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Trends in Parasitology

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Spotlight

Hijacking of host mitochondria by *Toxoplasma gondii* and SARS-CoV-2

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Mitochondria regulate energy production, cell cycle, and immune signaling. Li *et al.* recently reported that *Toxoplasma gondii* induces the shedding of mitochondrial outer membrane to promote its growth. Intriguingly, the hijacking of host mitochondria has been shown to play an essential role in the pathogenesis of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Mitochondria are often referred to as powerhouses or energy factories of cells because they generate most of the energy we need. They are bound by a double-membrane system, which consists of an inner membrane and an outer membrane, with a small intermembrane space (IMS) in between. Besides their roles in energy production, fatty acid oxidation, and cell division and differentiation, recent studies have revealed that mitochondria regulate cell death and immune signaling [1]. On the one hand, mitochondria are required for major host immune responses, including reactive oxygen species (ROS) production and macrophage activation [2,3]. On the other hand, plant and animal pathogens and parasites manipulate mitochondrial metabolism, dynamics, and functions to reprogram host immunity and promote their survival [1,4]. Despite all these major advances, how pathogens and stresses trigger mitochondrial remodeling has remained elusive. Recently, Li *et al.* demonstrated that an effector from the human parasite *T. gondii* induces the formation of structures positive for the outer mitochondrial membrane (SPOTs) to promote the growth of this parasite [5].

Li *et al.* focused on *T. gondii* because this intracellular parasite tethers host mitochondria to its parasite vacuole [5]. *T. gondii* is a single-celled protozoan parasite, which infects up to one-third of the human population and most warm-blooded animals [6]. Li *et al.* found that mitochondria shed their 'skins' or SPOTs during infection by *T. gondii.* By analyzing the protein content in the SPOTs, Li *et al.* revealed that SPOTs are positive for outer mitochondrial membrane (OMM) markers, while inner mitochondrial membrane (IMM) and IMS markers are absent from SPOTs.

As an intracellular parasite, *T. gondii* lives in a membrane-bound vacuole (Figure 1A). SPOTs are produced at the mitochondria–*Toxoplasma* interface, where the OMM is tethered to the parasite vacuole membrane. Previous studies have shown that the association of *T. gondii* with host mitochondria is completely dependent on the parasite effector *T. gondii* mitochondrial association factor 1 (TgMAF1). Indeed, the authors proved that TgMAF1 is required for the formation of SPOTs [5]. To investigate how TgMAF1 induces SPOT formation, Li *et al.* examined the protein complex associated with TgMAF1 during *T. gondii* infection. It was found that TgMAF1 copurifies with the host mitochondrial import receptor TOM70. TOM70 mediates the interaction between TgMAF1 and the OMM translocase SAM50 (Figure 1A). This enables *Toxoplasma* to hijack mitochondrial outer membrane and shed SPOTs.

Both TOM70 and SAM50 are required for the *Toxoplasma*-induced SPOT formation [5]. SAM50 is the only component in the mitochondrial protein import machinery that plays a critical role in bridging OMM and IMM. By targeting SAM50, TgMAF1 induces the disassembly of the mitochondrial IMS bridging (MIB) complex, which comprises SAM50, MIC60, and MIC19, thereby promoting SPOT formation (Figure 1A). Consistent with these data, the loss of SAM50 itself in mitochondria is sufficient to induce structures that resemble SPOTs without infection.

Mimicking host factors is a common strategy that is shared by many virulence factors from a wide range of pathogens and parasites to cause diseases [7]. The biogenesis of mitochondria requires the import of many precursor proteins or preproteins. TOM70 functions as a receptor of preprotein translocase by interacting with the chaperone–preprotein complex. TgMAF1 hijacks TOM70 by mimicking a mitochondrial preprotein (Figure 1A). By promoting the formation of SPOTs, TgMAF1 not only inhibits TOM70 import function but also facilitates the degradation of mitofusion 1 (MFN1) and mitofusion 2 (MFN2), both of which mediate nutritional defense against *T. gondii* [5]. Future structural studies will help us better understand the molecular basis for mimicking a mitochondrial preprotein by TgMAF1.

Given the critical roles of TOM70 in mitochondria biogenesis and essential functions of mitochondria in host–pathogen interactions, it makes sense that other pathogens or parasites would also target TOM70. In fact, TgMAF1 from *T. gondii* is not the only virulence protein that interacts with TOM70. It was reported that Orf9b from SARS-CoV-2, which is the coronavirus that has caused the ongoing COVID-19 global pandemic, also hijacks TOM70 to suppress host defense [8]. A total of over 370 million positive cases and over 5.6 million COVID-related deaths have been recorded worldwide. This disease is causing huge economical loss and poses an unprecedented challenge to public health systems.

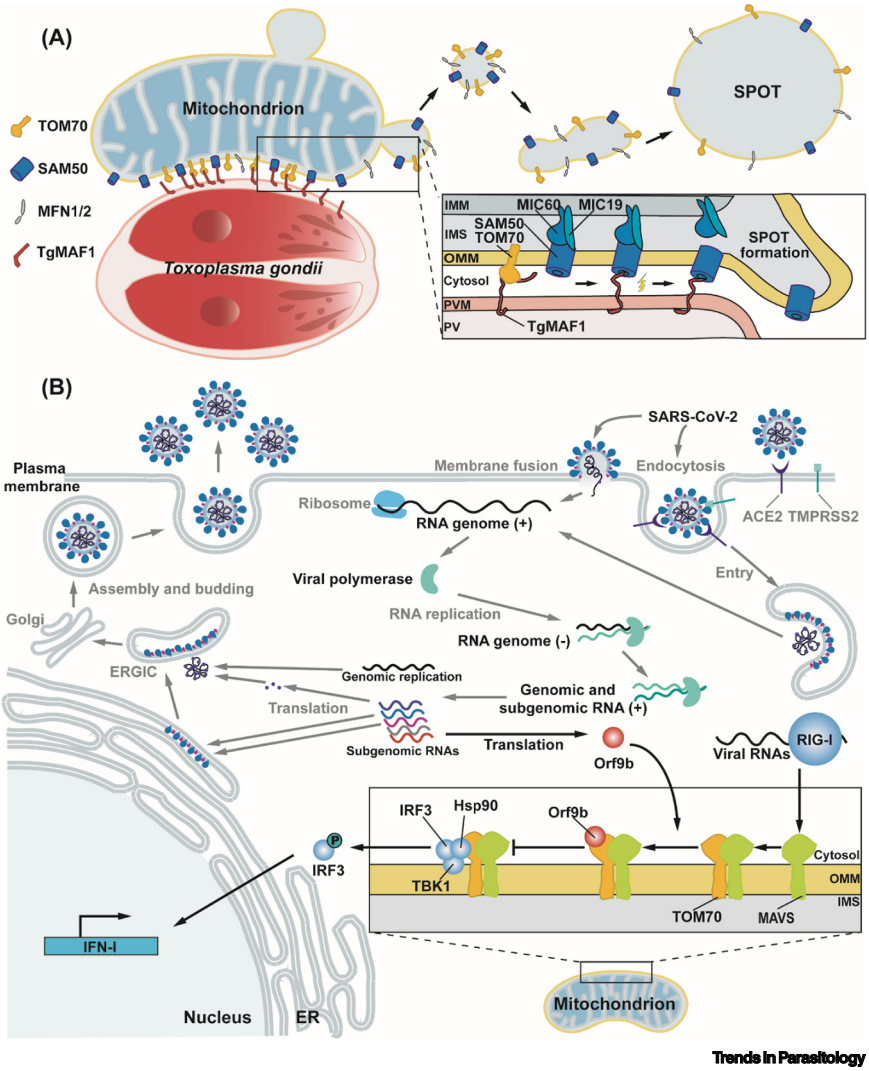

Figure 1. Schematic models of hijacking of the mitochondrial import receptor TOM70 by *Toxoplasma gondii* and SARS-CoV-2. (A) *T. gondii* effector TgMAF1 interacts with TOM70 to promote SPOT formation and facilitate MFN1/2 degradation. The secreted *T. gondii* effector TgMAF1, which interacts with TOM70, is required for the formation of SPOTs. TOM70 mediates the interaction between TgMAF1 and SAM50, thereby inducing the dissociation of the mitochondrial intermembrane space bridging (MIB) complex (SAM50, MIC60, and MIC19) and promoting SPOT formation. (B) Orf9b from SARS-CoV-2 or COVID-19 virus interacts with TOM70 and allosterically inhibits Hsp90–TOM70 interaction to suppress type I interferon (IFN-1) responses. Orf9b is encoded by an alternative open reading frame within the nucleocapsid gene of the virus RNA. Upon infection, Orf9b binds to the C-terminal domain of TOM70, which severely disrupts the interaction between EEVD motif of Hsp90 and the N-terminal domain pocket of TOM70. This may undermine the phosphorylation of IRF3 by TBK1, weakening the expression of genes required for IFN-1 responses. Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment; IMM, inner mitochondrial membrane; IMS, intermembrane space; IRF3, interferon regulatory factor 3; MAVS, mitochondrial antiviral signaling protein; MFN1/2, mitofusin 1/2; OMM, outer mitochondrial membrane; Orf9b, open reading frame 9b; PV, parasite vacuole; PVM, parasite vacuole membrane; RIG-I, retinoic acid-inducible gene 1; SAM50, sorting assembly machinery 50 kDa subunit; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2; SPOT, structure positive for the outer mitochondrial membrane; TBK1, TANK-binding kinase; TgMAF1, *T. gondii* mitochondrial association factor 1; TOM70, translocase of the outer membrane 70; TMPRSS2, transmembrane protease serine 2.

Orf9b from SARS-CoV-2 is an alternative reading frame encoding an 11-kDa protein that is localized on the membrane of mitochondria. Orf9b sabotages the association of TOM70 with Hsp90 by interacting with TOM70 (Figure 1B) [8,9]. Based on a structural study and isothermal titration calorimetry assays, Gao *et al.* demonstrated that after Orf9b occupies the TOM70 C-terminal domain pocket, the binding affinity between Hsp90 and TOM70 is reduced by approximately 29-fold [9]. Previous studies have already shown that TOM70 functions as a key adaptor protein, which plays an essential role in antiviral responses [8]. TOM70 binds to Hsp90, resulting in the recruitment of the Hsp90–TNK1–IRF3 complex to mitochondria and subsequent phosphorylation of IRF3 (Figure 1B). Consequently, IRF3 is translocated into the nucleus to activate antiviral type I interferon (IFN-1) responses. Thus, Orf9b allosterically suppresses the interaction between TOM70 and Hsp90 to inhibit the antiviral IFN-1 response. Targeting TOM70 is just one of the several strategies that SARS-CoV-2 deploys to reprogram mitochondria; several groups have demonstrated that hijacking mitochondria plays an essential role for pathogenesis of SARS-CoV-2 and disease progression of COVID-19 [10]. For example, SARS-CoV-2 infection could cause mitochondria to release mitochondrial DNA and formyl peptides, both of which induce damage-associated molecular pattern (DAMP)-triggered immunity (DTI). Elevated DTI could lead to acute lung injury, especially in patients with a compromised immune system and pre-existing conditions, such as diabetes, cardiovascular disease, and cancer, due to the poor condition of their mitochondria. Therefore, mitochondria could be a therapeutic target for treating COVID-19 patients.

Besides *T. gondii* and SARS-CoV-2, many fungal, bacterial, and other viral pathogens, such as *Magnaporthe oryzae*, *Salmonella typhimurium*, *Vibrio cholerae*, *Chlamydia trachomatis*, *Pseudomonas syringae*, and

HIV, also modulate mitochondrial functions to promote infection [1,3,4]. *T. gondii* represents the first example of a pathogen that hijacks the mitochondrial outer membrane to form SPOTs [5]. Without a doubt, future studies from different pathosystems will provide more insights on how animal and plant pathogens and parasites remodel and reprogram host mitochondria to cause diseases.

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Declaration of interests

The authors declare no competing interests.

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