Structure and function of the parasitophorous vacuole in *Eimeria* species

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Abstract

The intracellular life-cycle stages of *Eimeria* are located in the host cell within a membrane-bound parasitophorous vacuole. The invasion process and the formation of the parasitophorous vacuole are mediated by characteristic organelles within the apical complex. During invasion, the parasitophorous-vacuole membrane is manipulated by the parasite and functions later in the development cycle as a molecular sieve, allowing the exchange of metabolites between parasite and host cell. Unlike the cyst-forming coccidia, there is little evidence of parasitophorous-vacuole membrane transformation in the later stages of the lifecycle of *Eimeria* species. Compared with the human pathogens *Plasmodium* and *Toxoplasma*, rather little is known about the parasitophorous vacuole and parasitophorous-vacuole membrane of animal pathogens of the genus *Eimeria*. © 1998 Australian Society for Parasitology. Published by Elsevier Science Ltd.

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1. Introduction

Parasites of the genus *Eimeria* are obligatory intracellular parasites mostly of intestinal cells, although some live in other cells and/or organs of invertebrates and vertebrates. Coccidiosis of domestic animals, cattle and chickens is due to infection with different *Eimeria* spp. and causes considerable economic losses. The animal-breeding industry spends millions of dollars each year on measures to control coccidiosis, mainly anticoccidial drugs.

The intracellular life-cycle stages of *Eimeria* parasites, including merozoites, schizonts (meronts) and gamonts, are located within the host cell in a membrane-bound parasitophorous vacuole (PV) [1]. The PV membrane (PVM) is formed during invasion of the motile stages of *Eimeria* parasites (sporozoites and merozoites). The invasion of *Eimeria* spp. is an active process and resembles closely that in other related species of Apicomplexa (*Toxoplasma, Plasmodium*). The PVM serves to protect the parasite against lysis by the host cell, but also constitutes a barrier between the host-cell metabolites and the parasite that depends on them. Since Eimerian parasites do not form cysts, modification of the PVM is usually not observed.

2. Organelles involved with invasion and parasitophorous-vacuole formation

The invasion process of *Eimeria* by the motile zoites is active, and characteristic organelles from within the apical complex (conoid, polar rings, mic-
ronemes, rhoptries and dense granules) are of functional importance. The function of the conoid and polar rings is so far unknown. Micronemes promote the attachment of parasites to the potential host cells [2]. The zoites come into contact with the epithelial cell [3, 4] and micronemes secrete their protein contents, which have been characterised [2, 5]. The known sequences of some microneme proteins [6] are very similar within the different apicomplexan species and indicate a common function. There is also evidence that, as well as the attachment function, micronemes are involved in motility since microneme knock-out mutants in Plasmodium lose the ability to move and invade host cell [7]. Rhoptries may have functions in the initial process of PV formation during invasion [8, 9] and have been shown to discharge their contents through a duct into the forming parasitophorous vacuole. In Toxoplasma at least 10 rhoptry proteins have been identified [10] and some of these proteins (ROP 2, 3, 4) are stably associated with the membrane lining the PVM. In Eimeria species, rhoptry proteins have been characterised in sporozoites of Eimeria tenella [11, 12] and merozoites of Eimeria nieschulzi [13]. Using rhoptry-specific antibodies, rhoptry proteins from E. tenella were shown to be associated with the PVM [11, 12] and in E. nieschulzi a 22-kDa rhoptry protein was shown to be exocytosed into the PV at invasion [13]. The total protein content of rhoptries of Eimeria spp. is very heterogeneous [14] and the protein contents may differ between rhoptries of sporozoites and merozoites from the same species, as indicated by rhoptry-specific antibodies [13, 14]. Dense granules are discharged after invasion in the cyst-forming Coccidia (Sarcocystis, Toxoplasma) and contribute to the modification of the PV and PVM in these species [15]. There is only little evidence that dense granules exist in Eimeria species and the function of this organelle is not yet known.

3. Transport across the parasitophorous-vacuole membrane

The PVM in Toxoplasma is permeable for charged and uncharged molecules of less than 1400 Da [17]. Microinjection experiments in host cells infected with E. nieschulzi have shown that molecules of up to 850 Da can pass the PVM, while molecules of 10000 Da are excluded from the PV [18]. Similar results have been obtained in Plasmodium. The experiments give evidence that the PVM may function as a molecular sieve. Postulated pores across the PVM probably provide nutritional channels that allow the passive transfer of molecules to the parasite.

The function of duct-like structures within infected host cells, marked by rhoptry-specific mAb [19], is not yet known. These structures resemble the postulated “parasitophorous duct” in Plasmodium [20–22], which was claimed to allow the diffusion of macromolecules from the extracellular medium into the parasitophorous vacuole. Obviously, the two models of transport into the PV are essentially incompatible: if a direct connection (“duct”) existed together with pores in the PVM, the host cell would leak low molecular weight solutes into the extracellular space.

The PVM in Toxoplasma-infected cells is fusion incompetent for lysosomes, protecting the parasite from lytic enzymes [23, 24]. No experiments have been performed yet to show fusion incompetence for the PVM in Eimeria-infected cells.

4. Modification of the parasitophorous vacuole during the life-cycle of Eimeria

In cyst-forming Coccidia, the PV is modified shortly after invasion. In Toxoplasma an intra-vacuolar network is formed with which secreted proteins of dense granules become associated [25]. In Sarcocystis, bradyzoites escape from the primary PV and a secondary PV derived from host-cell endoplasmic reticulum is formed and dense granules are exocytosed [26].

There is little evidence of transformation of the PV in Eimeria. The presence and exocytosis of dense granules have been postulated in E. tenella [16] and Eimeria papillata [27]. Electron-dense material has been reported in the PV of several Eimeria species [28–30]. Intravacuolar tubules are peculiar structures within the PV of Eimeria maxima macrogamonts [31]. In E. nieschulzi schizonts, the PVM bears “microvilli” protruding into the PV [34].
After differentiation of merozoites in schizonts, merozoites become active and leave the parasitophorous vacuole. The mechanism of merozoite release is poorly known, and may be active or passive. Parasite proteases may be involved also in *Eimeria* spp. as documented in *Plasmodium* [32, 33].

5. Conclusion

The PV is a crucial structure in the life-cycle of Coccidia, although there are a few exceptions where the PV is absent (*Theileria, Babesia*, certain stages of *Sarcocystis*). The PV is manipulated by the parasite and functions as a molecular sieve, allowing the exchange of metabolites between parasite and host cell. Compared with the human pathogens *Plasmodium* and *Toxoplasma*, rather little is known about the animal pathogens of the genus *Eimeria*. Understanding of the formation, modification and function of the PV would facilitate the development of agents interfering with the development of the parasites.

References


