Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Smart Medicine
DOI: 10.54254/2753-8818/2026.HZ37574

# *A Review of Interdisciplinary Research from Parasitic Immune Escape to Autoimmune Diseases and Tumor Diseases*

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***Abstract.*** Parasites have evolved complex immune escape systems during long-term coevolution with their hosts. The theory that parasites can reshape host immunity by secreting regulatory molecules provides new ideas for the study of autoimmune diseases and tumor immunology. The purpose of this review is to analyze this theory in detail, and to illustrate the interdisciplinary relationship between parasite immune escape and autoimmune diseases and tumors. This review summarizes the core mechanisms of parasite immune escape and its immunomodulatory pathways, and summarizes how parasite products alleviate autoimmune damage by inhibiting excessive inflammatory responses and restoring immune homeostasis. At the same time, the dual immunomodulatory effects of parasite molecules on the tumor microenvironment were elucidated by comparing the convergent immune evasion mechanisms between helminths and tumor cells. Shared signaling modules also enable the three diseases to form a unified pathological network. Although there are still many defects in the strategies of original parasite molecules for the treatment of autoimmune diseases and tumors, and most of the research results are still in the stage of animal models, parasite-derived molecules provide a vast resource for the development of parasitoid drugs for the treatment of autoimmunity and tumors.

***Keywords:*** Parasites, Parasite Immune Escape Mechanisms, Autoimmune Diseases, Tumors, Tumor Immune Escape

## 1. Introduction

In the long-term co-evolution process between parasites and hosts, parasites have developed unique immune escape strategies, which rely on secreted regulatory molecules to interfere with host immune pathways and induce immune tolerance to achieve colonization instead of rapidly killing the host. Traditionally, parasites are only regarded as pathogenic pathogens, but recent studies have found that their secreted molecules have powerful immune remodeling capabilities. At present, animal experiments have confirmed that some parasite products can alleviate autoimmune damage, and there is a convergence of immune escape mechanisms between parasites and tumors, but the cross-disease immune regulatory network among them has not been systematically sorted out. Given that there are still many problems in the clinical treatment of autoimmune diseases and tumors, the

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discovery of parasite-derived immunomodulatory molecules has important translational value. This paper systematically reviews the mechanisms of parasitic immune escape, analyzes the internal relationship between parasitic immune escape and autoimmune diseases and tumor immunity, summarizes the existing experimental evidence, and analyzes the limitations and future development directions of existing research, in order to provide a theoretical reference for the development of new immunomodulators for autoimmune diseases and tumors.

## 2. Mechanisms of parasite immune escape

The core effector molecules of the parasite secretome include ES secretory proteins, calcium binding proteins, protease inhibitors and polysaccharide metabolites. These molecules exhibit low toxicity and long-term effects, and can intervene in multiple host immune pathways at the same time, achieve multi-target co-regulation, and reshape the immune response in a mild manner. According to the paper of Maizels's group, worms can directly inhibit host signaling that recognizes TLRs and other receptors by secreting specific molecules. Inhibition of NF-κB and MAPK inflammatory cascade. Inhibition of the above pathways can directly down-regulate the pro-inflammatory factors (TNF-α, IL-6, IL-1β) and calm the local acute inflammatory storm [1]. In addition, it can upregulate Treg cells and inhibit the proinflammatory response and tissue damage caused by Th1/Th17 excessive immunity.

## 3. Cross-boundary association of parasite immune escape mechanisms with autoimmune diseases

### 3.1. Core autoimmune pathology

The immune system breaks through its tolerance threshold, and T cells and B cells undergo abnormal clonal expansion and persistent activation in the absence of effective inhibitory signals. Proinflammatory cytokine storm leads to the loss of negative feedback regulation of the immune response, triggering a vicious cycle of extensive tissue damage and chronic inflammatory microenvironment. At the same time, the body produces high-affinity autoantibodies or sensitized lymphocytes, which mistakenly recognize its own tissue components as targets and initiate specific clearance, eventually leading to organ failure.

### 3.2. The reverse matching relationship between parasite immune regulation and autoimmune disease pathology and the improvement effect of confirmed parasite molecules on autoimmune diseases

#### 3.2.1. Parasite escape can inhibit hyperinflammation and restore immune homeostasis

In the paper Kikuchi Taisei's group published in 2022, Venestatin was shown to be a specific RAGE antagonist in glycation end-producs-mediated signaling [2]. As shown in Figure 1, by directly binding to RAGE, a key recognition damage receptor in asthma and autoimmune pathology, Venestatin inhibits the RAGE pathway and blocks the activation of key inflammatory pathways such as NF-κB and MAPK. The expression of downstream pro-inflammatory cytokines (such as IL-4, IL-5, IL-13, TNF-α) and chemokines was significantly decreased. It also effectively suppresses the "autoinflammatory damage" caused by overactivation of the immune system.

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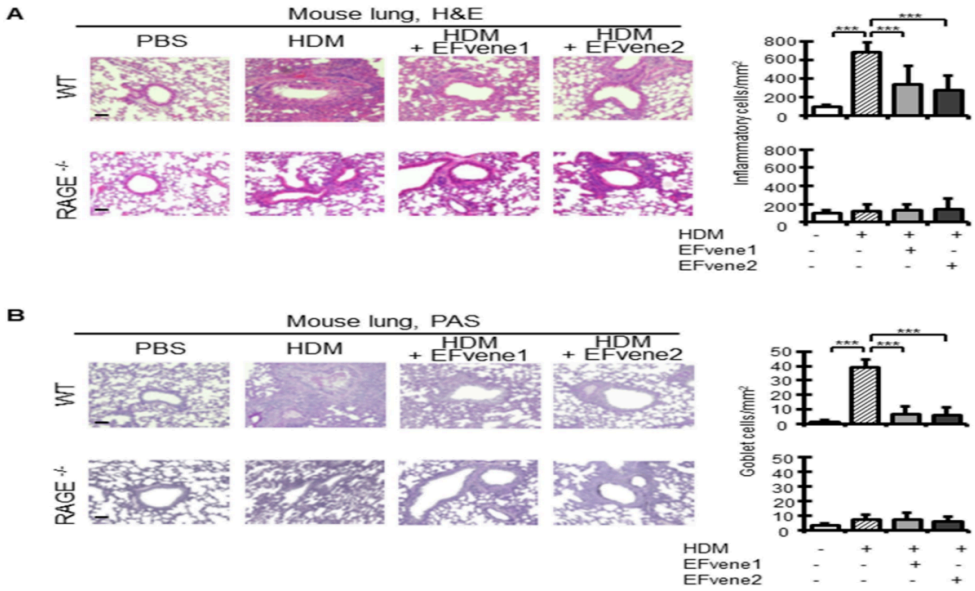



Figure 1. Treatment with EF-hand small peptides inhibited AAI/asthma pathogenesis in response to HDM extract treatment

As shown in Figure 1, histopathological evaluation of lung tissues was conducted to assess the therapeutic efficacy of EF-hand small peptides in a murine model of allergic airway inflammation (AAI) induced by house dust mite (HDM). Wild-type (WT) mice were subjected to intranasal administration of HDM (40 μg per mouse, targeting RAGE) either alone or in combination with EF-hand small peptides (EFvene1 or EFvene2; 20 μg per dose), four times per week for a duration of seven weeks. Mice receiving phosphate-buffered saline (PBS) served as the negative control group. Upon completion of the treatment regimen, animals were euthanized, and lung specimens were harvested, fixed, and processed for histological analysis using hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS) staining.

HDM challenge elicited marked peribronchiolar inflammatory cell infiltration and goblet cell hyperplasia within the bronchial mucosa. Notably, co-administration of EF-hand small peptides (EFvene1 or EFvene2) significantly attenuated these pathological alterations. Specifically, panel (A) demonstrates a substantial reduction in HDM-induced cellular infiltration surrounding the bronchioles, while panel (B) reveals a marked suppression of goblet cell hyperplasia in the bronchial epithelium. Quantitative data, expressed as mean ± standard deviation (SD), were derived from a total of 24 mice (n = 4 per group, pooled from two independent experiments). Statistical significance was determined, with ***$p < 0.001$ indicating highly significant differences. Scale bar represents 40 μm.

### 3.2.2. Proven ameliorative effects of parasite molecules on autoimmune diseases

The group of Kikuchi and Taisei also said in the paper that worm products can relieve asthma and allergic inflammation [2]. Harnett, Margaret M.'s group mentioned in the paper that filarial worms can secrete glycoprotein ES-62; Significantly inhibited the infiltration of IL-17+ lymphocytes and v8T cells in the joint, inhibited the activation axis of DC-Th17, and down-regulated TNF-a and IL-6 [3]. This mechanism can prevent the onset of arthritis and the occurrence of arthritis, reduce synovial inflammatory infiltration and joint damage. In the paper produced by the group of Melendez, Adriana J, we show that ES-62 inhibits the MyD88 signaling pathway, reduces the

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production of antinuclear antibodies (ANA) and anti-ds-DNA autoantibodies, and reduces proteinuria and lupus kidney damage in MRL/lpr lupus mice [4]. Grainger, J. R.'s group suggest that TGF-β mimogenic protein TGM secreted by T. spiralis can inhibit the differentiation of Th17 cells and the secretion of IL-17, and thus alleviate the autoimmune injury of the central nervous system [5].

## 4. Transboundary homology between parasite immune escape mechanisms and tumor immunity

### 4.1. Core characteristics of tumor immune escape

Tumors remodel the microenvironment through persistent chronic inflammatory signals and induce the accumulation of immunosuppressive cells such as Tregs and MDSCs, thereby constructing an inhibitory microenvironment that hinders anti-tumor immune responses. Under continuous antigen stimulation and inhibitory cytokines (such as IL-10 and TGF-β), effector Tregs are damaged and depleted, while macrophages are polarized into tumor-promoting M2 type.

### 4.2. Parasite escape VS tumor escape: a highly homologous mechanism

The paper *Cancer in disguise: a parasite* within details that the parasite mimics the host's "self" markers by secreting specific antigens or surface molecules, or directly upregulates inhibitory ligands on the host cell surface [6]. This allows the immune system to mistake the invader for normal body tissue, thus avoiding triggering a strong, aggressive immune response. Both parasites and tumor cells transmit inhibitory signals by binding to the PD-1 receptor on the surface of T cells, leading to the inhibition of effector T cell function or even to a state of exhaustion, which can be shown in Figure 2.

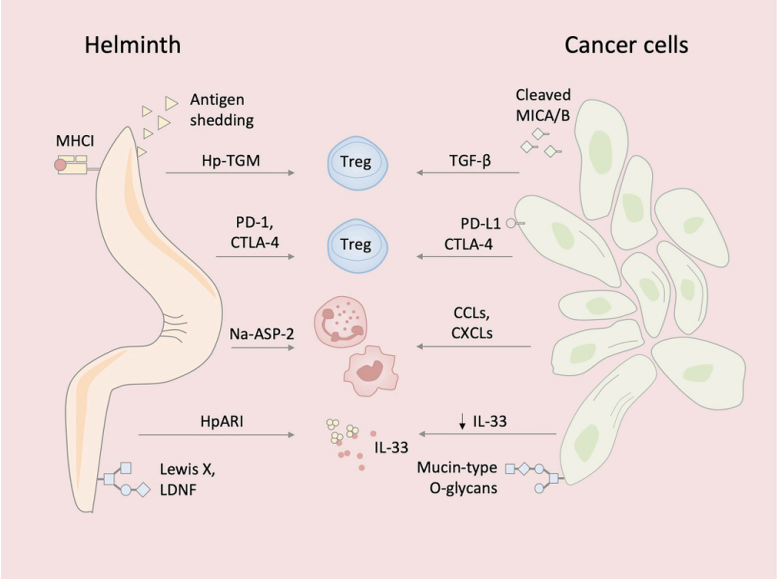



Figure 2. Shared immune evasion strategies between helminths and cancer cells

As shown in Figure 2, helminths employ a sophisticated array of strategies to subvert host immune surveillance. These mechanisms include the expansion of regulatory T cell (Treg) populations, driven by immunomodulatory cytokines and molecular mimics of transforming growth

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factor-beta (TGF-β), such as Hp-TGM from Heligmosomoides polygyrus. Furthermore, helminths induce the upregulation of inhibitory immune checkpoint receptors, including programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), on host immune cells. Antigenic variation is achieved through the shedding of surface molecules and molecular mimicry, utilizing host-like glycan structures (e.g., Lewis X, LDNF) or by acquiring host major histocompatibility complex (MHC) class I glycoproteins. Modulation of the innate immune response is also critical; helminths secrete chemokine mimics like Necator americanus Ancylostoma Secreted Protein-2 (Na-ASP-2) to recruit myeloid cells and release inhibitors such as H. polygyrus alarmin release inhibitor (HpARI) to block the release of epithelial alarmins like interleukin-33 (IL-33).

Strikingly, neoplastic cells deploy a convergent repertoire of immune evasion tactics. Tumors similarly recruit Tregs and upregulate immune checkpoint ligands to induce T cell exhaustion. They engage in antigen modulation through the proteolytic shedding of stress-induced ligands like MHC class I chain-related proteins A and B (MICA/B), which leads to the downregulation of the activating receptor NKG2D on natural killer (NK) cells. Additionally, tumors frequently downregulate MHC class I expression to escape cytotoxic T lymphocyte recognition, foster an immunosuppressive microenvironment through the infiltration of myeloid-derived suppressor cells, and inhibit IL-33-mediated signaling pathways. These parallels underscore a remarkable example of convergent evolution, where distinct pathogenic entities—parasitic helminths and malignant tumors—have independently evolved analogous molecular strategies to circumvent host immunity.

### 4.3. Bidirectional regulation of tumor microenvironment by parasite molecules

Zhou's team indicates that moderate inhibition of chronic inflammation can reduce the proliferation, mutation and accumulation of tumor cells mediated by inflammation, but complete excessive immunosuppression will disrupt the anti-tumor immune surveillance [7]. *Cancer in disguise: a parasite within* also mentions that when a large number of regulatory T cells and M2-type macrophages gather around the lesion, these cells will secrete anti-inflammatory cytokines such as IL-10 and TGF-β [6]. They will form an immunosuppressive microenvironment locally, consolidating the immune tolerance state, and providing a favorable environment for long-term parasitic survival or the continuous growth of tumors. Nicolas's group proposes that blocking RAGE could be a potential target for parasite molecules in the intervention of the tumor microenvironment [8].

## 5. Unified immune regulatory network for three types of diseases

Parasites, autoimmune diseases and tumors share a common signaling module: the RAGE-NF-κB-MAPK inflammatory axis, Treg expansion and M2 macrophage polarization. In the paper mentioned above, RAGE-NF-Kβ-MAPK is discussed in detail within three types of diseases [8]. In parasitic infections, Venestatin blocks RAGE, inhibits the downstream NF-Kβ-MAPK, and induces local tolerance; in autoimmune diseases, the excessive activation of RAGE drives excessive inflammation of NF-kβ/MAPK, mediating tissue damage; in tumors, the continuous activation of RAGE maintains chronic inflammation promoting tumor growth, accumulating M2-TAM and Treg. Thus, although it is the same RAGE core axis, their activation degrees are different, resulting in completely opposite pathological outcomes. This discovery provides a molecular basis for the unified regulatory network. *Cancer in disguise: a parasite within* clearly states that when parasites secrete molecules, they moderately down-regulate NF-κβ-MAPK, inducing Treg/M2, achieving physiological tolerance, and controlling host tissue damage [6]. Meanwhile, due to the excessive

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activation of RAGE-NF-κβ-MAPK in autoimmune diseases, Treg function is impaired, M1 is skewed, and immune homeostasis is disrupted. Tumors also, because malignant cells hijack the same pathway, continuously induce Treg/M2, forming malignant tolerance.

## 6. Conclusion

This article mainly discusses that parasite immune evasion is not merely a pathogenic mechanism, but rather a natural and precise host immune regulatory system. Its mechanism can simultaneously explain the inflammation of autoimmune diseases and the immune evasion of tumors. Parasite-derived molecules are important resources for future cross-border new drugs in autoimmune diseases and tumor immunology. However, the overall infection side effects of parasites are significant, making them unsuitable for direct clinical application. Most mechanisms remain in animal models, and the transformation into humans is insufficient. There is bidirectionality in tumor regulation, and most molecular targets have not been fully resolved. In the future, AI can be applied for target discovery and precise molecular screening. Based on parasite genomics and secretomics, new immune regulatory molecules can be screened. AI can predict protein-host receptor interactions of parasites, quickly discover cross-border targets, and improve drugability for precise treatment of anti-inflammatory in autoimmune diseases and remodeling of the tumor immune microenvironment.

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