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Modulation of ERK and AKT pathways as the potential therapeutic targets for *Toxoplasma gondii* infection

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Abstract

Toxoplasmosis is a zoonotic disease caused by *Toxoplasma gondii*, which can infect humans through oocysts or undercooked meat. It can cause varying symptoms, including congenital toxoplasmosis. Early detection and treatment are beneficial, and antimicrobial treatment can prevent or resolve symptoms. The disease has a complex life cycle, with felids being the definitive host. Understanding the signaling pathways is crucial for effective therapeutic strategies. Toxoplasma invasion is regulated by the microtubule cytoskeleton, affecting macrophages and innate immunity cells. Calcium binding proteins and focal adhesion kinase-2 have been identified as key regulators of calcium signaling in Toxoplasma. Calcium signaling is crucial for parasite biology and drug development. The ERK pathway plays a significant role in host-parasite interactions and immune responses. This pathway plays a critical role in the spread of Toxoplasma by manipulating host cell migration. Toxoplasma infection can activate the ERK signaling pathway, leading to the inhibition of apoptosis in host cells. This inhibition of apoptosis is believed to have a positive effect on the survival and replication of the parasite in the host. The Akt signaling pathway, also known as the PI3K/Akt pathway, is crucial in parasitic diseases, modulating host immune responses and parasite survival. Host AKT activation is important for *T. gondii* proliferation which is related to reduction of ROS in host cells. More investigation is required to fully understand how these signals contribute to the pathophysiology of Toxoplasma infection and to identify possible therapeutic targets for the management of parasitic illnesses.

Introduction

Toxoplasma gondii is the parasite that causes the zoonotic disease toxoplasmosis. Many warm-blooded animals, including humans, are susceptible to infections (1). Consumption of undercooked meat containing tissue cysts or ingestion of oocysts excreted in the feces of infected cats is the main routes of transmission of the disease to humans (2). In humans, toxoplasmosis can have different manifestations depending on the individual immune response (3). Congenital toxoplasmosis is of particular concern as it can lead to serious

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complications in newborns (4). Early detection of infection during pregnancy and timely initiation of treatment have been associated with favorable outcomes (5). Studies have shown that active infections can be treated, and antimicrobial treatment of *T. gondii* in animal models has resulted in the prevention or elimination of disease symptoms (6). Toxoplasmosis can also affect the central nervous system (CNS). The manifestations of CNS toxoplasmosis can vary depending on the immune response of the individual (7). In immunocompromised individuals, such as HIV/AIDS patients, toxoplasmosis can cause severe neurological symptoms, including encephalitis and brain abscesses (8).

T. gondii has a complex life cycle that includes both sexual and asexual phases. The feline family, particularly cats, is the definitive host of *T. gondii*, where the sexual cycle occurs (9). Humans and other warm-blooded animals are intermediate hosts for the asexual cycle. The asexual cycle begins when an intermediate host ingests oocysts excreted in the feces of the infected cats or by consuming uncooked meat containing tissue cysts. Once inside the host, the oocysts release sporozoites that invade the host cells and differentiate into tachyzoites. Tachyzoites proliferate rapidly in host cells and cause acute infection (10). During acute infection, tachyzoites can spread throughout the host's body and invade various tissues and organs (11). They can also cross the placenta and cause congenital infections in pregnant women (12). Under certain conditions, such as immune pressure or stress, tachyzoites can differentiate into bradyzoites and form tissue cysts. These cysts develop mainly in the brain, muscles, and other tissues and lead to chronic infections (13). The cysts can remain in the host for life. When an intermediate host is eaten by a cat, the cysts are digested, releasing bradyzoites that can reproduce sexually in the cat's intestines. This leads to the production of oocysts, which are excreted in the feces and complete the sexual cycle (14). The life cycle of *T. gondii* involves a delicate balance between the parasite and the host's immune response. The parasite uses various mechanisms to escape the host's immune system and cause a chronic infection (15).

T. gondii modulates signaling pathways to invade host cells

The obligate intracellular parasite *T. gondii* infects a significant proportion of the world's population (16). Understanding the signaling pathways involved in the interaction between *Toxoplasma* and its host is crucial for elucidating the mechanisms of infection and developing effective therapeutic strategies. *T. gondii* modulates host cell responses and manipulates host cell physiology to provide survival advantages (17). Invasion of host cells by *Toxoplasma* involves a complex process consisting of parasite contact, attachment, motility, and penetration (18). Several studies have focused on the regulation of apoptosis pathways and impairment of host cell immunity, signaling, and invasion mechanisms by Toxoplasma (19).

One study found that induction of dendritic cell (DC) migration following Toxoplasma infection increased parasite dissemination (20). The migration of Toxoplasma-infected DCs depended on live intracellular parasites and the G Protein Coupled Receptor (GPCR) signaling pathway, but not on specific chemokine receptors or Toll/interleukin-1 receptor signaling (20). In vivo, Toxoplasma-infected DCs reached the mesenteric lymph nodes and spleen in similar or higher numbers than lipopolysaccharide-stimulated DCs (21). Toxoplasma invasion is temporally regulated by the host microtubule cytoskeleton (22). The initial interaction between Toxoplasma and host cells is mediated by surface antigens of the parasite, resulting in a loose, low-affinity contact (22). Activation of the invasion motor and release of apical organelles in Toxoplasma depend on calcium-dependent signal transduction pathways (23). Toxoplasma infection also affects host cell signaling, particularly in macrophages and other cells of innate immunity (24). The parasite suppresses pro-inflammatory cytokine responses in

macrophages, leading to dysregulation of host cell signaling (24). Furthermore, the absence of profilin, an actin-binding molecule, in Toxoplasma impairs parasite motility and host cell invasion (25). Invasion of host cells by Toxoplasma is accompanied by changes in the parasite's gene expression, reflecting a switch from proteins involved in invasion and motility to proteins involved in metabolism and DNA replication (26). This switch in gene expression is related to the establishment of the intracellular environment and the unique relationship between the G1 phase and invasion (27).

An important signaling pathway associated with Toxoplasma infection is the calcium signaling pathway. Calcium signaling plays a crucial role in various processes during the lytic cycle of Toxoplasma, including invasion, egress, and replication of the parasite (28). Calcium binding proteins and focal adhesion kinase-2 have been identified as key regulators of calcium signaling in Toxoplasma (28). The discovery of new players in calcium signaling not only improves our understanding of the biology of these parasites but also provides potential targets for the development of drugs, vaccines, and diagnostic tools (28).

ERK and Akt signaling pathways targeted by *T. gondii*

The extracellular signal-regulated kinase (ERK) signaling pathway, also called as the mitogen-activated protein kinase (MAPK/ERK) pathway (Figure 1), is a highly conserved intracellular signaling pathway involved in cell proliferation, differentiation and survival. It is activated by numerous extracellular stimuli, including growth factors, cytokines, and environmental stressors. Upon stimulation, ERK phosphorylates and activates downstream targets, including transcription factors, leading to the regulation of gene expression (29). In the context of parasitic diseases, the ERK signaling pathway has been linked to host-parasite interactions and the modulation of immune responses (30). For example, in malaria, *Plasmodium falciparum* infection has been shown to activate the ERK signaling pathway in host immune cells such as monocytes and macrophages. This activation contributes to the production of pro-inflammatory cytokines and the regulation of the immune response against the parasite (31). Similarly, the ERK signaling pathway was found to be involved in modulating the host immune response during Leishmania infection. Studies have shown that Leishmania parasites can activate the ERK pathway in host macrophages, leading to the production of anti-inflammatory cytokines and suppression of host immune defenses (32). Besides its function in immune regulation, the ERK signaling pathway may also be involved in intracellular survival and replication of parasites. For example, during *T. gondii* infection, activation of ERK signaling was associated with inhibition of apoptosis in host cells, promoting survival and replication of the parasite (33). Overall, the ERK signaling pathway plays an important role in parasitic diseases by modulating the host immune response, promoting parasite survival, and potentially influencing disease progression.

A study by Lambert et al. (2006) focused on the induction of dendritic cell (DC) migration during *T. gondii* infection and its impact on parasite dissemination. The transmigration of infected DC across endothelial cell monolayers was made possible by the active invasion of DC by Toxoplasma, which the authors found to induce a state of hypermotility. This migration was found to be dependent on ERK signaling, as inhibition of ERK activation significantly reduced the migration of infected DC (20). These results suggest that ERK signaling plays a critical role in the spread of Toxoplasma by manipulating host cell migration. Another study by Mammari et al. (2019) provided an overview of the apoptotic pathways modulated by *T. gondii*. The authors reported that Toxoplasma infection can activate the ERK signaling pathway, leading to the inhibition of apoptosis in host cells. This inhibition of apoptosis is believed to have a

positive effect on the survival and replication of the parasite in the host. The study also highlighted the involvement of other signaling pathways such as Phosphoinositide 3-kinases (PI3Ks), Akt (protein kinase B) (PI3K/AKT) and c-Jun N-terminal kinase (JNK) in the modulation of apoptosis by Toxoplasma (19). In a previous study, the intracellular connections of the PI3K/AKT and MAPK signaling pathways in the regulation of Toxoplasma-induced interleukin (IL)-23 and IL-12 production in human THP-1 cells are discussed. This study highlights the involvement of TLR2 and TLR4 in cytokine production and the role of PI3K and MAPK signaling pathways in modulating IL-23 and IL-12 production (34).

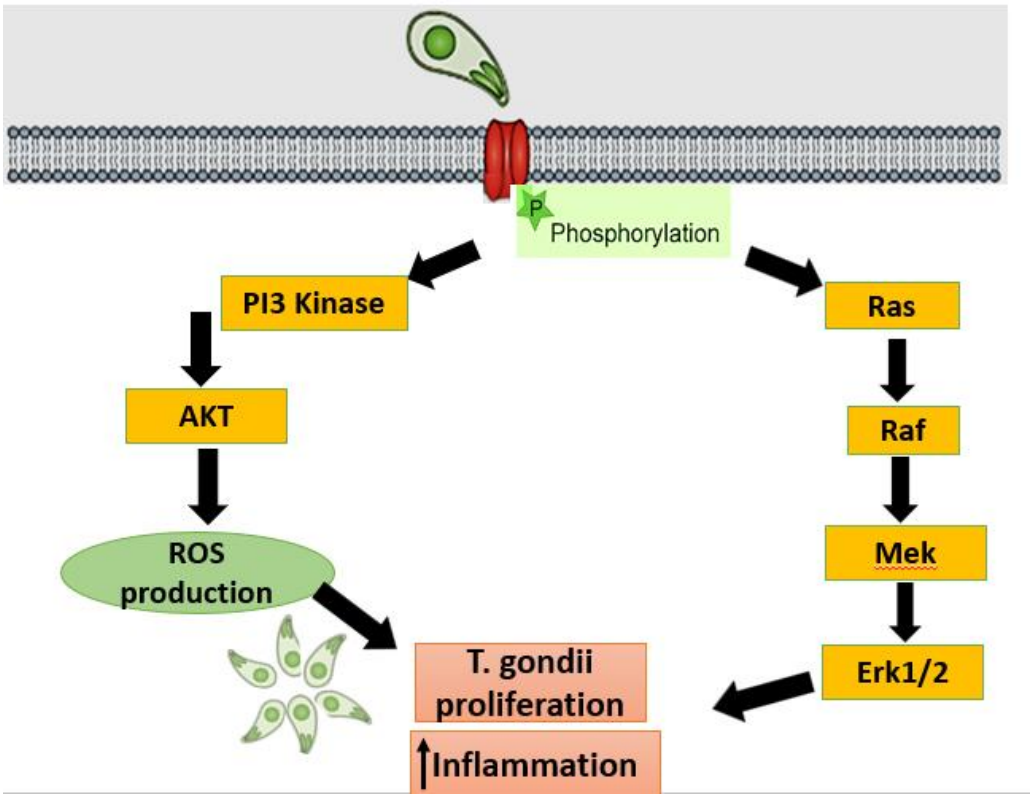

Fig. 1. ERK and Akt signaling pathways targeted by *T. gondii*

The Akt signaling pathway, also called the PI3K/Akt pathway, is a critical intracellular signaling pathway involved in several cellular processes, including cell survival, cell proliferation, growth and metabolism. This signaling pathway has been extensively studied in the context of parasitic diseases and demonstrated its importance in host-parasite interactions and disease pathogenesis (35). In the context of parasitic diseases, the Akt signaling pathway is involved in modulating the host immune response and parasite survival. For example, in malaria, *P. falciparum* infection has been shown to activate the Akt pathway in the host's immune cells, leading to the production of pro-inflammatory cytokines and the regulation of immune responses against the parasite (36). In Leishmania infection, the Akt signaling pathway was found to play a role in the survival and replication of the parasite in host cells. Studies have shown that Leishmania parasites can activate Akt signaling in the infected macrophages, promote cell survival, and inhibit apoptosis. This activation of

Akt contributes to the establishment and persistence of the infection (37). In the context of Toxoplasma infection, *T. gondii* activates the AKT pathway in a dose-dependent manner through toll-like receptors (TLR) 2 and TLR4 (19). The AKT pathway's activation may contribute to the modulation of apoptosis and the persistence of Toxoplasma in host cells. Apart from its role in apoptosis regulation, the AKT pathway has also been implicated in other cellular processes relevant to Toxoplasma infection. For instance, long-term depression mediated by metabotropic glutamate receptors in the mouse hippocampus requires activation of PI3-kinase and AKT (38). This suggests that the AKT pathway may play a role in synaptic plasticity and neuronal function, which may be relevant to the neurological manifestations of Toxoplasma infection. A study by Yu et al. (2015) provides insights into the role of Akt isoforms in vascular diseases. While this reference does not specifically focus on parasitic diseases, it highlights the importance of Akt isoforms in various cellular processes relevant to parasitic infections, such as cell movement, proliferation, and signal transduction. The study highlights that the three Akt isoforms (Akt1, Akt2, and Akt3) have different tissue expression profiles and can have different functions in different cell types (39). A study by Karanovic et al. (2019) examined the association between PI3K and Toxoplasma infection in patients with activated PI3-kinase δ syndrome type 2 (APDS2). The authors reported that *T. gondii* can evade host defense by activating the PI3K/AKT signaling pathway, which decreases intracellular reactive oxygen species (ROS) through NOX4 suppression. This activation of the PI3K/AKT pathway leads to phosphorylation and inactivation of the transcription factor FOXO1, thereby preventing the transcription of p22 phox, a component of the NADPH oxidase complex involved in ROS production (40). These studies suggest that PI3K plays a role in Toxoplasma infections by modulating host immune responses. Stimulation of the PI3K/AKT signaling pathway by *T. gondii* could help the parasite evade host defense mechanisms by reducing ROS production. Furthermore, PI3K appears to be involved in the regulation of cytokine production during Toxoplasma infection, with inhibition of PI3K leading to a reduction in IL-23 production.

Conclusion

The intracellular parasite *Toxoplasma gondii* induces host AKT activation to prevent autophagy-mediated clearance. Cellular MAP Kinases (ERK. P38, JNKs) are also activated during the parasite invasion. In summary, ERK and PI3K/AKT signaling play an important role in Toxoplasma infections by influencing host immune responses, facilitating the spread of the parasite and also contributing to the inhibition of apoptosis in host cells, thereby improving survival and promotes parasite replication and cytokine production. More investigation is required to fully understand the ways in which these signals contribute to the pathophysiology of Toxoplasma infection and to identify possible therapeutic targets for the management of parasitic illnesses.

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Ethical approval

Not applicable.

Conflict of interest

The authors declared no conflict of interest.

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