Published in final edited form as:

Trends Parasitol. 2015 June ; 31(6): 229–230. doi:10.1016/j.pt.2015.04.003.

Apicomplexan cell cycle flexibility: centrosome controls the clutch

Chun-Ti Chen and Marc-Jan Gubbels

Department of Biology, Boston College, Chestnut Hill, MA 02467, USA

Abstract

The centrosome serves as a central hub coordinating multiple cellular events in eukaryotes. A recent study in *Toxoplasma gondii* revealed a unique bipartite structure of the centrosome, which coordinates the nuclear cycle (S-phase and mitosis) and budding cycle (cytokinesis) of the parasite, and deciphers the principle behind flexible apicomplexan cell division modes.

Keywords

Toxoplasma gondii; centrosome; Apicomplexa; endodyogeny; schizogony

The phylum Apicomplexa comprises many pathogens responsible for important diseases in both animals and humans, including malaria, toxoplasmosis and cryptosporidiosis. Apicomplexan parasites have complex life cycles involving transmission between different hosts species and replication inside distinct cell types. Not only different species display different replication modes, but also the same species undergoes distinct division modes in different life cycle stages. These flexible replication modes can be classified by the number of sequential combinations of DNA synthesis (S phase) and mitosis (M) (nuclear cycle) followed by single round of cytokinesis (budding cycle) [1]. For instance, during intra-erythrocytic development, *Plasmodium* spp. divides by schizogony, where the nuclear cycle unfolds in an asynchronized fashion, generating an odd number of nuclei in a syncytium [2]. Differently, in *Sarcocystis neurona*, a large polyploid nucleus is generated after multiple round of S-phase without karyokinesis. Though these two parasites undergo a diverse nuclear cycle, the last round of mitosis across all apicomplexans is connected to a final budding cycle to ensure that a single copy of genetic material is properly encapsulated into each daughter cell. These distinct division modes confer apicomplexan parasites the ability to generate adjustable amount of progenies in one cycle and allow the parasite to cope with different cellular environments in a broad range of host and tissue types. Since the advent of electron microscopy in the late 1960s we have known the morphology of the various development modes, but only recently have strides in both genetics and fluorescence microscopy started to lift the veil on the molecular mechanism behind these enigmatic division modes.

The *Toxoplasma gondii* tachyzoite has presented itself as a great model system to study the biology of apicomplexan replication. This haploid parasite replicates asexually by the simplest replication mode, termed endodyogeny, where the budding cycle (cytokinesis) is tied to only a single nuclear cycle (S/M) generating two cells per cycle. It is known that the centrosome serves as a central hub by nucleating spindle microtubule and scaffolding the components of daughter cells [3]. However, the mechanistic coordination of these two events remains largely unclear. In an elegant recent study, Suvorova and colleagues systematically searched for orthologs of known centrosomal proteins in *Toxoplasma* and used these reagents to evaluate the phenotypes of previously isolated temperature sensitive cell division cycle mutants [4]. Localization studies with the candidate centrosomal proteins led to the surprising discovery of two different core structures making up the parasite's centrosome. The centrosomal structure distal from the nucleus, named the outer core, contains TgCentrin1, TgSAS6, TgSfi1, γ -tubulin, and the Aurora kinase TgArk1, whereas the centrosomal structure closest to the nucleus, named the inner core, contains Cep250-Like protein 1 (TgCEP250-L1). Interestingly, a protein homologous to human Cep250/c-NAP1 (TgCep250) localizes to both inner and outer cores during cell division. To better understand the mechanics and function of the bipartite centrosomal architecture, a series of mutants provided several insights. Temperature-sensitive mutants with defect in outer core components, such as TgSfi1, resulted in failure of daughter cell budding, while leaving mitosis unaffected. Since the physical connection of inner core and the centrocone (spindle pole) remains intact in a TgSfi1-deficient background, this finding suggests a mitosis organizing function for the inner core, but, moreover, illustrates that the cores can function independently, and that it is possible to uncouple budding from mitosis. In a reciprocal experiment, Chen and Gubbels showed that in a TgCep250-deficient inner core line, the budding cycle persists but mitosis is disrupted [4]. These observations suggest that the different cores likely associate with different functions of the centrosome, i.e. the inner core for mitosis and the outer core for organizing daughter budding.

The bipartite centrosome model provides a clear model on how the centrosome can separate the nuclear cycle from the division cycle. By first multiplying its inner core and leaving the outer core undeveloped, the mother cell will only trigger the nuclear cycle without inducing daughter budding (Figure 1). In the last round, the outer core will fully develop and recruit daughter cell building blocks. The parasite proteins underlying this switch will be very interesting as novel and specific drug targets.

The distinct protein composition and replication sequence of centrosome inner and outer cores suggest that the centrosome is tightly regulated in a spatio-temporal manner. Indeed, a candidate of pericentriolar matrix (PCM) component, TgMAPK-L1, transiently surrounds the centrosome during S-phase, and vanishes during division. With a TgMAPK-L1 deficient parasite line, it was shown that TgMAPK-L1 limits centrosome core duplication to only once per cell cycle, and promotes the connection of the nuclear centrocone and the daughter basal complex [4]. Furthermore, a previously reported kinase, TgNek1-2, that plays a role in centrosome splitting, showed similar localization pattern to TgMAPK-L1 but resides towards the centrosome [3]. In the absence of TgNek1-2 activity, the centrosome duplicates but remains clustered, resulting in formation of a single daughter bud and failure of mitosis

[3]. Even though mutation of TgNek1-2 affects outer core morphology, the budding machinery remains functional. It is likely that TgNek1-2 promotes proper function of the inner core, and may contribute to the linear alignment of the centrosome inner and outer cores, and the centromere.

Future studies may focus on the crosstalk between the inner and outer core, and how replication of both cores fits into the cell cycle regulation. In higher eukaryotes, the key cell cycle regulators cyclin-dependent kinases initiate the centrosome cycle upon S phase [5, 6]. However, in *T. gondii*, centrosome duplication occurs during G1 phase, where its separation marks the G1/S phase boundary [7-9]. How this cell cycle regulation translates into biology of centrosome duplication remains to be explored in apicomplexan parasites. A previous study has shown that the centrosome rotates to the basal end of the nucleus prior to duplication and separation [10]. Dynamic movement of the nucleus and the centrosome may provide a spatial cue to trigger the following cell cycle events. In all, Suvorova's study sheds light on the functional regulation and structure of the centrosome that plays a pivotal role in the apicomplexan division cycle.

Acknowledgments

This work was supported by National Institutes of Health grants AI107475 and AI081924.

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Figure 1. A model for apicomplexan parasite cell division powered by a bipartite centrosome A haploid interphase zoite harbors inactive centrosomal inner (green) and outer (red) cores (left panel). An active inner core (bright green) drives the nuclear cycle (S-phase and mitosis; karyokinesis is optional and not covered by this model), whereas the quiescent outer core inhibits the budding cycle between the repeatedly nuclear cycles (middle panel). When both inner and outer core are active (bright green and bright red, respectively), a single round of the nuclear cycle is coupled to the budding cycle, and two daughter cells are formed per round (right panel).