Review

Excretory-Secretory Products and Surface Proteins in *Toxocara* spp.: Unlocking the Mechanisms of Immune Evasion and Persistence

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Abstract | *Toxocara* spp., particularly *Toxocara canis* and *T. cati*, are parasitic nematodes which cause toxocariasis, a zoonotic disease with major public health importance. The persistence of these parasites within host tissues is largely attributed to their sophisticated immune evasion strategies. A key factor is their secretion of excretory-secretory products (TESPs), which are composed of a variety of biologically active molecules including mucins, C-type lectins, proteases, and antioxidant enzymes. These components modulate both innate and adaptive immune responses by dampening inflammatory signaling and shifting the immune response toward a Th2-dominated and regulatory T-cell (Treg) profile. Tc-MUC-1, a non-glycosylated mucin, can interact with key macrophage proteins such as cofilin-1 and FABP5, impairing phagocytosis and inflammatory gene expression. Furthermore, surface-associated antioxidant enzymes like Cu-Zn superoxide dismutase and glutathione S-transferase protect the larvae from oxidative damage by neutralizing reactive oxygen species. Proteases such as cathepsin L facilitate antigen processing and presentation, which are essential for initiating type 2 immunity. Complement evasion is also evident through the expression of paramyosin, preventing membrane attack complex (MAC) formation. Additionally, several metabolites within TESPs including lactic acid, glucosamine, and medium- and long-chain fatty acids like oleic acid and linoleic acid exhibit anti-inflammatory and wound-healing properties, further supporting parasite persistence. Collectively, these immune-modulatory strategies not only ensure the survival of Toxocara larvae within host tissues but also contribute to the chronic and often subclinical nature of the infection. Understanding these mechanisms offers potential for novel therapeutic and diagnostic advancements.

Keywords | Excretory-secretory products, Immune evasion, Immune modulation, Parasite-host interaction, *Toxocara* spp.

Received | October 31, 2025; **Accepted** | November 24, 2025; **Published** | January 24, 2026
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Citation | Kurnia V, Dewi MA, Purwani MR, Umar BN, Widodo A, Yustinasari LR (2026). Excretory-secretory products and surface proteins in *Toxocara* spp.: Unlocking the mechanisms of immune evasion and persistence. Adv. Anim. Vet. Sci., 14(2):269-275.
DOI | https://dx.doi.org/10.17582/journal.aavs/2026/14.2.269.275
ISSN (Online) | 2307-8316

INTRODUCTION

Toxocara spp., particularly *Toxocara canis* and *Toxocara cati*, are zoonotic nematodes that are widely recognized as the causative agents of toxocariasis in both humans and animals (Chen *et al*., 2018). Transmission typically occurs via ingestion of embryonated eggs from contaminated environments such as soil or food (Otero *et al*., 2018).

Following ingestion, the larvae hatch in the small intestine and subsequently migrate to various host organs, including the liver, lungs, central nervous system, and eyes, giving rise to clinical syndromes such as visceral and ocular larva migrans (Morsy, 2020). Clinical signs observed in dogs infected with *Toxocara* spp. include a pot-bellied appearance, poor coat condition, weakness, and diarrhea. These symptoms were more prominent in puppies (Savitri et al., 2020). In many endemic regions, especially those with inadequate hygiene and poor veterinary control, *Toxocara* infection remains a significant public health concern. Although often subclinical, chronic toxocariasis can lead to long-term immunological, neurological, and even cognitive impairments in both humans and animals (Mizgajska-Wiktor *et al*., 2017).

The ability of *Toxocara* spp. to establish persistent infections is largely attributed to their capacity for immune evasion and modulation. One of the most critical strategies involves Toxocara excretory-secretory products (TESPs), a complex mixture of proteins, enzymes, and glycoproteins that facilitate immune interference. These TES molecules interact directly with host immune proteins and play a pivotal role in modulating inflammatory signals, thereby influencing both innate and adaptive immune responses (Abou El-Naga and Mogahed, 2023; Raulf *et al*., 2021). As such, TESPs are not merely metabolic waste but serve as biologically active modulators, enhancing parasite survival by dampening host immunity.

These immunomodulatory effects of TESPs are mediated through interactions with key immune cells such as dendritic cells, macrophages, and T lymphocytes. By suppressing the activation of effector immune cells and shifting the immune profile toward a more tolerogenic phenotype characterized by increased regulatory T cells (T-regs) and elevated levels of anti-inflammatory cytokines like IL-10 and TGF-β, *Toxocara* spp. creates a favorable immunological niche. This tolerogenic environment allows larvae to persist in host tissues for extended periods without eliciting strong inflammatory or cytotoxic responses, contributing to the chronicity of toxocariasis (Amor *et al*., 2022; Bakhshani *et al*., 2024; Waindok and Strube, 2019).

The concept of helminths as 'active architects' of host immunity is well established in parasitology, particularly through studies on *Schistosoma* and *Fasciola* that show their ability to reprogram host immunity toward regulatory or Th2-dominant profiles. *Fasciola* achieves persistence by reaching the bile ducts, maintaining localized immune modulation that supports survival during reproduction. In contrast, *Toxocara* spp. remain developmentally arrested in paratenic hosts without reproduction, residing in multiple organs and drive both local and systemic immune reprogramming, a phenomenon described as 'immunological architecting.' Although both infections are chronic, *Fasciola* maintains a localized environment, whereas *Toxocara* induces systemic immune adaptation. In *Schistosoma*, immune modulation is dynamic, shifting from early Th1 cytokines such as IFN-γ to Th2 and regulatory responses, while *Toxocara* induces a consistent Th2 profile from the early stages of infection (Masamba and Kappo, 2021; Resende *et al*., 2015).

Importantly, these findings suggest that *Toxocara* spp. is not merely a passive evader of immunity, but an active architect of its immunological environment. Rather than hiding from immune detection, the parasite reprograms host immunity to maintain its long-term survival with minimal host pathology. This active immunological shaping underscores the evolutionary sophistication of helminthic parasites and invites further investigation into the molecular tools they utilize for immune interference.

Therefore, this review aims to comprehensively explore the immune evasion mechanisms used by *Toxocara* spp., with a focus on the role of excretory-secretory products in host-parasite immunological interactions. Emphasis will be placed on the specific mechanisms by which TESPs modulate immune responses and contribute to chronic infection. In doing so, we highlight their potential as both biomarkers for diagnostic purposes and as molecular templates for the development of novel immunomodulatory therapies

GLYCOPROTEINS AS KEY IMMUNOMODULATORS

Helminth parasites release soluble TESPs and extracellular vesicles to deliver antigens and regulate host immune activity. These parasites predominantly elicit a Th2-skewed immune response, characterized by the production of IL-4, IL-5, and IL-13, which subsequently inhibits proinflammatory Th1 cytokines such as TNF-α, IFN-γ, and IL-17 (Bashi *et al*., 2014).

Both mucins and C-type lectins are predominant components of TESPs and play crucial roles in immune evasion by modulating host immune responses and mediating interactions with host cells. The host initially recognizes *Toxocara* larvae through C-type lectin receptors (CLRs) such as MGL-1, DC-SIGN, and MCL, which detect the parasite's glycan-rich surface. MCL binding to *Toxocara* antigen limits dendritic cell secretion of pro-inflammatory cytokines such as IL-6 and TNF-α. This indicates that *Toxocara* recognition does not induce a classical inflammatory response. Instead, it immediately activates tolerogenic signaling. Through these glycoprotein–CLR interactions, the parasite establishes an early anti-inflammatory and regulatory environment that drives the

host immune response toward long-term tolerance (Raulf *et al*., 2021).

During early infection, larval migration through host tissues induces epithelial stress that releases alarmins, initiating type 2 polarization via ILC2 and basophils. However, Toxocara does not rely solely on this host-driven response. Its TESPs including mucins and lectins, reinforce and sustain the Th2 and regulatory milieu while suppressing Th1 and Th17 pathways. Thus, Th2 polarization in toxocariasis arises from a dual mechanism, host-derived alarmins trigger it and parasite-derived factors maintain immune tolerance that enables larval persistence (Resende *et al*., 2015; Długosz *et al*., 2015).

Table 1: Bioactive constituents of *Toxocara* spp. TESPs and their mechanisms.

No	Excretory-secretory products	Role
1	Tc-MUC-1	Interferes with macrophage phagocytosis and inflammatory gene expression via FABP5 and CFL1 binding
2	Tc-MUC-2 to Tc-MUC-5	Induce Th2 cytokines (IL-5, IL-6, TGF-β); suppress Th1/Th17 cytokines
3	C-type lectins (CTLs)	Mediate host cell adhesion, immune interference, antibody evasion
4	Cathepsin L (CTSL)	Facilitates MHC-II antigen processing by cleaving invariant chain; supports Th2 initiation
5	Cu-Zn Superoxide Dismutase	Neutralizes ROS from host immune cells, reducing oxidative damage
6	Glutathione S-transferase (GST)	Detoxifies oxidative stress molecules; immunomodulatory effects
7	Paramyosin	Binds complement proteins to inhibit MAC formation and prevent lysis
8	Lactic acid	Anti-inflammatory
9	Glucosamine	Preserves mitochondrial integrity; inhibits IL-1β, NLRP3 inflammasome
10	γ-Aminobutyric acid (GABA)	Promotes tissue repair and wound healing
11	Oleic and linoleic acid	Dual role: anti-inflammatory and pro-wound healing
12	Lauric and palmitic acid	Modulate TLR-mediated responses; lauric acid = anti-inflammatory

As summarized in Table 1, recombinant mucins such as Tc-MUC-2, Tc-MUC-3, Tc-MUC-4, and Tc-MUC-5 have been shown to stimulate murine splenocytes to produce cytokines associated with Th2 responses and immune regulation, including IL-5, IL-6, and TGF-β. In contrast, stimulation with the whole TES mixture induces additional secretion of IL-4 and IL-10 while suppressing TNF-α levels, suggesting a shift toward an anti-inflammatory and tolerogenic immune profile. Moreover, the downregulation of IFN-γ and IL-17 expression indicates suppression of Th1 and Th17 pathways, which are typically involved in parasite clearance. These findings support the concept that mucins and TES not only serve as physical barriers for larval protection but also function as active immunological modulators that foster a host tissue environment favorable for parasite persistence (Długosz *et al*., 2015; Sperotto *et al*., 2017).

The non-glycosylated Tc-MUC-1 protein from *T. canis* interacts directly with two key macrophage proteins: cofilin-1 (CFL1) and fatty acid-binding protein 5 (FABP5). The interaction with CFL1, a regulator of actin dynamics and cell migration, may impair macrophage motility and phagocytic activity, thereby facilitating immune evasion by the larvae. Meanwhile, the association with FABP5, which is involved in lipid metabolism and inflammatory signaling pathways such as NF-κB and PPAR, suggests that Tc-MUC-1 may also influence the transcriptional regulation of pro-inflammatory genes. These findings imply that Tc-MUC-1 functions as a critical immunoevasive molecule by directly targeting essential macrophage signaling pathways, ultimately dampening host immune responses and promoting larval survival within host tissues (Sperotto *et al*., 2017; Zhou *et al*., 2022).

C-type lectins (CTLs) are major components of the surface coat of helminths, including nematodes such as *T. canis*. The presence of CTLs on the larval surface enables direct interaction with host cells, facilitating adhesion, tissue invasion, and evasion of immune detection. Furthermore, the elaboration of a specialized mucin-rich surface layer on the cuticle of *Toxocara* spp. contributes to the parasite's ability to disengage from antibody binding and inflammatory cells, often triggering localized inflammatory responses in regions where the larvae have already migrated away. This mechanism underscores the role of CTLs as essential elements in the parasite's immune evasion strategy, as these molecules not only recognize and bind specific carbohydrates on host cell surfaces but also interfere with immune activation pathways (Harcus *et al*., 2009; Maizels, 2013; Raulf *et al*., 2021; Wang *et al*., 2025).

ENZYMATIC ARSENAL FOR DEFENSE AND MODULATION

Proteases found in larval extracts include members of the cysteine protease C1 family, notably cathepsins B, L, and Z. Among these, cathepsin L (CTSL) plays a pivotal role as a lysosomal protease involved in critical biological processes such as antigen presentation and inflammasome activation. CTSL, as listed in Table 1, specifically mediates the degradation of the invariant chain associated with

MHC class II complexes within acidic endosomes as a key step in the loading of antigenic peptides. In the absence of CTSL's proteolytic activity, MHC class II molecules fail to effectively remove the residual class II-associated invariant chain peptide (CLIP), thereby impairing the presentation of antigens to $CD4^+$ T cells and compromising the initiation of an efficient type 2 immune response (da Silva *et al*., 2018; Purkon *et al*., 2022; Zhao *et al*., 2024).

Toxocara spp. express surface-associated antioxidant enzymes, including copper-zinc superoxide dismutase (Cu-Zn SOD) and glutathione S-transferase (GST). Similarly, in *Fasciola hepatica*, the secreted forms of SOD and GST play essential roles in protecting the parasite against oxidative stress, which may arise from both endogenous metabolism and the host immune response. These enzymes function by neutralizing reactive oxygen species (ROS) generated by immune effector cells such as macrophages and neutrophils. Specifically, superoxide dismutase catalyzes the dismutation of superoxide radicals into hydrogen peroxide, which is subsequently detoxified, thereby limiting oxidative damage to parasitic tissues (Calvani *et al*., 2022; da Silva *et al*., 2018; Driss *et al*., 2016; Wahyudi and Soedarsono, 2015; Witasari *et al*., 2016).

EVASION OF HUMORAL IMMUNITY

To evade immune attacks mediated by the host complement system, parasites have evolved sophisticated complement evasion strategies, including the recruitment of host-derived complement regulatory proteins. Several parasites such as *Toxocara*, *Trichinella*, *Schistosoma*, and *Clonorchis* secrete paramyosin on their surface, which can directly bind to terminal complement components such as C8 and C9, thereby inhibiting the assembly of the membrane attack complex (MAC) and enhancing the parasite's survival within the host (Shao *et al*., 2019; Sun *et al*., 2015). A follow-up study by Kang *et al*. (2022) specifically mapped the C9-binding domain of *Clonorchis sinensis* paramyosin to its C-terminal fragment (Leu731–Leu780), which effectively inhibits C9 polymerization. This finding highlights that paramyosin not only serves as a structural muscle protein in the parasite but also functions as a key immunoevasive molecule. By interfering with complement activation, paramyosin contributes significantly to the parasite's ability to avoid immune-mediated lysis and persist within the host (Kang *et al*., 2022; Soleymani *et al*., 2021; da Silva *et al*., 2018).

BIOACTIVE METABOLITES AND LIPIDS

As presented in Table 1, several polar metabolites found in *Toxocara* excretory-secretory products (ESPs), including lactic acid, malic acid, glucosamine, alanine, glycerol, tryptophan, and glutamine, have demonstrated anti-inflammatory and immunosuppressive properties (Chiu *et al*., 2019; Choi *et al*., 2017; Hearps *et al*., 2017; Nuzula *et al*., 2024; Muhammad *et al*., 2025; Rakhmiyati *et al*., 2023; Romaus Sanjurjo *et al*., 2019; Wangchuk *et al*., 2020). Additionally, γ-aminobutyric acid (GABA), also detected in the ESPs, has been shown to promote wound healing (Romaus Sanjurjo *et al*., 2019). Furthermore, medium- and long-chain fatty acids (MLCFAs) such as lauric acid and palmitic acid present in the ESPs contribute to anti-inflammatory activity (Howe *et al*., 2022; Saraswathi *et al*., 2020). Notably, oleic acid and linoleic acid possess dual functions, serving not only as anti-inflammatory agents but also enhancing tissue repair and wound healing (Gallelli *et al*., 2020; Rodrigues *et al*., 2016; Santa *et al*., 2023).

COMPARATIVE IMMUNOLOGY AND TRANSLATIONAL POTENTIAL

Compared with trematodes such as *Fasciola hepatica*, which rely heavily on cathepsin proteases and paramyosin as dominant secretory components facilitating tissue penetration and immune evasion, the TESPs repertoire is notably enriched in mucin-like glycoproteins and C-type lectins. These differences indicate distinct evolutionary trajectories, while trematodes evolved proteolytic and surface-masking strategies adapted to biliary or hepatic niches, *Toxocara* spp. optimized carbohydrate-rich secretions to sustain chronic tissue migration and orchestrate immunomodulation in hosts (Soleymani et al., 2024).

TESP of *T. canis* and the somatic extract of *T. cati*, demonstrate strong disease-modifying potential by dampening pathological inflammation. TESP reduces the expression of T-bet, a key transcription factor driving Th1-mediated neuroinflammation in experimental Allergic Encephalomyelitis without inducing a compensatory rise in GATA-3, suggesting targeted suppression of proinflammatory pathways rather than a shift toward an excessive Th2 response, while *T. cati* somatic extract attenuates allergic airway inflammation by decreasing peribronchiolitis, perivasculitis, eosinophilic infiltration, and Th2 cytokines IL-4 and IL-5, accompanied by enhanced IL-10 production. (Aragón-Franco *et al*., 2017; Bakhshani *et al*., 2024). These findings highlight the potential of TEPS as natural immunomodulatory candidates that could be further explored for the development of alternative therapeutic approaches for autoimmune diseases such as multiple sclerosis or allergic asthma, although additional research is needed to identify the specific antigenic components responsible for this protective effect, dose–response optimization, long-term

toxicity evaluation, and tissue-targeted delivery approaches will be essential to ensure safety and therapeutic precision.

Taken together, these findings underscore the complex and multifaceted strategies employed by *Toxocara* spp. to evade host immune responses and ensure long-term survival within host tissues. By deploying a diverse arsenal of excretory-secretory products including immunomodulatory proteins, surface-bound lectins, antioxidant enzymes, and bioactive metabolites, the parasite is able to manipulate host cellular signaling, suppress pro-inflammatory pathways, and impair antigen presentation. Such immune-evasive mechanisms not only facilitate larval persistence and tissue migration but also contribute to the chronicity and underdiagnosis of toxocariasis. Despite the growing number of proteomic and metabolomic studies characterizing TESPs, it is still unclear whether the presence of metabolites concentrations exceed baseline levels in host tissues. Further work will be essential to validate the proposed roles of individual TESP components in immune evasion.

Beyond shaping early immunological events, these same TESPs also hold translational relevance, particularly in diagnostics. Several TESP components already show strong translational promise. The glycoproteins TES-120, TES-32, and TES-26 have demonstrated high diagnostic sensitivity and are currently the most reliable markers of active infection. Their stage-dependent secretion profiles and strong immunogenicity make them suitable candidates for assays capable of distinguishing active infection from past exposure or potentially estimating parasite burden (Mesa-Arango *et al*., 2022).

A deeper understanding of these molecular interactions offers valuable insight into host–parasite dynamics and may provide a foundation for developing novel diagnostic tools, immunotherapeutic interventions, or vaccine candidates targeting key virulence factors of *Toxocara* spp. Although most mechanistic insights discussed in this review derive from in vivo murine infection models, they represent the most physiologically relevant approach currently available for studying *Toxocara*–host interactions. Further validation in human systems will be essential to confirm the translational relevance of these mechanisms.

CONCLUSION

Toxocara spp. exhibit an impressive repertoire of immune evasion strategies that facilitate their persistence within host tissues, despite robust immune surveillance. Central to this evasion is the role of excretory-secretory products (TESPs), which act not merely as metabolic by-products but as biologically active molecules that modulate host immune responses. TESPs, including mucins, C-type lectins, and proteases play a pivotal role in downregulating Th1/Th17-driven inflammation while promoting a tolerogenic, Th2-skewed environment conducive to larval survival. Molecules such as Tc-MUC-1 directly interfere with macrophage signaling, while others like cathepsin L impair antigen presentation by disrupting MHC class II processing.

Future research should prioritize identifying the most functionally dominant TESP components and determining how these key molecules coordinate parasite–host communication over time. Deep comparative analyses across helminths may uncover conserved immune-modulatory strategies that can guide the design of unified diagnostic markers or targeted interventions. There is also a strong need to establish standardized experimental frameworks for evaluating TES-derived molecules, enabling clearer translation of basic findings into practical diagnostic, therapeutic, or vaccine-oriented applications.

ACKNOWLEDGEMENTS

The author would like to thank Universitas Airlangga for providing an academic environment that supports scientific exploration.

NOVELTY STATEMENT

Immune evasion in *Toxocara* infection can be reframed as a coordinated process driven by excretory-secretory products rather than isolated molecular effects. By integrating evidence on glycoproteins, enzymatic components, and bioactive metabolites, this article highlights the concept of *Toxocara* as an active architect of host immune tolerance, shaping a sustained Th2–regulatory environment that enables long-term larval persistence.

AUTHOR'S CONTRIBUTION

The manuscript must clearly state the contribution of each author and should convince editors that each author has contributed significantly to the study. Vidya Kurnia: conceptualization, methodology, formal analysis, writing original draft, resources, data curation, visualization, project administration. Merdiana Ayu Dewi: validation, investigation, writing review and editing, resources, data curation. Meli Rizki Purwani: validation, writing review and editing, data curation. Bala Ningi Umar: data curation and editing. Agus Widodo and Lita Rakhma Yustinasari: writing review and editing.

Generative AI and AI-assisted technology statement

Generative AI tools were used solely for language editing

and grammar improvement. The authors reviewed, verified, and approved all content. No AI tools were used for data analysis, interpretation, or creation of scientific content.

Conflicts of interest

The authors have declared no conflict of interests regarding the publication of this article.

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