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Immune Evasion Mechanisms of Trichinella Spiralis Infection in Humans

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Abstract. Trichinosis is a major zoonotic parasitic disease caused by Trichinella spiralis, distinguished by a highly specialized life cycle. Adult worms transiently colonize the intestine, while newborn larvae invade skeletal muscle cells via the bloodstream, reprogramming them into nurse cells encased within a collagenous capsule, thereby enabling long-term persistence in immunocompetent hosts. Despite the host's strong innate and adaptive immune responses, muscle larvae can persist for months to decades due to a multi-stage, multi-target immune evasion mechanism. This review systematically summarizes the principal mechanisms by which T. spiralis escapes host immune attack during the migratory, settlement, and long-term coexistence phases. Studies show that during invasion, larvae secrete Plancitoxin-1. This nuclease specifically degrades the DNA backbone of neutrophil extracellular traps (NETs), freeing the parasite from NET entanglement and killing it, thereby facilitating muscle invasion. During settlement, parasite-derived calreticulin (TsCRT) binds complement C1q with high affinity, competitively blocking the classical activation pathway. This cooperates with the physical barrier of the dense collagenous capsule surrounding the nurse cell to establish a local immune-privileged niche. In the long-term coexistence phase, T. spiralis secretes a macrophage migration inhibitory factor homolog (TsMIF) that mimics CD74 receptor engagement, shifting macrophages from a pro-inflammatory killing state to an anti-inflammatory tolerant state. Concurrently, parasite-released extracellular vesicles penetrate the capsular barrier, delivering miRNAs and other bioactive molecules to remotely suppress Th1/Th17 responses and expand Th2/Treg populations, achieving systemic immunosuppression. These coordinated mechanisms illustrate an evolutionary progression from passive avoidance to active manipulation of host immunity.

Keywords: Trichinella spiralis, immune evasion, Plancitoxin-1, macrophage migration inhibitory factor (MIF), extracellular vesicles

1. Introduction

Trichinella spiralis is a significant zoonotic parasite worldwide, and trichinellosis continues to pose a substantial public health threat [1]. The choice of T. spiralis as a model for dissecting immune evasion is based on its unique pathogenic features. It exhibits a typical "same-host obligate parasitism" life cycle: the adult worm resides transiently in the small intestinal epithelium. At the

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same time, newborn larvae travel via the bloodstream to invade striated muscle cells for long-term residence. It is the sole identified multicellular nematode that specifically targets and inhabits host skeletal muscle cells intracellularly. Remarkably, the invading larvae do not kill the host cell; instead, through a battery of secreted effectors, they transform terminally differentiated myofibers into a structurally and metabolically remodeled nurse cell around which a composite parasitic capsule forms. This intricate remodeling process secures a relatively immune-privileged niche within an immunocompetent host, enabling the parasite to survive for months to decades. The clinical manifestations of trichinellosis closely parallel the parasite's developmental stages. The intestinal phase presents with non-specific gastrointestinal discomfort, whereas the larval migration and muscular phases cause systemic damage and classic symptoms—persistent fever, edema, marked eosinophilia, and severe myalgia. In severe cases, involvement of the myocardium and central nervous system can lead to fatal myocarditis or meningoencephalitis. Although the host rapidly mounts adaptive immunity, including a Th2-type inflammatory response and high-titer specific antibodies, muscle larvae not only survive long-term but also establish persistent infection upon repeated exposure, strongly indicating that T. spiralis has evolved a sophisticated and efficient immune-evasion toolkit. Elucidating these mechanisms will not only reveal the molecular basis of prolonged host–parasite coevolution but also provide a theoretical foundation for designing novel antiparasitic vaccines and immunotherapeutic targets [2, 3]. Here, we systematically review the major modes and molecular mechanisms by which T. spiralis evades host innate and adaptive immunity and constructs a local immune-privileged microenvironment during human infection.

2. Interaction between T. spiralis and the host immune system

Host recognition of T. spiralis is a dynamic process spanning the entire course of infection—from intestinal invasion and hematogenous larval migration to ultimate muscle residence. Innate and adaptive immunity, utilising separate receptors and mechanisms, systematically detect and enhance "non-self" signals, forming an accurate and ongoing monitoring network.

The innate immune system serves as the first line of defense, recognizing both the molecular signatures of the parasite and the tissue damage it causes. Intestinal macrophages and dendritic cells express Toll-like receptors (TLRs), particularly TLR2 and TLR4, which directly recognize components such as proteases and heat shock proteins in T. spiralis excretory-secretory (ES) products [4]. Through MyD88-dependent signaling, these receptors trigger the secretion of pro-inflammatory cytokines, rapidly recruiting neutrophils and inflammatory monocytes to the site of infection. C-type lectin receptors mediate more refined recognition: mannose receptors and DC-SIGN on dendritic cells precisely capture unique glycosylation modifications on the worm surface and ES antigens, especially phosphorylcholine-rich glycoproteins. This recognition not only conveys a "pathogen invasion" signal but also decisively shapes the subsequent maturation pathway of dendritic cells, laying a critical foundation for the initiation of adaptive immunity. Simultaneously, the physical harm inflicted by adult worms infiltrating the intestinal epithelium serves as a significant risk indicator. Injured epithelial cells release IL-25, IL-33, and TSLP, which bypass antigen-specific recognition to directly activate tissue-resident group 2 innate lymphoid cells (ILC2s). Within a very short time after infection, ILC2s produce large amounts of IL-5 and IL-13, creating an initial type 2 inflammatory microenvironment that is indispensable for the subsequent polarization of a dominant Th2 response. As newborn larvae exit the intestine and enter the circulation, antigens shed from the worm surface can also activate the complement system via the alternative pathway, generating the anaphylatoxins C3a and C5a. These molecules directly chemoattract eosinophils and trigger mast cell degranulation, amplifying local inflammation into an

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acute systemic reaction with vasoactive amine release, which forms an important basis for the systemic hypersensitivity and inflammation typical of the larval migratory phase.

Adaptive immune recognition is built upon the inflammatory landscape shaped by innate immunity and is characterized by high antigen specificity and memory potential. Dendritic cells carrying intact T. spiralis antigens migrate from infected tissues to lymph nodes and spleen, where they present processed worm peptides via MHC-II molecules to naïve $CD4^+$ T cells. At this stage, the early microenvironment already provides low concentrations of IL-4, supplied by mast cells and basophils. Under this cytokine bias, $CD4^+$ T cells recognize T [5]. spiralis epitopes preferentially differentiate into Th2 effector cells, producing a signature cytokine profile dominated by IL-4, IL-5, and IL-13. This dominant Th2 polarization is the most prominent immunological hallmark of the host anti-*Trichinella* response [6]. B cells recognize T. spiralis through surface membrane-bound immunoglobulins that can directly bind intact worm antigens or ES products. Upon internalisation and processing of immunodominant epitopes, they transmit MHC-II–peptide complexes to follicular helper T cells in exchange for critical helper signals. With T cell help, B cells undergo proliferation, class switching, and maturation, ultimately differentiating into plasma cells that secrete high titers of specific antibodies, predominantly IgG1 and IgE. Notably, specific IgG1 efficiently opsonizes migrating newborn larvae and mediates antibody-dependent cellular cytotoxicity (ADCC) via Fcγ receptors on macrophages and eosinophils, thereby directly killing parasites. This sequential cascade —from innate recognition and dendritic cell presentation to Th2 polarization and antibody effector functions—constitutes the host's immune blueprint for clearing T. spiralis. Nevertheless, it is specifically through this stringent acknowledgement and effector pressure that muscle-stage larvae can endure over extended periods and establish chronic infection, highlighting the complexity of T. spiralis immune evasion mechanisms, which will be the focal point of the subsequent detailed analysis.

3. Immune evasion mechanisms of T. spiralis

3.1. Invasion phase

During the migratory phase, host neutrophils initiate a specialized defense program termed NETosis, releasing neutrophil extracellular traps (NETs)—web-like structures composed of DNA fibers studded with antimicrobial proteins [7]. These NETs physically ensnare the larvae and, via their associated bactericidal proteins, impede larval dispersal and viability. T. spiralis counteracts this by secreting Plancitoxin-1, a protein that selectively identifies and destroys the DNA backbone of NETs [8]. Once the DNA scaffold is broken, the entire meshwork collapses, enabling the larvae to escape entrapment and killing and to continue their migration toward muscle tissue. This NET-degrading escape mechanism is critical for the parasite's survival and successful colonization of the host. Given that planctoxin-1 plays an indispensable role in this immune evasion step, researchers have proposed it as a highly promising vaccine candidate. Inducing a potent immune response against Plancitoxin-1 via pre-emptive vaccination could block this key escape route, thereby opening a completely novel strategy for trichinellosis prevention and control.

3.2. Settlement phase

During the settlement phase, complement-mediated attack represents another major immune barrier that T. spiralis larvae must overcome, and the parasite-derived calreticulin (TsCRT) plays a key role in this process. The classical complement pathway is initiated when C1q binds to the Fc regions of

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IgG or IgM within immune complexes, which subsequently triggers the activation of C4 and C3, culminating in the formation of the membrane attack complex and the generation of opsonizing and pro-inflammatory cleavage fragments [9]. However, T. spiralis cleverly intervenes at this activation step by secreting TsCRT. TsCRT binds to host C1q with high affinity, and its binding site overlaps with the globular head region of C1q that recognizes immune complexes, thereby competitively preventing C1q from engaging surface-bound specific IgG antibodies. Once C1q is sequestered by TsCRT, downstream deposition of C4 and C3 is markedly reduced, effectively inhibiting complement-mediated opsonophagocytosis and downstream inflammation. The parasite is thereby shielded from identification and elimination by complement receptors on phagocytes. This inhibitory effect does not act in isolation but cooperates with other immunomodulatory mechanisms of the settlement stage. On the one hand, the collagenous capsule physically blocks the infiltration of host effector molecules. On the other hand, TsCRT actively suppresses complement-mediated attack at the molecular level. Together, these coordinated actions ensure the immune-privileged status of the nurse cell microenvironment, enabling muscle larvae to survive for months to years.

3.3. Long-term coexistence phase

During the long-term coexistence phase, muscle larvae hijack host immune signaling by secreting a macrophage migration inhibitory factor (MIF) homolog, TsMIF [10]. Host MIF typically binds to the CD74 receptor on the surface of monocytes/macrophages, activating the ERK/MAPK pathway to promote macrophage recruitment, adhesion, and the release of pro-inflammatory cytokines such as TNF-α, thereby acting as a key driver of inflammation. TsMIF, which shares high structural homology with host MIF, also binds to CD74, but its engagement results in antagonistic activity: it fails to trigger downstream pro-inflammatory signaling efficiently, instead inhibiting macrophage migration, reducing the expression of pro-inflammatory factors, and upregulating anti-inflammatory mediators such as IL-10 [11]. Through this molecular mimicry, T. spiralis converts a host signal intended to orchestrate an immune attack into a command that appeases the immune response, diverting local macrophages from a pro-inflammatory, microbicidal state to an anti-inflammatory, tolerant state. This mechanism synergizes with the complement silencing by TsCRT and the NET degradation by Plancitoxin-1, constructing a multi-layered immune-privileged microenvironment—from molecular recognition to cellular effectors—that ensures the long-term survival of larvae in muscle tissue. The TsMIF–CD74 axis reveals a sophisticated evolutionary strategy by which parasites reshape immune responses through mimicry of endogenous ligands, and it also provides a theoretical basis for designing blocking vaccines targeting TsMIF to restore macrophage bactericidal function.

3.4. Physical sequestration

The "physical sequestration" phase of T. spiralis is epitomized by a unique protective structure—the nurse cell-capsule complex. After newborn larvae invade host skeletal muscle cells, they profoundly reprogram the myocytes, converting them into nurse cells. The larvae then induce the deposition of copious collagen fibers around the complex, forming a thick, dense collagenous capsule. This capsule mechanically separates the parasite from surrounding normal tissue, forming a physical barrier that effectively blocks direct contact and immune effector cell attack, such as phagocytes and cytotoxic T cells, thereby creating a local "immune-privileged" site. Active angiogenesis around the capsule supplies nutrients and oxygen to the larva. Yet, the molecular sieve properties of the capsule still restrict the free entry of large molecules, such as antibodies and complement components.

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However, physical isolation alone is insufficient against systemic immune surveillance, and the capsule cannot completely seal off molecular exchange. This is where parasite-secreted extracellular vesicles (EVs) play a crucial role [12]. These EVs can penetrate the capsular barrier, enter the circulation, and deliver bioactive molecules—including miRNAs and proteins—to distant host immune cells. Thus, while the local physical barrier provides protection, EVs actively and remotely suppress pro-inflammatory Th1/Th17 responses and expand anti-inflammatory Th2/Treg populations, establishing a systemic immunosuppressive microenvironment [13]. Physical blockade and remote EV-mediated immunoregulation form an exquisite partnership. This synergy enables T. spiralis to parasitize muscle for years and clearly demonstrates a strategic escalation from "passive avoidance" to "active manipulation" of host immunity.

4. Discussion

Through a multi-stage, multi-target immune evasion strategy, T. spiralis converts the host's rigorous immune surveillance into a tolerant microenvironment conducive to long-term parasitism. During migration, Plancitoxin-1 degrades the DNA backbone of NETs, freeing larvae from innate immune entrapment. In the settlement phase, TsCRT competitively binds C1q to block the classical complement pathway and, in concert with the physical barrier of the nurse cell-collagen capsule, builds a local immune-privileged niche. During long-term coexistence, TsMIF, via molecular mimicry, hijacks the CD74 receptor to divert macrophages from a pro-inflammatory killing state to an anti-inflammatory tolerant state. At the same time, extracellular vesicles penetrate the capsule to deliver miRNAs and other effectors, systemically inhibiting Th1/Th17 responses and expanding Th2/Treg populations. These concerted mechanisms clearly depict an evolutionary upgrade from "passive avoidance" to "active manipulation" of host immunity, and they provide a clear theoretical foundation for the design of vaccines and immunotherapies targeting Plancitoxin-1, TsCRT, TsMIF, and other critical effectors.

5. Conclusion

However, significant gaps remain in our mechanistic understanding. Whether T. spiralis actively downregulates MHC-I/II or hijacks immune checkpoints such as PD-L1/CTLA-4 to block adaptive recognition is barely explored [14]. The logic by which EV cargos (proteins, mRNAs, miRNAs) coordinately modulate host pathways, together with the question of whether EV surface molecules possess "addressin" signatures that direct immune cell targeting, remains unelucidated [15]. The spatiotemporal dynamics of the nurse cell microenvironment—from myocyte reprogramming and collagen capsule formation to immune cell polarization—and the sequential program of first suppressing attack, then inducing tolerance, are unmapped, and it is unconfirmed whether vesicular miRNAs impose long-lasting epigenetic imprints that sustain tolerance for years. Future research should leverage singlecell and spatial multiomics to construct highresolution atlases and resolve molecular hijacking in situ, employ in vivo genomewide CRISPR screens or secretory protein display libraries to identify host dependency factors and novel immunomodulatory ligands, adopt microfluidic organonchip platforms to simulate larval migration and capsule formation for realtime observation of EV trafficking and immunomodulation, and focus on EVderived miRNAs using transcriptomics, ChIPseq, and methylation sequencing to systematically validate their target networks and assess whether epigenetic reprogramming occurs in host immune cells. Integrating these technologies promises to propel the study of T. spiralis immune evasion from singlemolecule descriptions toward a systematic, dynamic, and multidimensional dissection.

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