles of the nucleus.
Crossover interference: nonrandom, widely spaced crossovers along chromosomes. Most eukaryotes average only a few crossovers per chromosome pair per meiosis.
Diakinesis: the fifth and final stage of prophase I in meiosis. Chromosomes further condense, and four tetrads are clearly observed.
Diplotene: the fourth of five substages of prophase I in meiosis. Here, the synaptonemal complex disassembles but homologous chromosomes remain tightly bound at chiasmata.
Double-strand breaks (DSBs): DNA damage in which both strands of the double helix are severed, driving genomic instability. DSBs are deliberately formed during meiosis to initiate homologous recombination.
Endomitosis: replication and division of chromosomes in the absence of concomitant nuclear division, resulting in numerous genome copies within a cell.
Equational division: occurs during meiosis II; it does not reduce the chromosome number in daughter cells, rather the chromosomes replicate and are equally distributed into two daughter cells.
Holliday junction: a cross-shaped structure that forms during genetic recombination, with two double-stranded DNA molecules becoming separated into four to exchange segments of genetic information.
Homologous recombination: the exchange of genetic material between two strands of DNA at homologous regions.
Kinetochore: a macromolecular structure that connects the centromeric DNA of a sister chromatid to microtubules of the spindle apparatus responsible for chromosome segregation during cell division.
Leptotene: the first of five substages of prophase I in meiosis, in which duplicated chromosomes condense

The mature ookinete contains four, distinct single genomes (indicated by the four clusters of kinetochores) for a prolonged period within a single nucleus. It is not clear what happens in the oocyst – does an early reductive division pre-empt formation of haploid sporozoites or is there further DNA replication and endomitosis without cytokinesis until haploid sporozoites bud off from the cell body? This is precisely what happens during asexual schizogony, and it is interesting that this cell division strategy seems to be pervasive in both asexual and sexual cycles. Additionally, in many species with asymmetric meiosis (e.g., the human female), one haploid genome is selected to form the gamete and the other three are 'eliminated' through a process favoring selfish **centromeres** that bias transmission to the egg [13]. Could this also occur in *Plasmodium* or are all four haploid genomes from each ookinete represented in the sporozoites from an oocyst (Box 1)?

Molecular makeup of meiosis: are highly divergent conventional components there?

It is well established that *Plasmodium* meiosis is divergent from that of model organisms, and several meiotic genes are lacking or yet to be annotated; functional studies of putative meiotic genes are urgently required. Comparative genomics studies have revealed *Plasmodium* candidates for several proteins involved in early DSB formation, recombination and repair (including a PRDM9-like gene known as Zfp, TOP6A, SPO11-2, BRCA2, MND1, RAD50, RAD51, MRE11, and DMC1); however, only four of these genes (PRDM9-like, BRCA2, DMC1, and MRE11) [14–17] along with SMC2 [18] have been subjected to functional analysis and found to be essential for oocyst formation and sporogony. No homologs of crossover proteins MSH4/5, MLH2/3, and MER3 have been identified, suggesting that there is no **crossover interference**, and only class II crossovers are made as found in the fission yeast *S. pombe* [19]. Genes for many key components of sister chromatid cohesion, such as WAPL, REC8, and Shugoshin, are absent or highly diverged beyond present detection limits (Figure 2). A recent study of *Plasmodium* kinetochore subunits identified AKiT4 as a putative Monopolin ortholog based on a predicted 3D structure comparison using Hidden Markov Model searches and AlphaFold2 modeling [20], suggesting that homologous kinetochores might be fused together during meiosis I as found in the budding yeast *S. cerevisiae* [21]. Similar bioinformatic analyses [20] will be very useful in elucidating functional orthologs of several apicomplexan proteins, including candidate SC proteins (Box 1).

Although a tripartite SC is formed [10], no homologs of transverse filament (e.g., SYCP1) or central element (e.g., human SYCE1-3, TEX12, SIX6OS1) proteins have been identified. Interestingly, a recent study using Hidden Markov Model (HMM-vs-HMM) homology detection protocols identified extensively divergent *Plasmodium* candidate orthologs of human axial element components SYCP2 and 3, consistent with the presence of HOP1, their direct interaction partner, and microscopic observations [22]. To identify additional and/or novel components that play a role in cohesion or crossover regulation, or form the SC, will require more sensitive protein sequence homology detection protocols, in-depth proteomic analyses of interaction partners, and functional genetic studies, for each of the candidate meiotic proteins.

Not all eukaryotes have all core meiosis genes but still perform meiosis. For example, *S. pombe* and the ciliate *Tetrahymena* appear to lack an SC, but carry out meiosis, albeit in a different way [4,23]. It is of interest to determine how and when meiosis in *Plasmodium* diverged from other protistan lineages like dinoflagellates and ciliates, which, together with apicomplexans constitute the eukaryotic infrakingdom of Alveolata, and why key genes were lost or diverged beyond recognition. A clear example of such widespread divergence among eukaryotes is entry into meiosis, which is tightly regulated by different components in different species. In plants, these include AGO9, SWI1, CDC45, and XRI1 [24]; in humans and mice, OCT4, DAZL, STRA8, SOX2 [25]; and in budding yeast (e.g., *S. cerevisiae*), the Inducer of MEiosis 1 (IME1), a

from diffuse chromatin into long, thin strands.

Ookinete: a highly motile stage in the *Plasmodium* life cycle that differentiates from the zygote and invades the mosquito midgut.

Reductive division: the first of two divisions in meiosis, resulting in half the number of chromosomes being inherited by each daughter cell.

Reversible protein phosphorylation: the mechanism of activating or deactivating protein function by kinase addition, or phosphatase removal, of a phosphate group.

Sister chromatids: two copies of the same chromosome formed by DNA replication, connected to each other at the centromere.

Sporogony: a phase of *Plasmodium* asexual replication occurring in the oocyst on the basal surface of the mosquito midgut that produces hundreds of haploid motile sporozoites.

Sporozoite: elongated, crescent-shaped invasive stage, produced in oocysts, which migrates to the mosquito salivary glands and is injected into the vertebrate host by the mosquito during a bloodmeal. The sporozoite then moves to the liver and infects hepatocytes.

Synaptonemal complex (SC): a meiosis-specific, multiprotein zipper-like complex that mediates and maintains synapsis along the full length of each pair of homologous chromosomes during prophase of meiosis I.

Zygotene: the second of five substages of prophase I in meiosis. Homologous chromosomes undergo synapsis mediated by the synaptonemal complex.

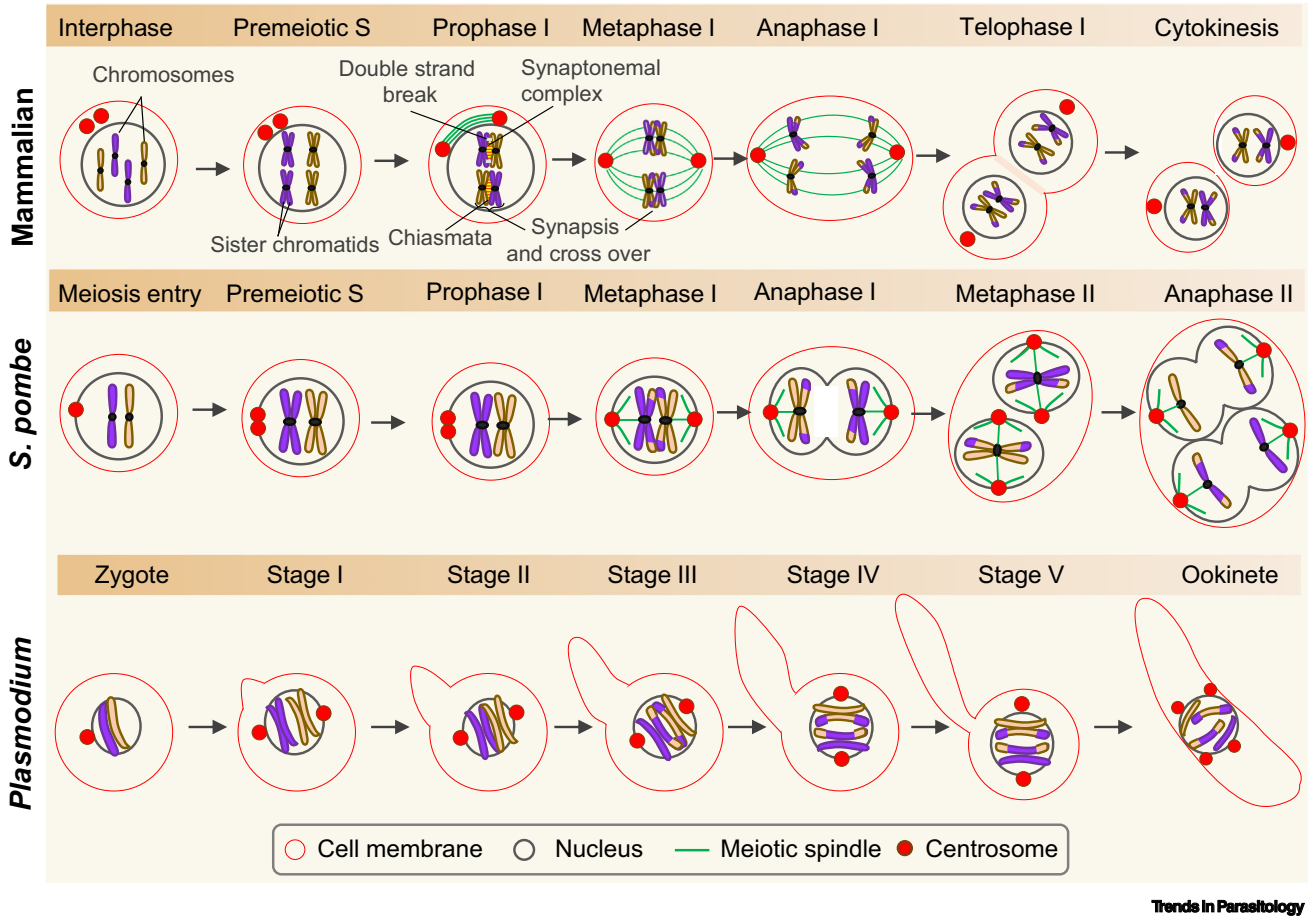

Figure 1. Schematic of meiosis in mammals, *Schizosaccharomyces pombe* and *Plasmodium*. The events of meiosis I in mammals showing similarity to *S. pombe* and *Plasmodium*. Meiosis II events in *Plasmodium* are more like those in *S. pombe*. Indicated in the top panel are the synaptonemal complex (SC), crossover events, and chiasmata; definitions of these terms are in the glossary.

transcription factor and master regulator of core meiotic proteins DMC1 and REC8 [26,27]. However, no clear ortholog of any of these components has been identified in *Plasmodium*. In *S. pombe*, entry into meiosis is controlled by the RNA recognition motif (RRM) protein MEI2 [4], which has a putative *Plasmodium* homolog, whereas in *S. cerevisiae* IME2, a protein kinase (PK), with sequence similarity to both cyclin-dependent- and mitogen-activated PKs, is required for multiple key events in the meiotic cell cycle [28]. A basic BLAST search identifies several *Plasmodium* cyclin-dependent and mitogen-activated PKs with greater sequence similarity to IME2 (e.g., PF3D7_0417800-cdc2-related PK 1 and PF3D7_1431500-mitogen-activated PK 1), suggesting that PK activity may also be a master switch of meiosis in *Plasmodium*.

Post-translational regulation of meiosis: driving the process through divergent regulation

Meiosis dynamics are tightly regulated by RPP with both PKs and protein phosphatases (PPs) having important roles. Research has been primarily focused on the role of PKs, in part because the larger number of PK genes may provide greater specificity than the few PP genes in eukaryotic genomes [29]. However, the role of PPs during meiosis is becoming increasingly evident.

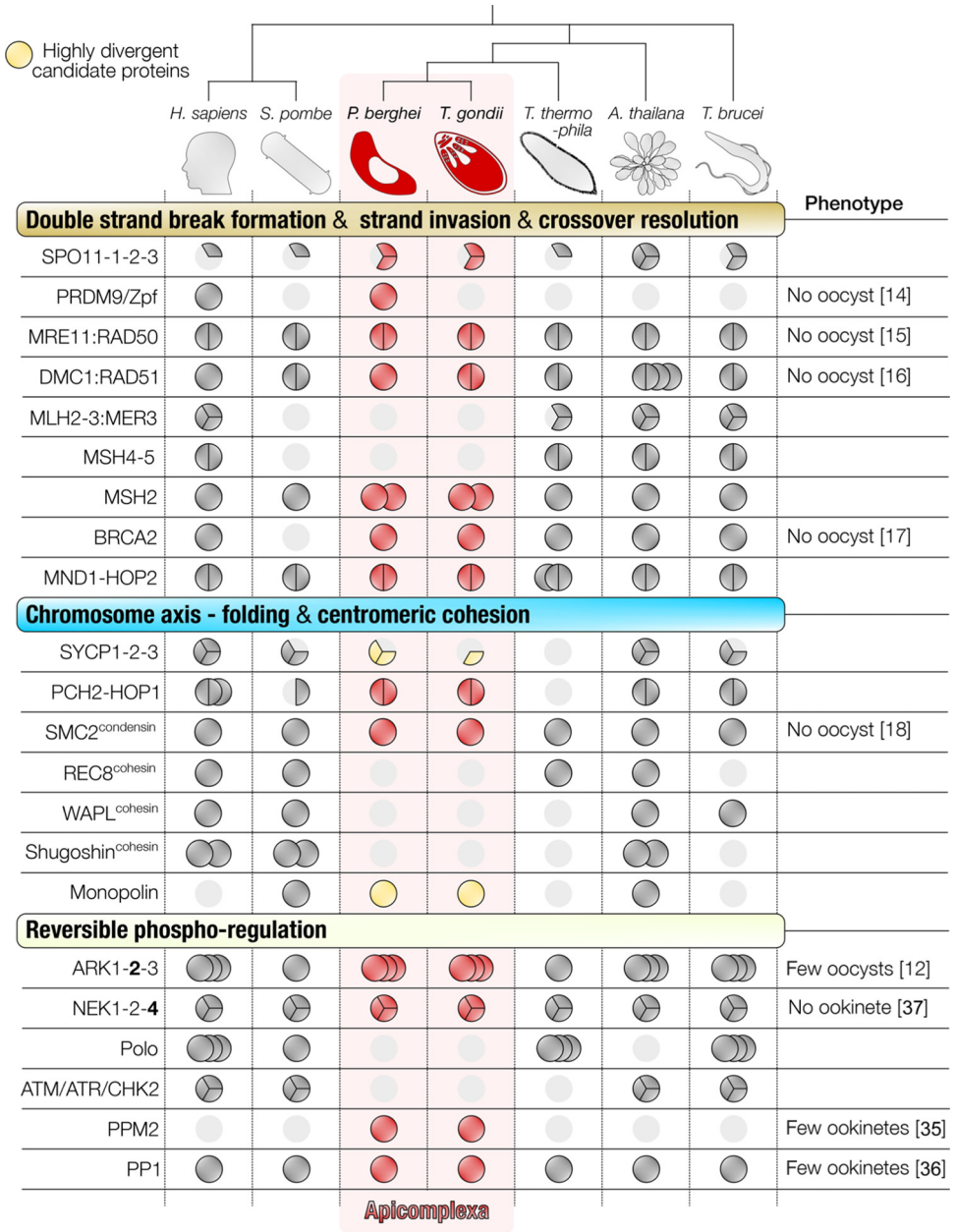

Figure 2. Phyletic profiles of predicted meiotic genes in a selection of eukaryotes. Full colored circle indicates presence. The number of circles/parts indicates the number of paralogs in specific lineages. Light gray circles/parts indicate an absence. Abbreviations: ARK, Aurora kinase; ATM/ATR/CHK2, ataxia telangiectasia mutated/ataxia telangiectasia and Rad3 related/checkpoint kinase 2; CAPH2, condensin-2 complex subunit H2; DMC1, DNA meiotic recombinase 1; MLH, MutL homologue; MND1, meiotic nuclear divisions 1; MRE11, meiotic recombination 11; MSH, MutS homolog; NEK, NIMA-related kinase; PCH2, pachytene checkpoint protein 2; PRDM9, PR/SET domain 9; SPO11, sporulation-specific protein 11; SYCP, synaptonemal complex protein; WAPL, Wings apart-like.

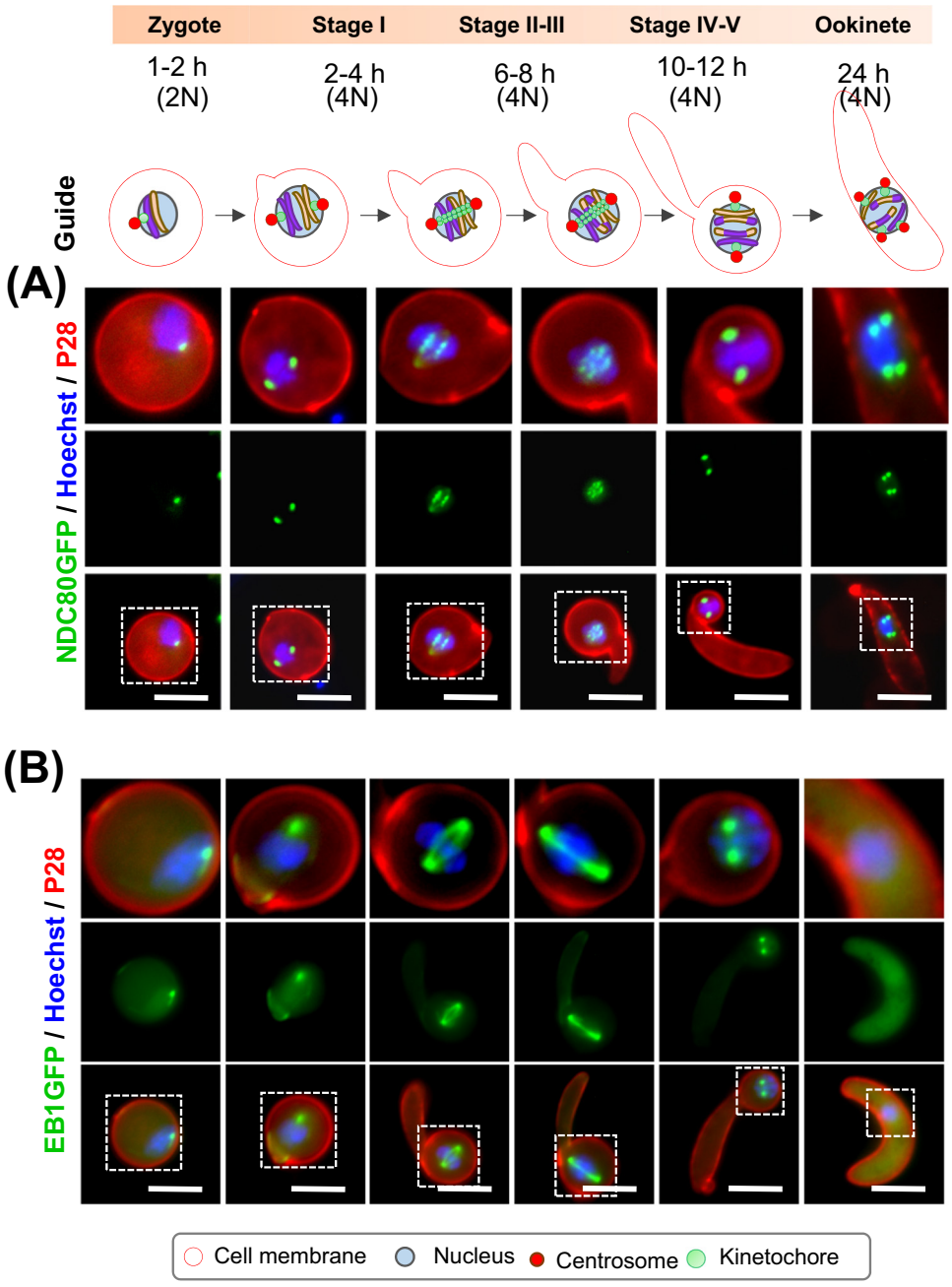

Figure 3. Spatiotemporal profile of kinetochore marker NDC80 and microtubule-associated protein EB1 during meiosis in *Plasmodium*: live cell imaging showing the dynamic location of NDC80 (A) and EB1 (B) during the various stages of ookinete development in which meiosis takes place [11,12]. DNA is stained with Hoechst (blue), and P28 (red) is a cell-surface marker of zygote and ookinete stages. Inset panels show magnified views of GFP/P28 signal. Scale bars: 5 μm.

In yeast and mammals, PK and PP activities are key to checkpoint analysis of centromere coupling and DNA crossover [30,31]. The core PK signaling network for checkpoint control consists of the DNA damage sensors ATR/ATM and transducer CHK2, which sense

Box 1. What technological advances may fill the current gaps in knowledge of how *Plasmodium* meiosis works?

Imaging approaches

New super-resolution microscopy techniques – such as stimulated emission depletion (STED) microscopy, structured illumination microscopy (SIM), and expansion microscopy – can achieve resolution at tens of nanometers [12,42], allowing visualization of subcellular structures such as organelles, meiotic spindles, synapses, and molecular complexes [42,43]. SBF-SEM (serial block-face scanning electron microscopy) and FIB-SEM (focused ion beam scanning electron microscopy) enable high-resolution 3D-imaging of cells and tissues, and may allow analysis of the structure and organization of the SC, spindle dynamics and chromosome segregation.

Comparative genomics and evolutionary biology

A key problem for the analysis of apicomplexan parasites is how to detect highly divergent functional homologs of proteins found in other eukaryotes. Iterative homology detection protocols using Hidden Markov Model (HMM) comparisons have successfully identified some highly divergent homologs in *Plasmodium* [11,22]. The advent of tertiary structure prediction tools like AlphaFold2 [20] will allow homology detection by protein structure comparisons for Apicomplexa. With the sequence of many genomes becoming available [44], and better homology detection tools, we may soon be able to assess more accurately whether a gene is truly absent from a genome. Single-cell RNA-seq [45–47] will provide insights into transcriptional diversity and heterogeneity in apicomplexan species, in particular pinpointing the expression of meiotic and mitotic genes and pathways in different cell types and developmental stages, to provide a complementary approach to identify novel genes. Additionally, DNA content of isolated single oocysts could be analyzed to determine whether all four haploid genomes from individual ookinetes are represented in the sporozoites from a single oocyst.

Functional genetic and proteomics approaches

Various new approaches including clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9-based gene modification and deletion screens can be used to perform protein structure–function analyses and assess their role in *Plasmodium* meiosis [48]. Proteomics-based approaches like BioID (TurboID, miniTURBO) and phosphoproteomics can be used to identify proteins that are differentially expressed or modified during meiosis [49,50]. These approaches will help to uncover key signaling events important for meiosis in *Plasmodium*, and potentially identify new therapeutic targets for drug development.

replication protein A (RPA)-coated single-stranded DNA. Cell-cycle progression through meiosis and SC disassembly are tightly regulated by two kinases, the polo-like kinase 1 CDC5 and CDC7, with the latter functioning in complex with the segregation factor Dbf4 [32,33]. However, while an ortholog of RPA has been identified in *Plasmodium*, this is not the case for CDC5 and CDC7 kinases. Both pre-meiotic S-phase, primarily studied in yeast, and mitosis rely heavily on CDK activities, and several CDKs are encoded in the *Plasmodium* genome [38]. Several PPs have been implicated in control of meiotic progression in models, many with homologs in *Plasmodium,* including PP2A, PP4, and PP6 [34]. Each of these parasite PPs has been shown to be likely essential for asexual development in vertebrate hosts [35], and recently PP1 has also been implicated in meiotic progression [36].

Our functional genetic screens of the *Plasmodium berghei* protein kinome and phosphatome indicated that a Never in mitosis A (NIMA)-related kinase (NEK4) and PP2C-related metallo-dependent phosphatase (PPM2) regulate the earliest stages of meiosis during zygote development. Deletion of each gene resulted in significant reduction in ookinete numbers, gross morphological changes (Figure 4), and complete ablation of oocyst development [35,37,38]. In addition, the DNA content of both mutants was significantly less than tetraploid, indicating that meiotic DNA replication had initiated but then aborted prior to completion. In PPM2-mutant gametocytes, expression of numerous meiosis-related genes and some PKs (including NEK4 and SRPK2) was significantly affected (Figure 4). Interestingly, PPM2 is N-myristoylated (an important acylation catalyzed by *N*-myristoyltransferase, NMT; [39]) and therefore may be targetable by NMT inhibitors [40]. PP1 may have a function in

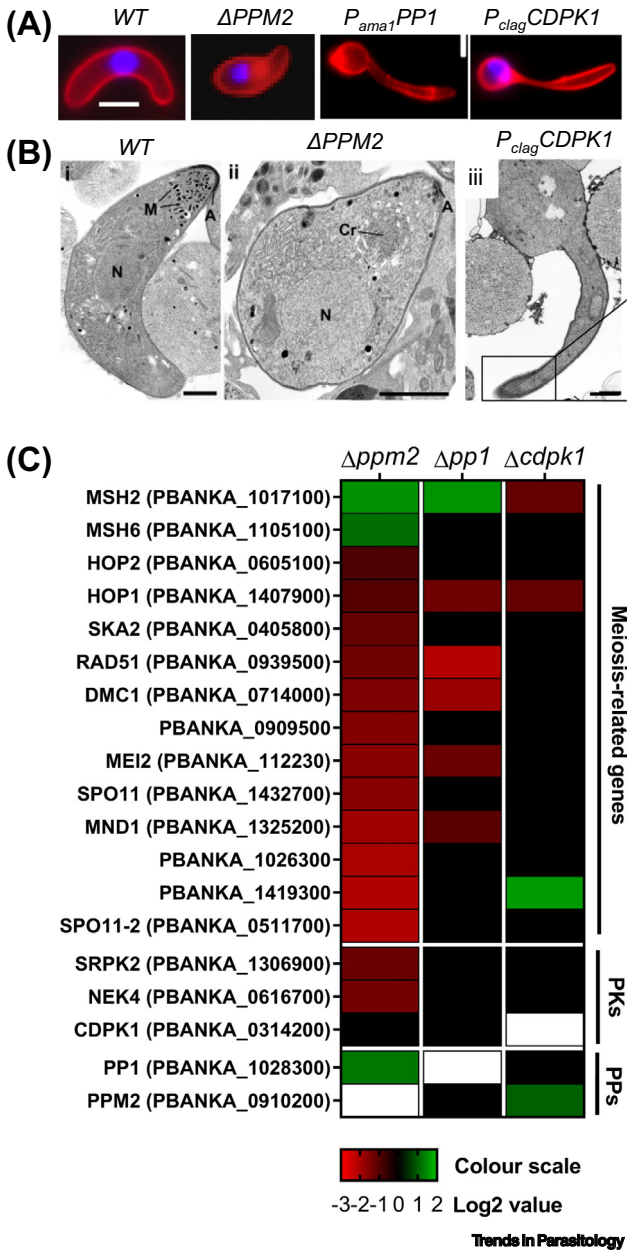

Figure 4. Functional analysis of protein phosphatases (PPM2 and PP1) and a protein kinase (CDPK1) shows defects in ookinete development and differential regulation of meiosis genes. (A) Live cell images showing the abnormal retort-shaped cells; *ΔPPM2* (knockout) cells have a bulbous shape while P_{ama1}*PP1* and P_{clag}*CDPK1* (downregulation) cells have a long thin protrusion attached to the main cell body. Wild-type (WT) zygotes differentiate into elongated 'banana shaped' ookinetes. P28 (red) is a cell-surface marker of zygote and ookinete stages. DNA is stained with Hoechst (blue). Scale bar: 5 μm. (B) Electron micrographs showing longitudinal sections through a WT crescent-shaped ookinete (i). Section through a Δ*PPM2* retort showing the bulbous shape of the parasite with normal structures in the cytoplasm but very few micronemes (ii). Section through a P_{clag}*CDPK1* retort showing thin elongated protrusion but no structural differences (iii). Abbreviations in all panels: A, apical membrane complex; Cr, crystalline body; M, micronemes; N, nucleus. Scale bar, 1 μm. (C) Transcriptomic analysis of Δ*PPM2* retort showing differential regulation of several genes involved during ookinete development. All data available at [35,36,41], and images compiled from the same publications.

meiotic cell division since its conditional knockdown affects the transcription of several meiosis-related genes [36]. Another study highlighted the role of the calcium-dependent PK CDPK1 in zygote differentiation [41]: a conditional CDPK1 knockdown severely affecting expression of meiosis-related genes (Figure 4). We showed that the divergent aurora-related kinase, ARK2 is located in the vicinity of kinetochores at the spindle apparatus during both mitosis and meiosis and drives spindle dynamics, scaffold formation, and chromosome segregation [12]. We suggest that control of early meiotic division in *Plasmodium* is regulated by several PKs and PPs, and that this will be a fruitful area of further research using a variety of new methodologies (Box 1).

Concluding remarks

Plasmodium meiosis is a very exciting field that promises to provide understanding of both conserved and divergent meiotic mechanisms in a range of socioeconomically important pathogens that have a devastating effect on global health. However, to date there have been few studies and these have been limited to phenotypic analysis of gene-disruption mutant parasites. Here, we describe both the conserved and the diverse features of *Plasmodium* meiosis compared to the process in model organisms, and highlight some new techniques and methodologies that will provide a greater understanding of this fascinating process. Whilst there is still a lot to learn (see Outstanding questions), technological developments (Box 1) will advance our understanding of meiosis across the Apicomplexa, and may facilitate development of targeted therapeutics, to greatly improve human and animal health.

Outstanding questions

There are two meiotic divisions in ookinetes but how and when does karyokinesis occur?

Do different or novel proteins constitute the SC in *Plasmodium* or are they just too highly divergent for bioinformatic detection?

At what point during zygote development does crossover and homologous recombination occur?

How are spindles and centrosomes organized during *Plasmodium* meiosis?

How are chromosomes segregated during *Plasmodium* meiosis?

What is the function of gene clusters during ookinete development implicated in meiosis?

How do post-translational modifications control meiosis in *Plasmodium*?

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Declaration of interests

The authors declare no competing interests.

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