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Research advances in interactions related to *Toxoplasma gondii* microneme proteins

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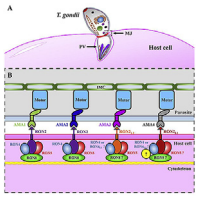
HIGHLIGHTS

- Functional and biological characteristics of *Toxoplasma gondii* microneme proteins (TgMICs) are reviewed.
- Protein-protein and protein-carbohydrate interactions related to TgMICs are reviewed.
- Interactions between TgMICs, between TgMICs and other components, between TgMICs and host components are reviewed.
- Ongoing questions and potential of exploring TgMICs as control strategies of *T. gondii* are presented.

GRAPHICAL ABSTRACT



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ABSTRACT

Toxoplasma gondii microneme proteins (TgMICs), secreted by micronemes upon contact with host cells, are reported to play important roles in multiple stages of the *T. gondii* life cycle, including parasite motility, invasion, intracellular survival, and egress from host cells. Meanwhile, during these processes, TgMICs participate in many protein-protein and protein-carbohydrate interactions, such as undergoing proteolytic maturation, binding to aldolase, engaging the host cell receptors and forming the moving junction (MJ), relying on different types of ectodomains, transmembrane (TM) domains and cytoplasmic domains (CDs). In this review, we summarize the research advances in protein-protein and protein-carbohydrate interactions related to TgMICs, and their intimate associations with corresponding biological processes during *T. gondii* infection, which will contribute to an improved understanding of the molecular pathogenesis of *T. gondii* infection, and provide a basis for developing effective control strategies against *T. gondii*.

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1. Introduction

Toxoplasmosis, caused by the obligate intracellular opportunistic pathogen *Toxoplasma gondii*, is a serious threat to human and animal health (Montoya and Liesenfeld, 2004; Elsheikha, 2008; Dubey, 2010). However, available therapies to treat toxoplasmosis are very limited, and no vaccine against *T. gondii* infection is clinically available, except for Toxovax® used in sheep (Buxton and Innes, 1995). In addition, the anti-parasitic drugs currently used have many limitations, such as emergence of drug-resistant parasites and chemical residues, and cannot effectively eliminate *T. gondii* cysts in the infected hosts (Dupouy-Camet, 2004; Vercruysse et al., 2004; Zhang et al., 2013). In these circumstances, elucidating the complex molecular mechanism of interactions between *T. gondii* and the host is urgently needed, which will provide foundation for developing new intervention strategies against *T. gondii* infection.

T. gondii infection is highly dependent on three unique apical secretory organelles, named micronemes, rhoptries, and dense granules (Morlon-Guyot et al., 2015). To date about 20 different kinds of *T. gondii* microneme proteins (TgMICs), including TgMIC1-TgMIC16, TgM2AP, TgAMA1, TgSUB1, TgSPATR, TgROM1, TgTLN4, and TgPLP1 have been identified (Garnett et al., 2009; Sheiner et al., 2010; Wang and Yin, 2015). To explore the molecular functions of TgMICs, numerous studies have been carried out with the application of different methods, such as bioinformatics analysis, gene knockout, proteomics, yeast-two-hybrid screen and co-immunoprecipitation (Co-IP) technologies, and progresses have been achieved over the last decades. By genetic manipulation, most TgMICs are proved to be critical virulence factors, and phenotypic consequences of *T. gondii* after disruption or modification of several TgMIC genes are shown in Table 1.

Also, many interactions related to TgMICs have been identified, in which their interactors can be one or more TgMICs, other components of *T. gondii* or components of host cells (Table 2). These interactions can lead to proteolysis of TgMICs, including several immature TgMICs (proTgMICs) undergoing proteolytic maturation into biologically active forms, and several TgMICs, especially the transmembrane (TM) microneme proteins being cleaved off the surface of the parasite, thus completing the active penetration process. Prior to a final cleavage, these TM microneme proteins are key players in powering parasite gliding motion, as their cytoplasmic domains (CDs) can bind to aldolase that is connected to parasite actomyosin system. TgAMA1 is able to form a ring-like structure called moving junction (MJ) together with TgRON2, TgRON4, TgRON5 and TgRON8, which facilitates firm attachment and serves as a molecular sieve. Most TgMICs contain modular structures that are homologous to adhesion domains or ligand domains from higher eukaryotic proteins, such as epidermal growth factor-like (EGF), chitin binding-like (CBL), microneme adhesive repeat (MAR), and thrombospondin type-1 repeat (TSR) domains (see Table 2). The variety of adhesion domains can enable the parasite to establish attachment with a wide range of host cell types. Also, the interactions between TgMICs and host cell receptors can lead to signaling events.

Despite the significant advances made (Bonhomme et al., 1999; Channon et al., 1999; Brossier et al., 2008; Kafsack et al., 2009; Muniz-Feliciano et al., 2013; Tomavo et al., 2013), knowledge on protein-protein and protein-carbohydrate interactions related to TgMICs, which are critical for parasite motility, attachment, invasion, signaling pathways and egress, are limited. In this review, we summarize the recent advances in the understanding of roles of these interactions in *T. gondii* infection pathogenesis. The discussion is structured to encompass the following three categories: the interactions between the microneme proteins, the interactions between microneme proteins and other components of *T. gondii*, and the interactions between microneme proteins and the components of the host cells.

2. Interactions between *T. gondii* microneme proteins

2.1. Correct targeting of the TgMIC1/MIC4/MIC6 complex relies on TgMIC1 and TgMIC6

TgMIC1/MIC4/MIC6 complex was the first to be identified in *T. gondii*, and the interaction between them was verified both *in vivo* and *in vitro* by Reiss et al. (2001). TgMIC6ΔCD, which was deleted CD and then lacked sorting signals, was retained