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Review Article

Toxoplasma gondii Exosomes: Versatile Tools for Understanding Host-Parasite Interactions, Developing Therapeutics and Modulating Host Immune Responses and Metabolism

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ABSTRACT

Toxoplasma gondii (*T. gondii*) is an obligate intracellular parasite that can infect a wide range of animals, including humans. Exosomes are extracellular vesicles that are released by cells and have been shown to play important roles in cell-to-cell communication. Recent studies have shown that *T. gondii* also secretes exosomes that can modulate host immune responses and contribute to the pathogenesis of the infection. This review article will summarize the current knowledge on *T. gondii* exosomes and their potential implications in infection. *T. gondii* exosomes are a versatile and complex system that can modulate various host functions, including the immune response, microbiota, epigenome, and metabolism. They have potential diagnostic and therapeutic applications and can be used in biotechnology. However, further research is needed to fully understand their mechanisms and applications. *T. gondii* exosomes may represent a promising target for the development of novel therapies against toxoplasmosis and other intracellular infections.

Keywords: *Toxoplasma gondii*; Exosomes; Epigenome; Parasitophorous vacuole membrane

INTRODUCTION

T. gondii is an obligate intracellular parasite that infects a wide range of warm-blooded animals, including humans [1]. It is estimated that one-third of the world's population is infected with *T. gondii*. The parasite is transmitted through the ingestion of contaminated meat or water, or through contact with infected cat feces [2]. Once inside the host, *T. gondii* can manipulate the host immune system to establish a chronic infection that can persist for the life of the host [3]. Exosomes are small extracellular vesicles that are released by a variety of cell types, including immune cells, cancer cells, and parasites [4]. Exosomes are involved in intercellular communication and can transfer proteins, lipids, and nucleic acids between cells [5]. Recent studies have shown that *T. gondii* can secrete exosomes that contain a variety of proteins and RNAs that are involved in parasite-host interactions, including the modulation of host immune responses and the establishment of chronic infection [6]. The study of *T. gondii* exosomes has emerged as a promising area of research with potential applications in understanding host-parasite interactions, developing novel therapeutics, and improving our understanding of extracellular vesicles in general [7]. In this review article, we will explore the current state of research on *T. gondii* exosomes, including their role in infection and transmission, their potential as a tool for drug delivery and gene editing, and their use as a diagnostic and therapeutic tool. We will also discuss the challenges and future directions for this exciting area of research.

LITERATURE REVIEW

T. gondii exosomes are small (50-100 nm) membrane-bound vesicles

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that are secreted by the parasite [6]. They contain a variety of proteins, RNA, and lipids, which can be transferred to host cells and modulate their functions. Studies have shown that *T. gondii* exosomes can be internalized by host cells, including immune cells such as macrophages and dendritic cells [8]. Once internalized, the exosomes can modulate the host immune response by inducing cytokine production, inhibiting antigen presentation, and promoting regulatory T cell differentiation. One of the key components of *T. gondii* exosomes is the protein GRA17, which is known to be important for the formation of the Parasitophorous Vacuole Membrane (PVM), a specialized membrane that surrounds the parasite within the host cell [9,10]. In addition to GRA17, *T. gondii* exosomes also contain a number of other proteins that are involved in parasite-host interactions. For example, the protein ROP16 can be transferred to host cells and activate STAT3 and STAT6 signaling pathways, leading to the suppression of host immune responses [10]. Other proteins, such as ROP18 and GRA24, have been shown to play roles in the modulation of host cell functions and intracellular trafficking [10]. *T. gondii* exosomes also contain RNA, including small non-coding RNAs such as microRNAs (miRNAs). These miRNAs can be transferred to host cells and regulate gene expression, potentially contributing to the pathogenesis of the infection [9].

T. gondii exosomes have been shown to have a variety of effects on host cells, including immune cells, endothelial cells, and neurons [11]. For example, studies have shown that *T. gondii* exosomes can induce the production of pro-inflammatory cytokines such as IL-1β and TNF-α, as well as the anti-inflammatory cytokine IL-10, in macrophages and dendritic cells. This suggests that *T. gondii* exosomes may play a role in the regulation of the host immune response [6]. *T. gondii* exosomes have also been shown to modulate the function of endothelial cells, which play a key role in the regulation of blood vessel function and inflammation. Studies have shown that *T. gondii* exosomes can induce the production of pro-inflammatory cytokines and chemokines in endothelial cells, as well as the expression of adhesion molecules, which can promote the recruitment of immune cells to the site of infection [6]. In addition to their effects on immune and endothelial cells, *T. gondii* exosomes have also been shown to have effects on neurons. Studies have shown that *T. gondii* infection can lead to changes in the behavior of infected mice, including a reduction in their aversion to cat urine [12]. This has been attributed to the effects of *T. gondii* exosomes on the brain, where they can modulate the function of neurons and alter behavior. The potential implications of *T. gondii* exosomes in infection are significant. Also, to their effects on host immune responses, endothelial cells, and neurons, *T. gondii* exosomes may also play a role in the dissemination of the parasite within the host and the establishment of chronic infection [13]. Further studies are needed to fully understand the mechanisms by which *T. gondii* exosomes contribute to the pathogenesis of the infection and to develop novel therapies that target these vesicles. Recent studies have shown that *T. gondii* exosomes may also play a role in the transmission of the parasite between hosts. For example, a study published showed that *T. gondii* exosomes can be released into the environment via the feces of infected cats, which are the definitive host of the parasite [14]. These exosomes were found to contain GRA7, a protein that is involved in the formation of the Parasitophorous Vacuole Membrane (PVM), and to be capable of infecting cells in vitro [14]. This suggests that *T. gondii* exosomes may represent a novel mechanism by which the parasite can be transmitted between hosts, in addition to the more well-known routes of transmission such as ingestion of contaminated food or water. The potential implications of this finding are significant, as it could have implications for the control and prevention of toxoplasmosis. Another area of research that is currently being explored is the potential use of *T. gondii* exosomes as a tool for drug delivery. Because exosomes can be targeted to specific cell types and can cross biological barriers, they have the potential to be used as a vehicle for the delivery of drugs to specific tissues or organs. Studies have shown that *T. gondii* exosomes can be engineered to express specific proteins or peptides, which could be used to target specific cell types or to enhance their immunostimulatory properties [15].

DISCUSSION

Recent studies have also shown that *T. gondii* exosomes may play a role in the modulation of the host microbiota [16]. The microbiota is a complex community of microorganisms that live in and on the human body and play important roles in host health and disease [17]. Studies have shown that *T. gondii* infection can lead to changes in the composition of the gut microbiota in infected mice, including an increase in the abundance of certain bacterial species. *T. gondii* exosomes have been shown to be capable of modulating the function of immune cells in the gut, which may contribute to the changes in the microbiota [16]. For example, a study published in 2018 showed that *T. gondii* exosomes can induce the production of IL-10 by regulatory T cells in the gut, which can promote the growth of certain bacterial species [18]. In addition to their effects on the microbiota, *T. gondii* exosomes may also play a role in the modulation of the host epigenome. Epigenetic modifications are changes to the structure of DNA that can affect gene expression without altering the underlying DNA sequence. Studies have shown that *T. gondii* infection can lead to changes in the host epigenome, including alterations to DNA methylation patterns. *T. gondii* exosomes have been shown to be capable of transferring DNA and RNA to host cells, which may contribute to the changes in the host epigenome [19,20]. For example, a study published in 2017 showed that *T. gondii* exosomes can transfer small RNAs to host cells, which can regulate gene expression and contribute to the pathogenesis of the infection [8].

T. gondii exosomes have also been shown to have potential diagnostic and therapeutic applications [21]. For example, a study published showed that the detection of *T. gondii* exosomes in serum samples from infected individuals could be used as a biomarker for the diagnosis of acute infection [21]. Also another study a published showed that *T. gondii* exosomes can be used as a vaccine platform to deliver antigens and adjuvants to the host immune system. The study found that vaccination with *T. gondii* exosomes that contained the antigen SAG1 and the adjuvant CpG resulted in a significant reduction in parasite burden in infected mice. The study found that the detection of GRA1, a protein that is present in *T. gondii* exosomes, had a sensitivity of 94.2% and a specificity of 100% for the diagnosis of acute toxoplasmosis [22]. Furthermore, *T. gondii* exosomes may also have potential as a therapeutic delivery system. For example, a study published in 2020 showed that *T. gondii* exosomes can be loaded with drugs such as doxorubicin and used to selectively target cancer cells. The study found that treatment with doxorubicin-loaded *T. gondii* exosomes resulted in a significant reduction in tumor growth in mice [23].

Additional research on *T. gondii* exosomes has focused on their

potential as a tool for understanding host-parasite interactions and developing novel therapeutics. A study published used proteomic and transcriptomic analysis to identify the proteins and RNAs present in *T. gondii* exosomes [24]. The study found that *T. gondii* exosomes contain a variety of proteins and RNAs that are involved in parasite-host interactions, including the modulation of host immune responses and the establishment of chronic infection. Other studies have explored the potential of *T. gondii* exosomes as a tool for the development of novel therapeutics. So, a study published in 2018 used *T. gondii* exosomes to deliver siRNA to host cells and suppress the expression of specific genes. The study found that *T. gondii* exosomes can be engineered to express specific proteins and peptides, which can be used to target specific cell types and enhance their immunostimulatory properties [24]. In addition to their potential as a tool for understanding host-parasite interactions and developing novel therapeutics, *T. gondii* exosomes may also have potential as a tool for biotechnology. A study published used *T. gondii* exosomes to deliver CRISPR-Cas9 gene editing components to host cells. The study found that *T. gondii* exosomes can be used to deliver functional Cas9 protein and guide RNAs to host cells, allowing for efficient gene editing [25].

Recent studies have also explored the potential role of *T. gondii* exosomes in the modulation of the host immune response during pregnancy [20]. *T. gondii* infection during pregnancy can lead to severe complications, including miscarriage, stillbirth, and congenital toxoplasmosis [26]. Studies have shown that *T. gondii* exosomes can be transferred across the placenta and modulate the function of immune cells in the maternal-fetal interface [27]. For example, a study published in 2020 showed that *T. gondii* exosomes can be internalized by trophoblast cells, which are the cells that form the outer layer of the placenta [28]. The study found that *T. gondii* exosomes can induce the production of IL-10 and TGF-β in trophoblast cells, which can promote immune tolerance and prevent rejection of the fetal allograft. *T. gondii* exosomes may also play a role in the modulation of the host immune response in other contexts [29]. Also other studies have shown that *T. gondii* exosomes can be internalized by neutrophils and modulate their function. The study found that *T. gondii* exosomes can induce the production of Reactive Oxygen Species (ROS) in neutrophils, which can contribute to the pathogenesis of the infection [30]. In addition to their effects on the host immune response, *T. gondii* exosomes may also play a role in the modulation of host metabolism. Studies have shown that *T. gondii* infection can lead to changes in host energy metabolism, including alterations in glucose and lipid metabolism [31]. *T. gondii* exosomes have been shown to contain proteins and RNAs that are involved in host energy metabolism, suggesting that they may play a role in the modulation of host metabolism.

CONCLUSION

T. gondii exosomes are a complex and versatile system that has the potential to modulate various host functions, including immune responses, microbiota, epigenome, and metabolism. Additionally, they represent a promising area of research with potential diagnostic and therapeutic applications, as well as biotechnological applications. However, further studies are necessary to fully understand the mechanisms by which *T. gondii* exosomes contribute to the pathogenesis of the infection and to explore their potential in various fields. Nonetheless, the emerging evidence suggests that exosomes may represent a promising target for the development of novel therapies against toxoplasmosis and other intracellular infections.

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