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Review

Erythrocyte invasion: Vocabulary and grammar of the *Plasmodium* rhoptry

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Abstract

Malaria is a dangerous infectious disease caused by obligate intracellular protozoan *Plasmodium* parasites. In the vertebrate host, erythrocyte recognition and establishment of a nascent parasitophorous vacuole are essential processes, and are largely achieved using molecules located in the microorganelles of the invasive-stage parasites. Recent proteome analyses of the phylogenetically related *Toxoplasma* parasite have provided protein catalogs for these microorganelles, which can now be used to identify orthologous proteins in the *Plasmodium* genome. Of importance is the formation of a complex between the proteins secreted from the rhoptry neck portion (RONs) and micronemes (AMA1), which localize at the moving junction during parasite invagination into the host cell. In this article I review the largely unexplored paradigm of the malaria merozoite rhoptry, focusing on the high molecular weight rhoptry protein complex (the RhopH complex), and speculate on its grammar during invasion.
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Keywords: Rhoptry; Parasitophorous vacuole; Erythrocyte; Invasion; Apicomplexa

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1. Introduction

Malaria is one of the most prevalent and deadly global infectious diseases, and is caused by the obligate intraerythrocytic stages of the apicomplexan parasite, *Plasmodium*. To invade host erythrocytes, merozoite stage parasites discharge the contents of their apical organelles, micronemes, rhoptries, and dense granules. For the other invasive forms of the malaria parasite in the mosquito vector, type I transmembrane proteins released from the micronemes have been shown to be critical for parasite gliding motility, for example TRAP in sporozoites and CTRP in ookinetes; these proteins adhere to environmental molecules using extracellular ligand domains and are powered by their own actomyosin motor machinery [1]. This mechanism is also proposed to drive parasite invagination into host cells.

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Although merozoites are considered to be not motile, a similar role is expected for the merozoite micronemal protein(s) during erythrocyte invasion. Compared to the micronemal molecules, the role of the rhoptry molecules are poorly understood in all apicomplexan parasites.

Among the three invasive forms of the malaria parasite, only merozoites and sporozoites possess the ability to form a parasitophorous vacuole (PV), in which the parasite develops and clonally produces multiple daughter invasive parasites for the next cell generation. The ookinete stage parasite simply penetrates mosquito midgut cells without generating a PV and appears not to possess a rhoptry, which emphasizes that the rhoptry is an important organelle for establishment of a PV for development within the host cell, but not for cell passage. Recently, some rhoptry molecules have been characterized in detail in another apicomplexan parasite *Toxoplasma gondii* [2], however, the conservation of rhoptry proteins between *T. gondii* and *Plasmodium* merozoites is not great. Thus, the knowledge obtained through the *T. gondii* research cannot be directly applied to most merozoite rhoptry proteins. In this review, I overview recent progress related to merozoite invasion, try to elucidate its grammar (Fig. 1), and describe rhoptry function particularly focusing on the high molecular mass rhoptry protein complex.

2. The RhopH complex: gene, protein, and complex

One of the major molecules within rhoptries of the *Plasmodium* merozoites is a complex of high molecular mass proteins (the RhopH complex or the HMW complex) [3,4]. The three major proteins comprising the RhopH complex were originally described in *P. falciparum* and were designated RhopH1 (155 kDa), RhopH2 (140 kDa), and RhopH3 (110 kDa) based on size order [5,6]. The RhopH complex was also characterized in the rodent malaria parasite *P. yoelii*, and each component designated PyRhopH1A (135 kDa), *Py*RhopH2 (140 kDa), and PyRhopH3 (100 kDa) after their *P. falciparum* homologs [7]. The *Pf*RhopH complex is assembled immediately after polypeptide synthesis, most likely in the endoplasmic reticulum, as assembly is not affected by treatment with Brefeldin A, which blocks protein transport from the endoplasmic reticulum to the Golgi apparatus [5].

The genes encoding the components of the RhopH complex have been identified in *P. falciparum* and *P. yoelii* [7–10]. The genes encoding RhopH1 are members of the *rhoph1/clag* gene family, which was originally defined by the cytoadherence linked asexual gene (*clag*) on chromosome 9 in *P. falciparum* (*clag9*) [9,11]. Thus in this review I employ 'RhopH1/Clag' (protein) and '*rhoph1 /clag*' (gene) as a family name, and 'Clag' (protein) and '*clag*' (gene) for each member.

Currently 5 *rhoph1/clag* genes can be found in the *P. falciparum* genome database: *clag2* (PFB0935w), *clag3.1* (PFC0120w), *clag3.2* (PFC0110w), *clag8* (MAL7P1.229), and *clag9* (PFI1730w). *clag8* was originally designated *clagb1* (or *clagBlob*, *clagb*, *clag7*) due to initial assignments and preliminary annotations by the *P. falciparum* Genome Sequencing Project, and was renamed based on the chromosomal location determined by linkage analysis of HB3 × Dd2 genetic-cross progeny [12]. The inheritance pattern of the *clag8* gene locus was matched with the HRPII gene locus, which was segregated to the subtelomeric region of chromosome 8 for a HB3 × Dd 2 cross [13]. However, the recently updated PlasmoDB 5.2 (3D7 line) assigned both HRPII and *clag8* loci to the subtelomeric region of chromosome 7. This discrepancy

Fig. 1. Erythrocyte invasion of the *Plasmodium* merozoites. (A) Rhoptry and microneme localization of known and potential *Plasmodium* merozoite molecules. *Plasmodium*-specific molecules are shown on the left side and molecules conserved with *Toxoplasma gondii* are shown on the right side. Proteins, for which the localization is not determined or hypothesized, are drawn with dashed line. Locations of ROP14, RON1, -2, -3, and -5 have been shown for *T. gondii* orthologs, but not for *Plasmodium*. Stomatin ortholog can be found in the *T. gondii* database, but the location remains unknown for *T. gondii*. Location of RBL has been proposed to be the rhoptry neck, but I consider it locates likely in the microneme based on the immuno-localization of *Pf*RH4 [53] and multiple biological similarity with EBL as discussed later. Homology between RhopH1/Clag and RON2 is emphasized with a star. Single or 7 transmembrane regions were predicted for *Plasmodium* RON2 or ROP14 orthologs by THMHH 2.0, respectively [54]. PF13_0019 and PF14_0346 were proposed as rhoptry proteins based on the homology with *T. gondii* rhoptry sodium/hydrogen exchanger *Tg*NHE2 and *Tg*ROP16, respectively [55]. However, PF13_0019 is an ortholog of *Tg*NHE1 located on the plasma membrane [56] and P F14_0346 is an ortholog of *Tg*PKG [57]. Ortholog of *Tg*NHE2 and *Tg*ROP16 cannot be found in the current *Plasmodium* database, thus PF13_0019 and PF 14_0346 are unlikely to be the rhoptry proteins. (B) TRAP family is known to participate parasite motility and cell invagination by associating with actomyosin machinery. Because the TRAP cytoplasmic tail can substitute for the EBL cytoplasmic tail, EBL possibly associate with actomyosin machinery [58]. In addition, EBL and RBL appear to be alternatively utilized for the invasion [59] and MTRAP, EBL and RBL can be cleaved by the same rhomboid protease *Pf*ROM4 [60]. Because of the reduced importance of the gliding motility for the merozoite, the role of the TRAP homolog to adhere to environmental molecules could be reduced and as a result MTRAP might have lost von Willebrand factor A domain and retain only single thrombospondin type 1 domain [61]. Instead, malaria merozoite possibly developed *Plasmodium*-specific ligands, EBL and RBL, which specifically recognize erythrocyte surface receptors. AMA1 appears to be released before schizont rupture [62], form a complex with rhoptry neck proteins, and cleaved by the subtilisin-like protease SUB2 [63], suggesting different role from EBL, RBL, and MTRAP. (C) Rhoptry neck proteins are released and form moving junction complex with microneme protein AMA1. The precise interaction between each molecule comprising this protein complex is not known. (D) The RhopH complex and RAP2 (thus likely RAP1 and RAP3) appear to be leaked through the junction between parasite and erythrocyte membrane. (E) After invasion, RAMA can be seen in parasitophorous vacuole [64]. Stomatin was detected on the erythrocyte cytosol side of the PV membrane. RhopH148 was not detected after invasion [65]. Locations for the RhopH complex proposed by multiple reports were shown. *P. chabaudi* ROPE (repetitive organellar protein) was proposed to associate with the erythrocyte cytoskeleton based on the protein structural analysis [66], however, the proposed binding site, the leucine–histidine–zipper region, was not conserved with *P. falciparum* ortholog (PFB0145c), thus I omitted the proposed ROPE localization from this scheme. (F) Domain structure of some rhoptry and microneme molecules of *P. falciparum*. Shaded box indicate region that does not keep homology throughout *Plasmodium* species, and frequently include repeat motif. Putative endoplasmic reticulum transporting signal peptide (S), transmembrane region (TM), and glycosylphosphatidyl inositol-anchor attachment signal (GPI) are indicated. Conserved Cys residues are indicated with vertical bars for RAP 1, -2/3, RhopH1/Clag, RhopH2, -3, RON2, and RON4. EBL and RBL are encoded in the multigene family and they vary extensively in size, thus only representative structures are shown. D1, D2, and D3 indicate AMA1 domain 1, 2, and 3, respectively. DBL, c-Cys, TSP, DUF1222, and PHB indicate Duffy-binding-like, C-terminal Cys rich domain, thrombospondin type 1 domain, domain with unknown function 1222, and prohibitin domain, respectively.

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