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A Systematic Review of Apical and Basal Complex Roles in *Toxoplasma gondii* Invasion and Egress

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Abstract

***Toxoplasma gondii* is an obligate intracellular protozoan parasite of major medical and veterinary importance worldwide. Successful infection depends on its ability to actively invade host cells, replicate intracellularly, and egress to infect new cells. These processes involve complex molecular coordination among specialized organelles that ensure parasite survival and propagation. In the past decade, numerous experimental studies employing advanced molecular and high-resolution microscopy techniques have revealed new insights into the structural and functional dynamics of *T. gondii*, highlighting the need to systematically review and integrate these findings. This systematic review aims to identify, synthesize, and analyze experimental studies related to the molecular mechanisms of *T. gondii* infection, including host cell invasion, intracellular replication, and egress. Relevant literature published between 2015 and 2025 was retrieved from the Scopus and PubMed database using specific keywords. Articles were screened based on predefined inclusion and exclusion criteria, and the selection process followed the PRISMA guideline. From an initial 44 articles, 14 met the eligibility criteria after title and abstract screening, and 10 experimental studies were included for full-text analysis. Methodological quality and risk of bias of the included studies were evaluated using the Quality Assessment Tool for In Vitro Studies (QUIN) and visualized using the robvis tool. The systematic synthesis of these findings provides an integrated understanding of the molecular basis of *T. gondii* invasion and egress.**

Keywords: Apical complex, Basal complex, Infection, *Toxoplasma gondii*

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Introduction

Toxoplasmosis is an important zoonotic disease in human and animal health. Animals that can serve as definitive hosts are cats or other members of the Felidae family, while intermediate hosts are all warm-blooded animals such as goats, cows, and sheep. Toxoplasmosis is found worldwide, particularly in tropical countries including Indonesia (Cerutti *et al.*, 2020; Delgado *et al.*, 2022).

Toxoplasma gondii, an obligate intracellular protozoan parasite, was first discovered in the rodent *Ctenodactylus gundi* by Nicolle and Manceaux in 1908 and was named the following year. The species name comes from the words "toxo-" meaning bow and "plasma" meaning life, based on its bow-shaped morphology. Additionally, the word "gondii" comes from the first host in which the species was found(Attias *et al.*, 2020; J. P. Dubey, 2016).

This species has various life stages as a survival strategy. Its infectious stage can be

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in the form of sporulated oocysts found in cat feces and tissue cysts found in the tissues of other animals that are intermediate hosts (Attias *et al.*, 2020; Dubey, 2016) .

This species is an obligate intracellular parasite, meaning that when it infects a host, it must invade cells and multiply to continue living. Cell invasion is also a strategy for obtaining nutrients and surviving the immune response. *T.* gondii's ability to invade cells is due to the role of unique structures on its apical end, known as the apical complex. In addition to *T. gondii*, there are various species such as *Cryptosporidium* spp. that have this complex, which are grouped into the phylum Ampicomplexa (Frénal *et al.*, 2017; Portes *et al.*, 2020) .

The apical complex gives *T. gondii* the ability to invade almost all types of cells in the host's body (Guérin *et al.*, 2017; Portes *et al.*, 2020) . The invasion process involves all structures of the apical complex, namely the conoid, rhoptry, and microneme, in a complex series of steps. These three structures each play an important role in ensuring the success of the invasion process. During this process, a membrane-bound vacuole known as a parasitophorous vacuole (PV) forms within the host cell. It is within this vacuole that the parasite lives and reproduces (Clough & Frickel, 2017; Hakimi *et al.*, 2017) .

The process of *T. gondii* reproduction within the PV occurs through binary fission, which is asexual. Unlike invasion, in this process, the structure that plays an important role is the basal complex. The process of invasion into cells and binary fission are essential processes of *T. gondii* infection. This ability enables the parasite to successfully continue its life cycle. However, this does not occur simply; various stages support each other so that the invasion and division processes can occur successfully (Attias *et al.*, 2020; Frénal *et al.*, 2017) . Various studies have attempted to uncover this mechanism. Numerous experimental studies using molecular technology and high-resolution microscopy approaches have provided new findings on the structural and functional dynamics of parasites, necessitating a systematic review and synthesis of this evolving knowledge.

Therefore, this systematic review was compiled with the aim of reviewing, identifying, and synthesizing the results of recent experimental studies related to the role of the apical and basal complexes in the invasion and egress of *T. gondii*. Through an evidence-based approach, this study is expected to provide an integrative understanding of these mechanisms based on the latest research developments.

Methods

This literature review was compiled based on a literature search of several electronic databases. The databases used were Scopus and PubMed. The search strategy used keywords with the *query* "Toxoplasma gondii" AND ("apical complex" OR microneme* OR rhoptr* OR conoid OR "dense granule" OR AMA* OR RON* OR GRA* OR MIC* OR "basal complex" OR MORN* OR BCC*) AND (invasion OR invade* OR entry OR penetration OR "moving junction" OR egress OR exit*). The search criteria were limited to original research articles published between January 2015 and December 2025, written in English, and accessible in full text.

Duplicate articles were excluded prior to screening. The literature obtained was then reviewed based on the title and abstract. The screening process was based on the following inclusion criteria: (1) publication of experimental research related to the structure, protein, or function of apical or basal complexes; (2) focus on the *T. gondii* species rather than other Apicomplexa (e.g., *Plasmodium*, *Eimeria*, or *Cryptosporidium*). The exclusion criteria were: (1) Pure bioinformatics studies without experimental validation (analysis without laboratory data); and (2) Studies that only highlight non-apical secretion pathways without the involvement of apical or basal complexes. Fully accessible literature was reviewed further (full text assessment).

This review process follows the PRISMA flow diagram guidelines, with each step conducted systematically and documented (Haddaway *et al.*, 2022) . The literature generated from this process is then discussed with the addition of various other references. Risk of bias was assessed using the QUIN tool, which comprises 12 criteria (clearly stated aims, sample size calculation, sampling technique, comparison group, methodology,

operator details, randomization, outcome measurement, outcome assessor details, blinding, statistical analysis, and presentation of results). Each criterion was scored as adequately specified (2), inadequately specified (1), or not specified (0), criteria judged not applicable were excluded. The final score was calculated as the total score divided by twice the number of applicable criteria and expressed as a percentage, with >70% indicating low, 50–70% moderate, and <50% high risk of biasn(Sheth *et al.*, 2024). We prespecified two adaptations for studies using genetically modified parasites: randomization was considered not applicable when comparisons were made between genetically distinct lines or inducible-depletion conditions that cannot be randomly allocated, and assessor and blinding criteria were considered not applicable only when all primary outcomes were measured instrumentally. Domain-level judgments were visualized using the robvis Generic tool (McGuinness & Higgins, 2020).

Results and Discussion

Results

Based on the results of a literature search using specific keywords covering all structural components of the apical and basal complexes of Toxoplasma gondii between 2015 and 2025, 44 articles were found. An initial screening was conducted by reviewing duplicates, titles, and abstracts, resulting in 14 articles that met the criteria. However, after a full review of these articles, only 10 articles met the criteria. This systematic process is recorded and presented in the form of a PRISMA flow diagram in Figure 1.

During the review process, no publications were found that directly examined the structure, proteins, or function of the basal complex. Instead, all articles that met the criteria focused on the apical complex and its secretory organelles (conoids, micronemes, and rhoptries) that play a role in the invasion and motility of parasites. Table 1 lists the 10 articles used as the main references in this systematic review.

Nine studies were judged (QUIN scores) at moderate risk of bias and one at high risk, and none reached the threshold for low risk (Fig. 2). Aims, comparison groups, and outcome measurement were adequately reported in most studies. In contrast, sample size justification was not provided in any study, the sampling procedure was inadequately described in nine, and no study reported who assessed the outcomes or whether assessment was blinded, although most primary outcomes were counted manually. Operator details were not reported in six studies and only partially reported in four. Statistical analysis was inadequately specified in five studies, mainly because the test or the unit of analysis (biological replicate versus technical replicate, field, or vacuole) was unclear. Randomization was considered not applicable in all studies.

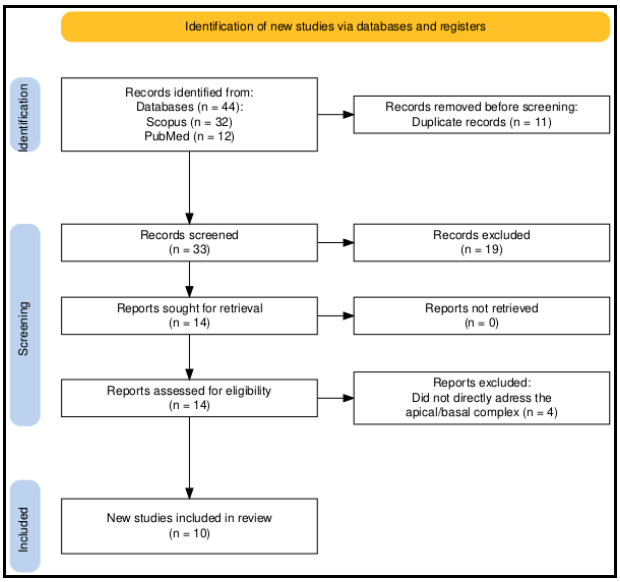


Figure 1. Systematic review process presented in a PRISMA flow diagram

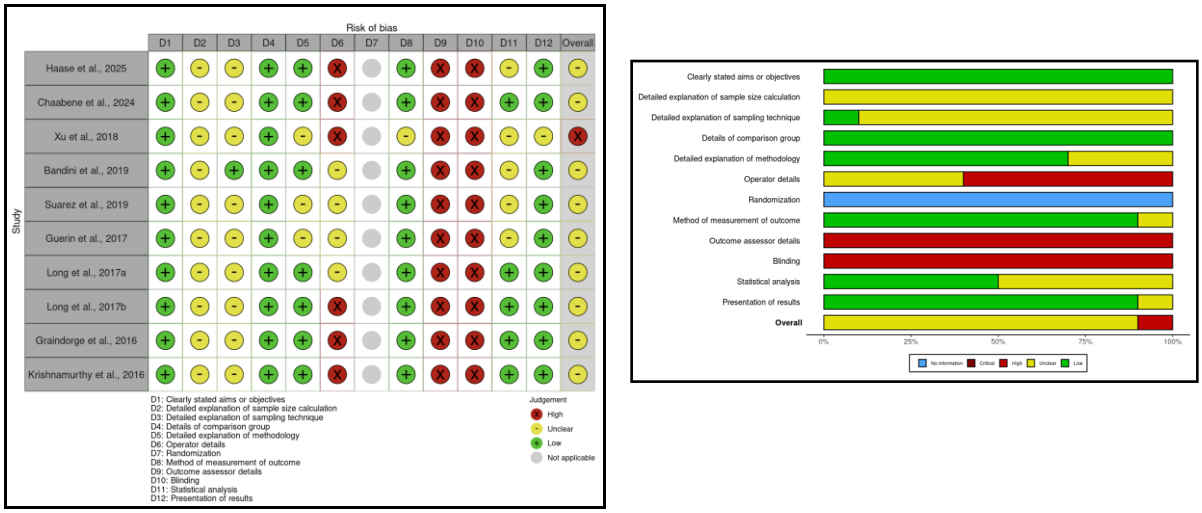


Figure 2. Risk of bias assessment of the ten included experimental studies using the Quality Assessment Tool for In Vitro Studies (QUIN). Green circles indicate low risk of bias, yellow circles denote unclear risk, red circles represent high risk, and grey circles indicate criteria that are not applicable (McGuinness & Higgins, 2020)

Table 1. Characteristics and key findings of the primary included studies in the systematic review

Author and Year	Type of Research	Structure Examined	Method	Key Findings	Conclusion Role
Haase *et al.*, 2025	Experimental (in vitro, in vivo)	Apical complex: RNG2 (cone–APR connector)	iU-ExM, Cryo-ET, and genetic knockdown for analysis of RNG2 position and function.	RNG2 bridges the conoid and the apical polar ring. Loss of RNG2 causes conoid dislocation and reduced motility and rhoptry secretion.	RNG2 acts as a major structural tether that maintains the integrity of the apical complex and supports parasite motility.
Chaabene *et al.*, 2024	Experimental (in vitro)	Apical complex: RDF3 (Rhoptry Discharge Factor 3)	Super-resolution microscopy, conditional knockdown, and immunoprecipitation.	RDF3 is required for rhoptry content release and moving junction formation. Loss of RDF3 inhibits host cell penetration.	RDF3 is an important regulator of rhoptry secretion in the early stages of parasite invasion.
Xu *et al.*, 2018	Experimental (in vitro, in vivo)	Apical complex: Rhoptry protein ROP38	Gene knockout, mouse infection, and gene expression analysis (RT-PCR).	Parasites lacking ROP38 show increased invasion but decreased IL-18 and TNF-α during early infection.	ROP38 regulates host immune response and invasion efficiency, acting as a virulence-controlling kinase.
Bandini *et al.*, 2019	Experimental (in vitro)	Apical complex: Microneme protein MIC2 with thrombospondin-like repeats	Mass spectrometry, gene knockout, and immunofluorescence.	O-fucosylation modification of TSR MIC2 is important for protein folding and transport to micronema.	Fucosylated MIC2 is important for initial adhesion and efficient invasion of host cells.
Suarez *et al.*, 2019	Experimental (in vitro)	Apical complex: Rhoptry protein RASP2 (Rhoptry Apical Surface Protein 2)	Conditional knockdown, lipid-binding assay, and high-resolution microscopy.	RASP2 interacts with rhoptry membrane lipids. Loss of this protein inhibits secretion and invasion.	RASP2 acts as a lipid-binding mediator that triggers rhoptry exocytosis during invasion.
Guérin *et al.*, 2017	Experimental (in vitro, in vivo)	Apical complex: RON4L1 moving junction complex	CRISPR/Cas9, co-immunoprecipitation, and immunofluorescence microscopy.	RON4L1 is a novel member of the moving junction that interacts with RON2, RON4, and AMA1.	RON4L1 is a novel component of the apical complex that stabilizes the moving junction during penetration.

Table 1. *Continue*

Author and Year	Type of Research	Structure Examined	Method	Key Findings	Conclusion Role
Long *et al.*, 2017a	Experimental (in vitro)	Apical complex: Conoid CPH1 (Conoid Protein Hub 1)	CRISPR/Cas9 knockout, high-resolution microscopy, and immunoelectron microscopy.	CPH1 maintains the conoid shape; its depletion causes deformation, motility disruption, and invasion failure.	CPH1 functions as a conoid hub protein that maintains the structure and mechanical function of the apical complex.
Long *et al.*, 2017b	Experimental (in vitro)	Apical complex: Calmodulin-like proteins (CaM1–3)	CRISPR/Cas9 tagging, AID degradation, and super-resolution microscopy.	CaM1–3 interacts with MyoH in the conoid; loss of this protein inhibits motility and invasion.	CaM1–3 is a conoid Ca^{2+} regulator that controls apical complex contraction and stability.
Graindorge *et al.*, 2016	Experimental (in vitro)	Apical complex: MyoH conoid motor (Myosin H)	Conditional knockdown, motility assays, and fluorescence microscopy.	MyoH depletion inhibits egress and invasion without affecting microneme secretion.	MyoH is the primary conoid motor that generates thrust for host cell penetration.
Krishnamurthy *et al.*, 2016	Experimental (in vitro)	Apical complex: AMA1–RON2	Microneme secretion assay and immunoprecipitation.	AMA1–RON2 interaction protects AMA1 from cleavage by ROM4/5 and enhances invasion efficiency.	AMA1–RON2 plays a role in stabilizing apical adhesins, strengthening parasite attachment to the host membrane.

Discussion

As a parasitic organism, *T. gondii* has a life strategy of changing its life form into various stages. In general, its life cycle is divided into two based on the type of reproduction, namely the sexual and asexual reproductive cycles. The sexual cycle occurs only in animals of the Felidae family (definitive host), while the asexual cycle occurs in all warm-blooded animals, including humans (intermediate host) (Dubey *et al.*, 2017).

Sexual reproduction begins when Felidae are infected with tissue cysts that release bradyzoites. Bradyzoites invade intestinal epithelial cells and divide by schizogony, producing merozoites. Merozoites can invade intestinal epithelial cells again or differentiate in the gamogony process into male (microgamet) and female (macrogamet) gametes. These gametes then mate to produce a zygote. The zygote then develops into an oocyst that is resistant to environmental pressures because it has a 5-layer oocyst wall (Attias *et al.*, 2020; R. Dubey *et al.*, 2017).

In the definitive host, oocysts are present in the feces. These oocysts sporulate in the environment 1-5 days after the feces are excreted. Sporulated oocysts are the infectious form that will infect intermediate hosts if ingested from contaminated soil, plants, or water. Sporulated oocysts produce sporozoites and transform into the tachyzoite stage. Tachyzoites are the proliferative stage capable of rapid division. Tachyzoites invade intestinal epithelial cells. Tachyzoites disseminate to various parts of the body and become bradyzoites, which form tissue cysts in skeletal muscle, myocardium, brain, and eye tissues. In contrast to tachyzoites, bradyzoites are characterized by slow division. Bradyzoites are also known as cystozoites. In addition to sporulated oocysts, humans can also become infected from tissue cysts when consuming infected food, through blood transfusions, organ transplants, and transplacentally from mother to fetus. Tachyzoites, which can invade intestinal epithelial cells, can cause acute infections. Tachyzoites that form bradyzoites with tissue cysts cause chronic infections (Dubey, 2016; Delgado *et al.*, 2022).

Morphology of the Invasive Stage: Tachyzoites, Bradyzoites, and Sporozoites

The takizoit, bradizoit, and sporozoite stages have similar structures despite slight differences in shape (Figure 3). All three have an elongated shape resembling a bow or crescent moon. The anterior end is narrow and blunt, while the posterior end is broad and rounded. Takizoit have a nucleus located in the middle of their body, while bradizoit and sporozoit have a nucleus located more towards the posterior end (Cerutti *et al.*, 2020; Delgado *et al.*, 2022).

Bradizoites are found inside tissue cysts and divide endodiogenically. Tissue cysts vary in size depending on the number of bradizoites present. Mature tissue cysts can contain hundreds of bradizoites. Tachyzoites have a flexible cytoskeleton in the form of microtubules, enabling them to move by gliding (*gliding motility*). This movement does not involve any visible aids such as flagella, cilia, or pseudopodia (Dubey, 2016; Frénal *et al.*, 2017).

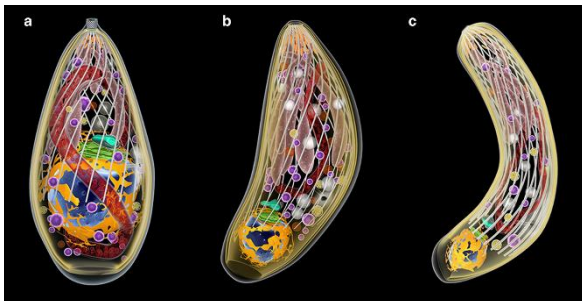


Figure 3. Illustration of the three stages of *T. gondii*: tachyzoite (a), bradyzoite (b), and sporozoite (c). Reproduced from Attias *et al.* (2020) under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0) (http://creativecommons.org/licenses/by/4.0/)

Like most members of the Ampicomplexa, *T. gondii* has a shape enclosed by a thin membrane vesicle known as the pellicle. The pellicle consists of three membrane layers: the plasmalemma and two layers that form the inner membrane complex (IMC). This complex protects the organelles, provides shape, and also plays a role in movement (Frénal *et al.*, 2017; Oliveira Souza *et al.*, 2022).

Within the pellicle, organelles such as the apical complex, micropori, mitochondria, endoplasmic reticulum, nucleus, dense granules, amylopectin granules, Golgi apparatus, and basal complex can be found. The apical complex is a specialized structure consisting of the conoid, rhoptry, and micronema (Dubey, 2016; Long *et al.*, 2017a) .

The conoid is located at the anterior end and is shaped like a tapered cylinder rich in tubulin. The conoid has a cavity with two apical rings (AR1 and AR2). At the posterior end of the conoid, there are two polar rings (PR1 and PR2). The PR1 ring regulates the apical boundary with the IMC, and PR2 is the center of organization and attachment of subpili microtubules/microtubule organizing center (MTOC). At PR2, 22 microtubules are attached, extending throughout the body and located below the IMC. In addition, there are also 2 microtubules located inside the conoid (internal microtubules) (Long *et al.*, 2017a).

Towards the posterior end of the conoid, there are roptres and micronemes. Roptres have a sac-like shape extending posteriorly. Their anterior end is narrow, forming a neck that widens posteriorly. A single organism may have 8 to 10 roptres. Unlike roptres, micronemes are rod-shaped and smaller in size than roptres. The number of micronemes is abundant but concentrated only in the apical region. The number of micronemes varies, being most abundant in sporozoites, followed by tachyzoites, and least in bradyzoites. Both organelles are secretory organelles that release secretions during invasion into the host cell (Frénal *et al.*, 2017; Graindorge *et al.*, 2016; Lebrun *et al.*, 2020).

Within the pellicle, dense granules are also found scattered from the anterior to the posterior. These granules are spherical in shape, contain a lot of protein, and are secretory organelles similar to roptria and macronema. Opposite the apical complex, at the posterior end of the IMC, a basal complex can also be found. Unlike the apical complex, this complex is morphologically inconspicuous and does not have a distinctive shape. The basal complex consists of the basal inner collar, the basal inner ring as the middle layer, and the most posterior structure resembling a bowl, the posterior cup (Tosetti *et al.*, 2019).

The apical complex and its role in the invasion process into the host cell

In general, the invasion process of the invasive stage *of T. gondii* involves stages that begin with gliding movement, recognition of the host cell through the conoid tip, recognition of the host plasma membrane (PM), formation of a *moving junction* complex, followed by secretion of micronemes, rhoptries, and dense granules (Attias *et al.*, 2020; Graindorge *et al.*, 2016) . The apical complex *of T. gondii* plays a crucial role in the invasion process into the host cell. The invasion process involves the secretion of proteins from organelles such as micronemes and rhoptries, which mediate host cell invasion (Portes *et al.*, 2020) .

The conoid is the center of signal processing for movement, including invasion. The conoid can *be retracted* and protruded, tilted, elongated, and shortened. The initial process of interaction between the conoid and host cells is a recognition process. The conoid responds to changes in intracellular calcium (Ca2+) levels by protruding. An increase in intracellular calcium levels is an important signal required for invasion. Subsequently, the AKMT protein regulates the initiation of movement (Sivagurunathan *et al.*, 2013) . During invasion, the AKMT protein is localized in the apical region, specifically in the conoid (Frénal *et al.*, 2017; Graindorge *et al.*, 2016; Jacot *et al.*, 2016) .

Rhoptry Neck Protein 2 (RNG2) is known to function as a mechanical link between the conoid and the apical polar ring (APR). Haase *et al.* (2025) found that RNG2 anchors the conoid via approximately 22 anchoring filaments that maintain the position and stability of the apical complex. The loss of RNG2 causes conoid dislocation, disruption of rhoptry secretion, and reduced invasion ability, confirming the importance of RNG2 as the primary anchoring structure in the *T. gondii* apical complex.

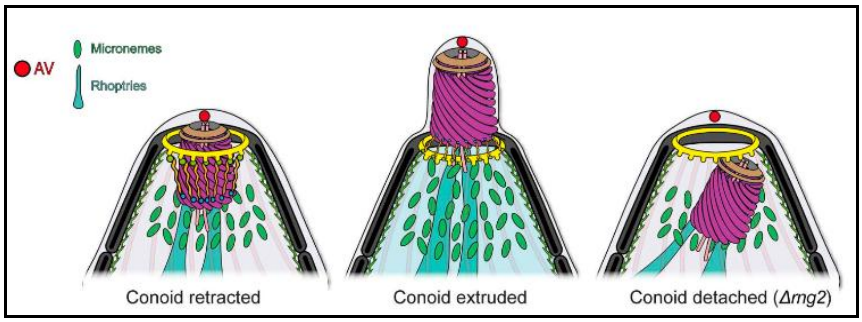


Figure 4. Model of RNG2 as an apical conoid molecular anchor. (Left) The conoid is folded in its normal position. (Middle) The conoid is inverted during the invasion process. (Right) In the Δrng2 mutant, the conoid is detached from the apical ring, indicating that RNG2 plays an important role as a molecular link between the conoid and the apical polar ring. Reproduced from Haase *et al.* (2025) under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0). (http://creativecommons.org/licenses/by/4.0/)

Additionally, the Conoid Protein Hub 1 (CPH1) protein also plays a crucial role in maintaining conoid integrity, functioning as a hub protein that connects various structural elements of the conoid. When CPH1 is eliminated, conoid deformation, motility disruption, and invasion failure occur. This reinforces that conoid stability is the main mechanical basis for successful parasite invasion (Long *et al.*, 2017b).

The recognition process is carried out by protruding the conoid, which involves the important role of the PR ring, which is the MTOC. The protrusion of the conoid causes its body to become slightly slender. In addition, micronema secretion and activation of the actinomyosin system occur, causing the movement process (Graindorge *et al.*, 2016).

Rhoptry Discharge Factor 3 (RDF3) protein is an important component that regulates the timely release of rhoptry contents. The RDF3 protein plays a role in the formation of tight junctions required for the initial penetration process. Parasites lacking RDF3 fail to release rhoptry proteins (RONs/ROPs) and are unable to form moving junctions, thereby preventing the invasion process from occurring (Ben Chaabene *et al.*, 2024) .

The rhoptry secretion mechanism is also controlled by Rhoptry Apical Surface Protein 2 (RASP2). Suarez *et al.* (2019) explain that RASP2 interacts with anionic lipids in the rhoptry membrane to trigger organelle exocytosis. Depletion of RASP2 causes complete failure of rhoptry content release despite normal organelle morphology, indicating the important role of RASP2 as a lipid exocytosis mediator supporting parasite invasion.

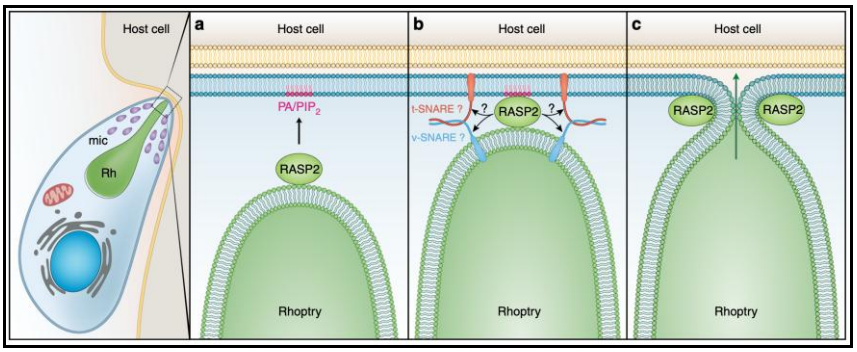


Figure 5. Role of RASP2: RASP2 binds to phospholipids (PA/PIP_2) (a); Association between the rhoptry and the parasite plasma membrane, which then triggers the assembly of the rhoptry docking/priming complex (b); Membrane fusion, an essential step before the release of roptry contents into the host cell (c). Reproduced from Suarez et al. (2019) under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0) (http://creativecommons.org/licenses/by/4.0/)

In addition to functioning in the invasion process, several rhoptry proteins are also involved in modulating the host immune system. In the study , it was found that *Rhoptry Protein 38* (ROP38) acts as a regulatory kinase that downregulates the expression of proinflammatory cytokines such as *Interleukin-18* (IL-18) and *Tumor Necrosis Factor-alpha* (TNF-α). The removal of ROP38 increases invasion but decreases immune activation, indicating the dual function of this protein in regulating virulence and evading the immune response.

Micronemes secrete microneme proteins (MICs) that play a role in the recognition and attachment of parasites to the host cell surface (Figure 6a). MICs proteins work alone or form complexes such as the MIC6-MIC1-MIC4 and MIC8-MIC3 complexes. Both complexes play a role in attaching to target cells, forming connections between parasite cells and target cells. In addition, there is also MIC2-M2AP, which plays a role in movement and penetration into cells (Reiss *et al.*, 2001; Zhu *et al.*, 2021) .

Post-translational modifications have been shown to be crucial in mediating microneme adhesion function. Bandini *et al.* (2019) showed that the *Thrombospondin-like Repeats* (TSRs) domain of MIC2 undergoes O-fucosylation modification by the enzymes POFUT2 and NST2. Mutations at the fucosylation site cause failure of MIC2 transport to the micronema and a decrease in adhesion ability. This confirms that glycosylation modification is a key factor in maintaining adhesion and invasion efficiency.

Most micronema proteins that have an attachment function are only temporarily present on the surface, but there are also those that remain on the apical surface of the parasite, such as apical membrane protein 1 (AMA1). The AMA1 protein interacts with *neck* proteins secreted by roptries (RONs) to form a complex that plays an important role during penetration, namely the *moving junction* (MJ) complex. The MJ complex consists of AMA1, RON2, RON4, RON5, and RON8 (Ferra *et al.*, 2020; Guérin *et al.*, 2017; Krishnamurthy *et al.*, 2016) .

The MJ complex forms *a moving junction*, enabling active penetration into the host cell through actinomyosin movement. The parasite compresses its body along the moving junction, resulting in penetration into the host cell (Figure 6c-d).

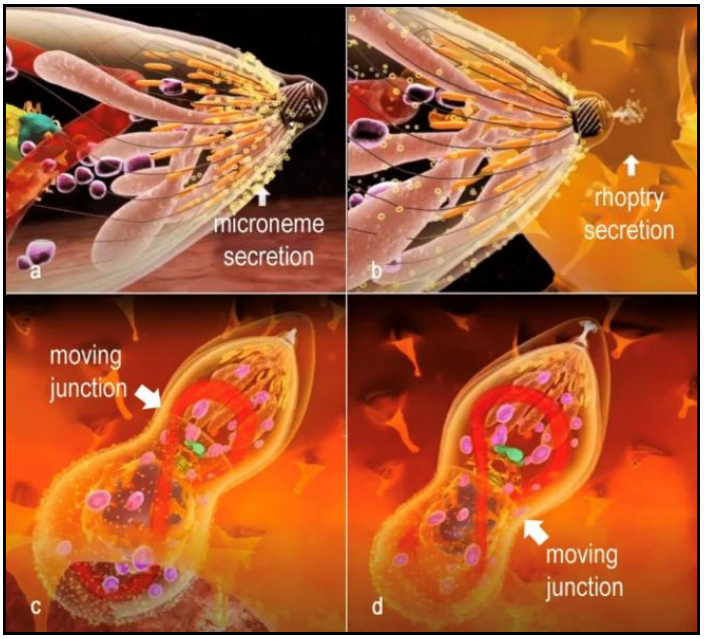


Figure 6. Process of invasion into the host cell: Secretion of micronemes and protrusion of conoids (a); Attachment and secretion of proteins from the rhoptri neck (c-b). A progressive moving junction is formed, the parasite enters the host cell and is enclosed within the parasitophorous vacuole (PV). Reproduced from Attias *et al.* (2020) under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0) (http://creativecommons.org/licenses/by/4.0/)

The AMA1 and RON2 complex plays a central role in MJ formation. The AMA1–RON2 interaction protects AMA1 from cleavage by *Rhomboid Protease 4 and 5* (ROM4/5) and increases invasion efficiency by up to 60%. Thus, AMA1–RON2 not only functions as an adhesin but also maintains apical membrane stability during penetration (Krishnamurthy *et al.*, 2016) .

Guérin *et al.* (2017) then identified Rhoptry Neck Protein 4-like 1 (RON4L1) as a new member of the moving junction complex. RON4L1 interacts with AMA1, RON2, and RON4, strengthening the mechanical connection between the parasite and the host cell. Depletion of RON4L1 causes failure of moving junction formation and reduces invasion efficiency. This suggests that the apical complex is dynamic and consists of many subcomponents that work synergistically to maintain adhesion strength during invasion.

Next, the basal roptri will secrete proteins (ROPs) that can affect host cell properties, immune responses, and form the parasitophorous vacuole membrane (PVM). The parasitophore vacuole (PV) is initially formed from the host plasma membrane (PM) but is modified and forms a new membrane (PVM) that becomes the boundary between the parasite and the host cell cytosol. It is within the PV that the parasite lives and divides (Clough & Frickel, 2017; Hakimi *et al.*, 2017).

After the PV is formed, the solid particles will massively secrete their proteins (GRA) into the PV lumen, PVM, or host cell. GRA proteins function more to maintain the stability and structure of the PV. However, there are also GRA that function for survival, such as regulating the immune response and host cell gene expression (Mercier & Cesbron-Delauw, 2015; Venugopal *et al.*, 2020) .

Once GRA is secreted, an intravacuolar network (IVN) begins to form within the PV. This IVN connects the parasites to each other in a curved shape. The IVN curves are formed by the GRA2 protein and stabilized by GRA6. The IVN enables the parasites to consume cytosolic materials. The GRA proteins associated with the IVN are GRA2, GRA4, GRA6, GRA9, and GRA12. In addition to what has been described, GRA also plays an important role in forming bradyzoite cysts and in the process of egress from the host (Dou *et al.*, 2014; Guevara *et al.*, 2019; Mercier & Cesbron-Delauw, 2015).

To systematically synthesise the cascade of molecular events, specific apical proteins, and secretory factors discussed throughout this section, their respective functions during host cell invasion and the consequences of their experimental disruption are summarized in Table 2.

The apical complex and its role in the process of exiting the host cell.

Egress from the host cell is important for T. gondii because it is the precursor to invasion of other host cells and the process of re-division. The success of the egress process is determined by the secretion of MIC and GRA, which will have a destabilizing effect on the host PV and PM (Delgado et al., 2022; Graindorge et al., 2016) .

The CDPK3 protein is known to play an important role because it is triggered when there is a decrease in potassium in the host cell environment. This decrease indicates that the host cell has been damaged by infection or attacked by the immune system. The triggering of this protein is an important signal for the parasite to exit the host cell (Frénal et al., 2017) . Next, the initiation of movement will occur by the AKMT protein. Unlike during invasion, when exiting the cell, the AKMT protein will be distributed in the cytosol (Jacot et al., 2016) .

The microneme will also secrete the PLP1 protein, which weakens the PVM, causing it to rupture. The parasite extends its conoid and moves within the PV, then breaks the PVM and moves through the host cell's PM (Guerra et al., 2018; Venugopal et al., 2020) .

Calcium ion (Ca^{2+}) regulation at the apical complex is mediated by Calmodulin-like Protein 1–3 (CaM1–3). CaM1–3 proteins directly interact with Myosin H (MyoH) on the conoid and are required for parasite motility and egress. Loss of CaM1–3 causes disruption of conoid contraction without affecting microneme or rhoptry secretion, confirming the role of these proteins as the primary regulators of Ca^{2+}-based mechanical activity (Long et al., 2017b).

Graindorge et al. (2016) shows that the conoid motor MyoH is the main driver that generates the thrust for initial penetration. Parasites with MyoH depletion can still attach

to host cells but fail to enter, indicating that MyoH initiates the critical conoid contraction step for invasion. MyoH activity is also required for egress, indicating that the conoid motility system plays a bidirectional role in both entering and exiting host cells.

To provide a concise synthesis of the regulatory cascade and mechanical drivers discussed, the specific molecular factors, environmental triggers, and distinct roles coordinating host cell egress are summarized in Table 5.

Table 2. Molecular Components of the Apical Complex and Secretory Organelles Mediating Toxoplasma gondii Host Cell Invasion

Organelle / Structure	Molecular Factor / Protein	Specific Role in Host Cell Invasion	Reference(s)
Conoid & Apical Polar Ring (APR)	RNG2	Functions as a mechanical linker; anchors the conoid to the APR via ~22 filaments to maintain structural integrity	Haase *et al.* (2025)
	CPH1	Functions as a conoid hub protein maintaining architectural stability and mechanical resilience	Long *et al.* (2017b)
	AKMT	Localizes to the apical conoid; regulates the initiation of gliding movement in response to intracellular Ca2+ elevation	Sivagurunathan *et al.* (2013); Frénal *et al.* (2017); Graindorge *et al.* (2016); Jacot *et al.* (2016)
Micronemes	Adhesin Complexes (MIC1/4/6, MIC3/8, MIC2–M2AP)	Secreted onto the surface to mediate host cell recognition, surface attachment, and active cellular penetration	Reiss *et al.* (2001); Zhu *et al.* (2021)
Micronemes	MIC2 (O-fucosylation via POFUT2 & NST2)	Post-translational O-fucosylation on thrombospondin-like repeats (TSRs) ensures correct protein folding and targeting to micronemes	Bandini *et al.* (2019)
Rhoptries (Neck & Bulb)	RDF3	Regulates the timely discharge of rhoptry contents (RONs/ROPs) required for moving junction assembly	Chaabene *et al.* (2024)
	RASP2	Interacts with rhoptry membrane anionic lipids (PA/PIP2) to trigger organelle docking, priming, and exocytosis	Suarez *et al.* (2019)
	ROP38	Acts as a regulatory kinase modulating early host immune responses; downregulates pro-inflammatory IL-18 and TNF-α	Xu *et al.* (2018)
	General ROPs	Discharged into the host cell cytosol and nucleus to modulate host properties, dampen immunity, and establish the PVM	Clough & Frickel (2017); Hakimi *et al.* (2017)
Moving Junction (MJ) Complex	AMA1–RON2 Complex	Core moving junction receptor-ligand pair; interaction protects AMA1 from ROM4/5 cleavage and stabilizes apical attachment	Krishnamurthy *et al.* (2016); Ferra *et al.* (2020)
	RON4L1	Novel moving junction component interacting with AMA1, RON2, and RON4 to provide structural stability during penetration	Guérin *et al.* (2017)
Dense Granules	General GRA Proteins	Secreted into the PV lumen, PVM, and host cytosol to maintain vacuolar architecture, regulate immunity, and modulate gene expression	Mercier & Cesbron-Delauw (2015); Venugopal *et al.* (2020)
	IVN-Associated GRAs (GRA2, GRA4, GRA6, GRA9, GRA12)	GRA2 forms and GRA6 stabilizes the tubulovesicular intravacuolar network (IVN), enabling nutrient acquisition from the host	Dou *et al.* (2014); Guevara *et al.* (2019); Mercier & Cesbron-Delauw (2015)

Table 3. Molecular Factors, Signals, and Mechanical Drivers in *Toxoplasma gondii* Host Cell Egress

Component	Organelle / Cellular Localization	Role in Host Cell Egress	Reference(s)
Secretory Proteins (MIC and GRA)	Micronemes and dense granules	Secreted to induce destabilization of the parasitophorous vacuole membrane (PVM) and host plasma membrane (PM)	Delgado et al. (2022); Graindorge et al. (2016)
CDPK3	Parasite signaling machinery	Triggered by a reduction in extracellular potassium (K+) resulting from host cell damage or immune attack; acts as a crucial initiation signal for egress	Frénal et al. (2017)
AKMT	Cytosol (redistributed from apical tip)	Diffuses into the parasite cytosol during egress to initiate motility pathways required for exiting the host cell	Jacot et al. (2016)
PLP1 (Perforin-Like Protein 1)	Micronemes	Secreted to weaken and rupture the PVM, enabling conoid extension, intra-vacuolar motility, and subsequent transit through the host PM	Guerra et al. (2018); Venugopal et al. (2020)
CaM1–3 (Calmodulin -like proteins 1–3)	Apical complex / conoid	Mediate Ca2+ regulation and interact directly with MyoH to govern conoid contraction and motility; disruption impairs conoid mechanical activity without altering organelle secretion	Long et al. (2017b)
MyoH (Myosin H)	Conoid motor apparatus	Functions as the primary molecular motor generating propulsion; coordinates conoid contraction to drive bidirectional parasite movement during both invasion and egress	Graindorge et al. (2016)

The basal complex and its role in binary fission

The basal complex in *T. gondii* is a dynamic and multifunctional structure located at the most basal end of the IMC, which is the membrane framework regulating cell division. Cell division occurs endogenously, i.e., the process of forming daughter cells (budding) within the host's body/internally (Delgado *et al.*, 2022; Gubbels *et al.*, 2022) . The basal complex plays a crucial role in this asexual division process, resulting in the formation of two daughter cells (Gubbels *et al.*, 2022) .

The basal region is where the building blocks of the cytoskeletal scaffold are added. This is the region that forms during daughter cell formation. The basal complex is known as a contractile ring that can stretch and narrow during the process of separating the parasite at the end of cell division (Gubbels *et al.*, 2020) . This is important because during the formation of daughter cells, proper segregation must occur to produce functional cells. The stability of this stretching ability is regulated by the MORN1 and BCC4 proteins. These two proteins are essential for the initial stages of cell division because they stabilize the growth of the basal end of the daughter cell and recruit other basal complex proteins (Gubbels *et al.*, 2020, 2022) .

The cell division stage begins with the formation of a thin cytoskeletal foundation with MORN1 and BCC4 proteins already available for the recruitment of other proteins. The cytoskeleton will form starting from the apical toward the basal. Next, when the daughter cell is halfway formed, the basal complex will solidify and narrow towards the posterior end. The division and narrowing process will continue until the organelles and daughter cells are separated (Gubbels *et al.*, 2022) .

Table 4. Molecular Regulators and Structural Roles of the Basal Complex during Toxoplasma gondii Binary Fission

Division Phase / Stage	Component / Protein	Role in Binary Fission	References (from text)
Budding Initiation & Scaffold Formation	MORN1 & BCC4	Stabilize the growth of the daughter cell basal end and recruit downstream proteins to establish the cytoskeletal foundation growing from apical toward basal pole.	Gubbels et al. (2020, 2022)
Elongation & Organelle Segregation	Contractile Ring (Basal Complex)	Acts as a dynamic contractile ring that stretches and constricts toward the posterior end when daughter cells are halfway formed, ensuring proper organelle segregation and division into functional cells.	Gubbels et al. (2020, 2022)
Cytokinesis & Rosette Organization	Interconnected Basal Complexes	Maintain the cytoplasmic bridge connecting tachyzoites inside the same vacuole, organizing parasites into a rosette structure and facilitating intercellular communication.	Gubbels et al. (2020, 2022)
Division Completion & Extracellular Transition	Posterior Cup	Forms as a replacement structure inside the IMC after the cytoplasmic bridge breaks and interconnected basal complexes disappear, establishing basal integrity for the extracellular parasite.	Delgado et al. (2022); Gubbels et al. (2020, 2022)

The plasma membrane will coat the daughter cell cytoskeleton, and interconnected basal complexes will also be visible. This will maintain the cytoplasmic bridge connecting the tachyzoites within the same vacuole. This event will cause the tachyzoites to form a flower/rosette-like structure. The cytoplasmic bridge will then break, and the interconnected basal complexes will disappear. The tachyzoites will form a replacement structure, namely the posterior cup, inside the IMC. At this point, the parasite is outside the host cell (extracellular). After the division process, the basal complex also plays a role in maintaining the cytoplasmic bridge formed between the parasites and the residues for intercellular communication (Gubbels *et al.*, 2020, 2022).

To provide a structured overview of the sequential events during endodyogeny, the molecular regulators, dynamic contractile transitions, and structural roles of the basal complex are summarized in Table 4.

Conclusion

The results of this systematic review indicate that the apical complex and basal complex play important roles in the success of *T. gondii* infection. The apical complex is involved in the invasion and egress processes through the coordination of conoid, microneme, and rhoptry activities that regulate adhesion, penetration, and release of the parasite from the host cell. Proteins such as RNG2, CPH1, RASP2, RDF3, and the AMA1–RON2–RON4 complex play a role in mechanical and secretory regulation, enabling the parasite to invade in a coordinated manner. Meanwhile, the basal complex plays a role in binary fission and daughter cell separation through the activity of proteins such as MORN1 and BCC4, which maintain structural integrity during cytokinesis.

Overall, this review highlights the interrelationship between structural and functional components in *T. gondii* that work synergistically to ensure successful invasion, replication, and egress. A deeper understanding of these mechanisms is expected to form the basis for the development of more specific and effective antiparasitic therapeutic strategies in the future.

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