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Helminth Therapy for Immune-Mediated Inflammatory Diseases: Current and Future Perspectives

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Abstract: Inflammatory bowel disease and allergic asthma, as typical immune-mediated inflammatory diseases (IMIDs), are associated with immune imbalance caused by complex interactions among environmental, genetic and bacterial factors. The changing immune imbalance of IMIDs not only causes serious pathological damages but also increases the difficulty of treatment. Helminths or helminth-derived molecules have been increasingly employed to treat IMIDs due to their immunoregulatory ability. Since helminth infection is not an appropriate treatment direction due to the complex immunoregulation and safety concerns, one of the new therapies is to harness the immunoregulation induced by the identified helminth-derived molecules using immune indexes as a guide. This review discusses the pathogenesis of inflammatory bowel disease and allergic asthma, and summarizes the therapeutic effect of helminths and the immunoregulatory mechanisms induced by helminth-derived molecules proposing therapeutic regimens.

Keywords: inflammatory bowel disease, allergic asthma, immunoregulation, IMIDs, helminth therapy, helminth-derived molecules

Introduction

Helminths, as ancient organisms, have existed throughout the history of human evolution and formed perfect ways to escape the immune response by interacting with the human immune system for a long time. The helminth-induced immune microenvironment can not only reduce the damage caused by invasion but also allow helminths to take advantage to their own survival and reproduction.¹ The improvement of health care, deworming and clean environments resulted in a low prevalence of helminth infection accompanied by an increasing incidence of immune-mediated inflammatory diseases (IMIDs), such as inflammatory bowel disease (IBD), allergic asthma and atopic dermatitis.² This negative correlation between helminth infections and IMIDs also agrees with the hygiene hypothesis³ and the so-called old friend hypothesis,⁴ both of which propose that recent increases in inflammatory diseases are partly linked to a lack of exposure to microorganisms. Therefore, the immunoregulation of helminths has great potential in treating IMIDs. IMIDs are characterized by an imbalance of CD4⁺ T cell subsets, including T helper type 1 (Th1) cells, T helper type 2 (Th2) cells, T helper type 17 (Th17) cells, T follicular helper (Tfh) cells B regulatory (Breg) cells and T regulatory (Treg) cells.⁵ Human infection with *Filaria* showed the proliferation of Treg cells and Th17 cells, and the significantly increase in IL-10 and IL-17A.⁶ Although *Necator americanus* or *Trichuris suis* therapies were effective for partly patients with IBD, the vast majority of trials of helminth therapy showed no clinical effect on IMIDs.^{7,8} *Trichuris suis* did not improve pollen-induced allergic rhinitis in clinical trials,^{9,10} and *Necator americanus* did not improve airway responsiveness in patients with asthma.¹¹ Traditional helminth therapy is completely dependent on the pathogen infection, showing that excretory-secretory products (ESPs) are responsible for helminths to regulate the host's immune system. The immune response induced by ESPs is multitudinous and unpredictable due to the complexity of the

components, resulting in uncertain therapeutic effect.^{12–14} In addition, another explanation is that helminth therapy may be a large difference in the prevention and treatment of IMIDs. The host's immune response induced by helminths may reduce susceptibility to IMIDs rather than treat IMIDs.¹⁵ Nevertheless, the therapeutic value of helminth-derived molecules can not be ignored. Although the limited research on the immunomodulatory mechanism of helminth-derived molecules, the treatment of IMIDs based on helminth-derived molecules has great prospects.

IBD and allergic asthma, two typical IMIDs, are prevalent worldwide. At present, there is still a lack of effective treatments for immune imbalance and patients suffer recurrence of clinical symptoms. This review summarizes the pathogenesis of IBD and allergic asthma, the therapeutic effects of helminths and helminth-derived molecules, and the immunoregulatory mechanism of helminth-derived molecules.

Inflammatory Bowel Disease

Symptoms and Pathogenesis

IBD is a chronic bowel disease characterized by abdominal pain, blood in the stool and weight loss, including Crohn's disease and ulcerative colitis.¹⁶ In recent years, the incidence of IBD has increased worldwide, but current treatments only improve symptoms and they are not fundamental therapies for IBD.¹⁷ Therefore, it is necessary to find new therapeutic strategies to achieve better treatment results.

IBD is associated with complex interactions among environmental, genetic and bacterial factors (Figure 1). It has been known that incidence rates increase if a group of people move from regions with low incidence rates of IBD to high prevalence areas.¹⁸ Therefore, changes in the living environment are associated with reduced susceptibility to IBD. With the development of the economy, human life patterns have undergone significant changes, such as unbalanced diet structure, tobacco dependence, insufficient exercise, and drug abuse. These changes can disrupt the balance between the immune response and immune tolerance, which are associated with the increasing incidence rate of IBD.^{19–21}

Genomics has found 163 genes related to the pathogenesis of IBD, including nucleotide-binding oligomerization domain 2 (Nod2), interleukin-10 receptor (IL-10R), caspase recruitment domain family member 9 (CARD9), interleukin-23 receptor (IL-23R) and protein tyrosine phosphatase non-receptor type 2 (PTPN2).^{22,23} Nod2 is an important intracellular receptor to regulate gut microbiota.²⁴ After activation by muramyl dipeptide derived from bacterial proteoglycan, Nod2 activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling pathway to produce antimicrobial peptides such as α -defensins in Paneth cells²⁵ (Figure 2). These peptides can directly regulate gut microbiota, which affect the development of intestinal inflammation.^{26,27} It has also been reported that Nod2 signaling in CD11c⁺ cells can drive the Th2-type immune response with the synergistic signals of tumor necrosis factor receptor superfamily member 4 ligand (OX40L) and thymic stromal lymphopoietin receptor (TSLPR).²⁸ Mutations in NOD2 lead to decreased the level of IL-10, but increase in mucosal bacteria. The decreased level of IL-10 causes disruption of the mucosal barrier and reduces susceptibility to colitis.²⁹ Consistently, patients with defective Nod2 show chronic inflammation driven by interleukin 12 (IL-12) and interferon-gamma (IFN- γ).³⁰ Mutations in genes encoding the IL10R subunit proteins are found in patients with early-onset enterocolitis, leading to hyperinflammatory immune

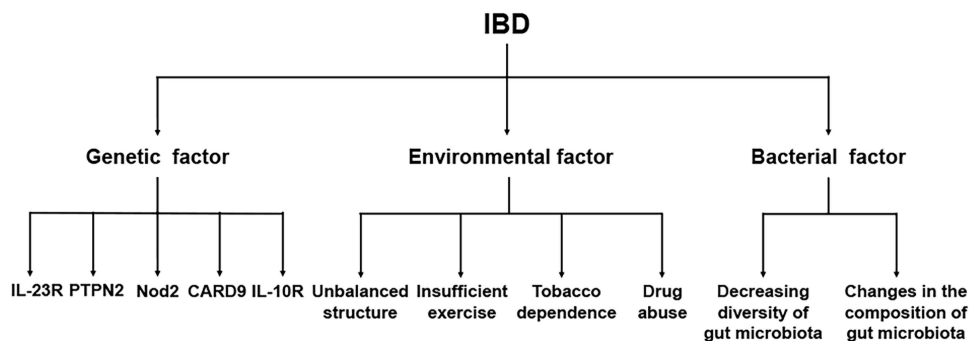


Figure 1 Classification of factors that can induce IBD.

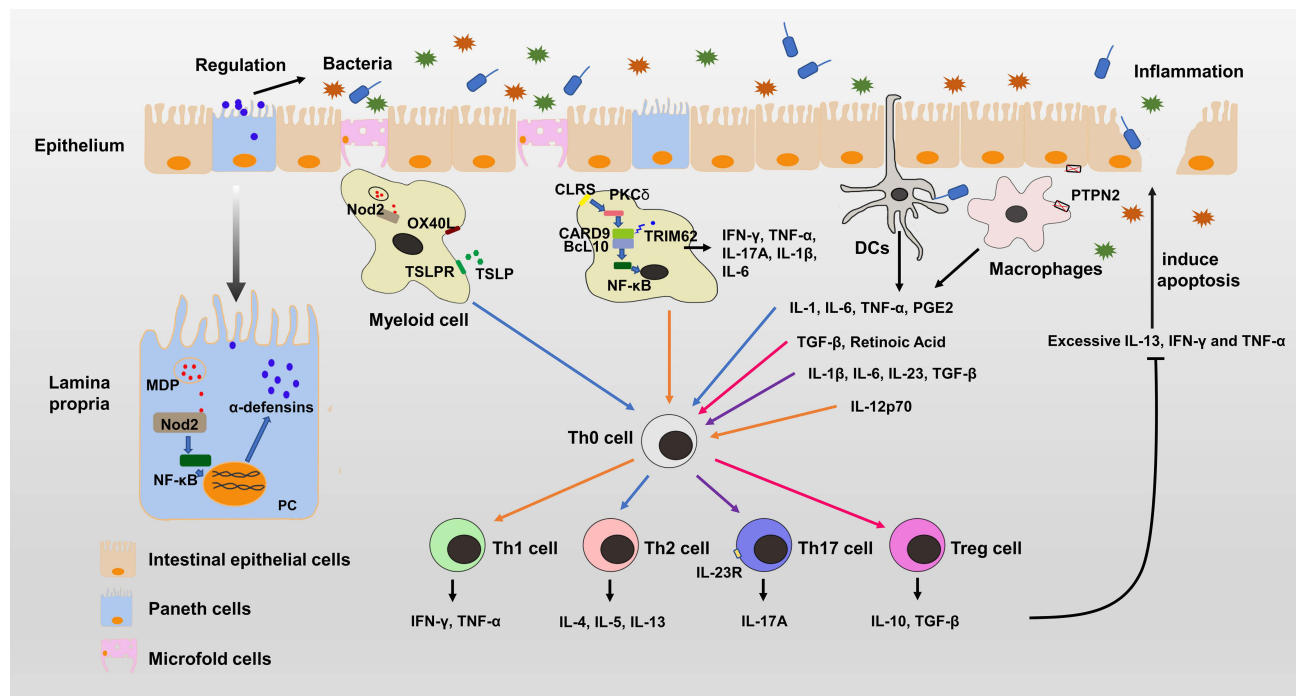


Figure 2 The pathogenesis of IBD. Nod2 is highly expressed in Paneth cells and myeloid cells. Nod2 activated by muramyl dipeptide can activate the NF- κ B pathway to produce α -defensins that directly regulate gut bacteria in Paneth cells. Nod2 signaling can drive the Th2-type immune response with the synergistic signals of OX40L and TSLPR. CARD9 is highly expressed in myeloid cells and can activate the NF- κ B pathway to secrete pro-inflammatory cytokines such as IFN- γ , TNF- α , IL-17A, IL-1 β and IL-6. When CARD9 mutates to CARD9^{S12N}, it can induce a Th2-type immune response. The IL-23 signaling pathway of Th17 cells is critical in the development of IBD. PTPN2 mediated interactions between intestinal epithelial cells and macrophages are necessary for maintaining the intestinal barrier function. The gut bacteria also affect the immune system by interacting with immune cells. DCs can induce Th0 cells to differentiate by producing different cytokines. Immune imbalance can cause excessive IL-13, IFN- γ and TNF- α to induce apoptosis of intestinal epithelial cells. Destruction of the intestinal barrier and invasion of the gut microbiota further leads to severe inflammation.

responses in the intestine.²³ CARD9 is a signaling adaptor protein downstream of many C-type lectin receptors and is highly expressed in B cells, T cells and myeloid cells.³¹ It has been reported that phosphorylation of CARD9 mediated by activated protein kinase C- δ can form the CARD9-BcL10 complex to activate the NF- κ B pathway.³² Meanwhile, the ubiquitination of CARD9 mediated by the ubiquitin ligase TRIM62 is essential for CARD9 activity.³³ CARD9 exon 11 integrity is critical for the formation of CARD9-BcL10 complex and maintains the number of lymphocytes and myeloid cells.³⁴ CARD9 signaling pathway can maintain intestinal immune homeostasis and gut microbiota, and mice with CARD9 deficiency have increased susceptibility to colitis.³⁵ IL-23 secreted by monocytes can activate IL-23R on the surface of immune cells and produce a large number of pro-inflammatory cytokines, such as IL-6, IFN- γ and tumor necrosis factor (TNF).³⁶ In addition, the interaction mediated by PTPN2 between intestinal epithelial cells and macrophages is necessary for maintaining the intestinal barrier function. Loss of PTPN2 in macrophages can promote classical activation of macrophages.³⁷ Excessive cytokines (TNF,³⁸ IFN- γ ³⁹) can induce apoptosis of intestinal epithelial cells and result in destruction of the intestinal barrier.

It should not be forgotten that the interaction between gut microbiota and intestinal tissue directly affect intestinal immune homeostasis (Figure 2). The antigen of gut microbiota can be taken up by mononuclear phagocytes via microfold cell-mediated transcytosis. Furthermore, Dendritic cells (DCs), under inflammatory stimulation, can send dendrites outside the epithelium and capture gut microbiota.⁴⁰ Many studies found that the gut microbiota in patients and mouse models showed less diverse with fewer *Faecalibacterium prausnitzii* or *Roseburia*, but with a significantly increased level of *Escherichia coli*, *Bacteroides vulgatus*, *Alistipes putredinis* and *Ruminococcus gnavus*.^{41–43} Meanwhile, butyrate derived from *Faecalibacterium prausnitzii* and *Roseburia* could induce Treg cells to alleviate intestinal inflammation.⁴⁴ Altered gut microbiota disturbs intestinal immune homeostasis and is associated to the development of IBD.

Drawbacks of Existing Treatments for IBD

The mainstay of clinical therapies for IBD includes 5-aminosalicylic acid, steroids, biological agents (anti-TNF- α antibodies), exclusive enteral nutrition and surgery.^{45,46} However, long-term administration of 5-aminosalicylic acid and steroids induces inflammation of the heart or pericardium and osteoporosis, although they can relieve pathological symptoms of IBD.⁴⁷ Few patients are suitable for biological therapy, which will increase the risk of infection and tumors.⁴⁸ Therefore, there is an urgent need to find a therapy with high safety.

Allergic Asthma

Symptoms and Pathogenesis

Allergic asthma is a subset of asthma, when patients are exposed to allergens, allergic asthma patients have symptoms such as wheezing, increasing airway mucus and airway hyperresponsiveness.⁴⁹ At the present, the prevalence of allergic asthma is steadily increasing worldwide, which brings medical and economic pressure to the individual and nations.^{50,51}

Allergic asthma is a complex disease caused by genetic and environmental factors. It has been reported that children from families with a genetic background of allergic asthma suffer from the disease more easily than those from families without any history of allergic asthma.⁵² Besides, a large number of genes are associated with allergic asthma, such as IL-33, ST2, TLR2, Nod2, IL-10, GATA3 and STAT6.^{53,54} IL-33/ST2 signaling pathway stimulates ILC2s and eosinophil proliferation and is associated with susceptibility to allergic asthma.⁵⁵ Antibodies targeting ST2 have been used in clinic and achieved remarkable results.⁵⁶ In addition, the living environment is a non-negligible factor in the development of allergic asthma. Epidemiological investigations have shown that the incidence rate of allergic asthma in children exposed to multiple bacteria in childhood is obviously lower than that in children with limited bacterial exposure.⁵⁷ Consistent with this, in a mouse model, low-dose LPS stimulation could prevent allergic asthma symptoms induced by house dust mites, which supported the protective effect of the immune response induced by microflora in allergic asthma.⁵⁸

The allergic reaction involves sensitization and effector stages (Figure 3). After stimulation with inhaled allergens, airway epithelial cells secrete large amounts of IL-25, IL-33, and TSLP, which can induce group 2 innate lymphoid cells (ILC2s) and Th2 cells to proliferate and secrete large amounts of IL-4, IL-5, and IL-13 and result in a strong Th2 immune response.⁵⁹ In addition, allergens processed by DCs can promote the differentiation of Tfh cells, which can induce plasmacytes to produce IgE in the germinal center.⁶⁰ When IgE binds to Fc receptors, mast cells are activated and release histamine, leukotriene, IL-5, and IL-13. IL-5 recruits more eosinophils into the lung tissue with the synergistic effect of chemokines CCL11 and CCL24. Eosinophils can aggravate lung allergic inflammation by releasing IL-4, IL-5, IL-13, IFN- γ , CCL3, and CCL5.⁶¹ IL-17A secreted by Th17 cells can induce airway smooth muscle contraction and stimulate epithelial cells to release CCL1, CCL2, and CCL5. These chemokines can recruit neutrophils into lung tissue and cause severe inflammation.⁶² Neutrophils and macrophages can secrete matrix metalloproteinase 9 to induce airway hyperresponsiveness.⁶³ When patients are exposed to allergens again, mast cells can be activated by IgE on their surface and quickly cause immune imbalance to induce an inflammatory response.

Changed Immune States in Different Stages of Allergic Asthma

It has been reported that childhood-onset patients show increasing levels of IL-4 and decreasing levels of IFN- γ , which are similar to characteristics of allergic reactions.⁶⁴ When allergic asthma develops into severe allergic asthma, it is often associated with mixed inflammation induced by Th2-type, Th17-type, and Th1-type immune responses. In clinical experiments, increasing levels of IL-4 and IFN- γ are found in the airway, bronchoalveolar lavage (BAL) and supernatant of whole-blood culture of patients with allergic asthma.^{65,66} Consistent with this, in a mouse model of ovalbumin (OVA)-induced allergic asthma, the levels of IL-4, IL-17A and IFN- γ in lung CD4⁺ T cells are higher than those in the control group.⁶⁷

Drawbacks of Existing Treatments for Allergic Asthma

Current clinical treatment options for allergic asthma include allergen immunotherapy, glucocorticoids and bronchodilators.^{68,69} In recent years, with further studies on the pathogenesis of allergic asthma, biological agents

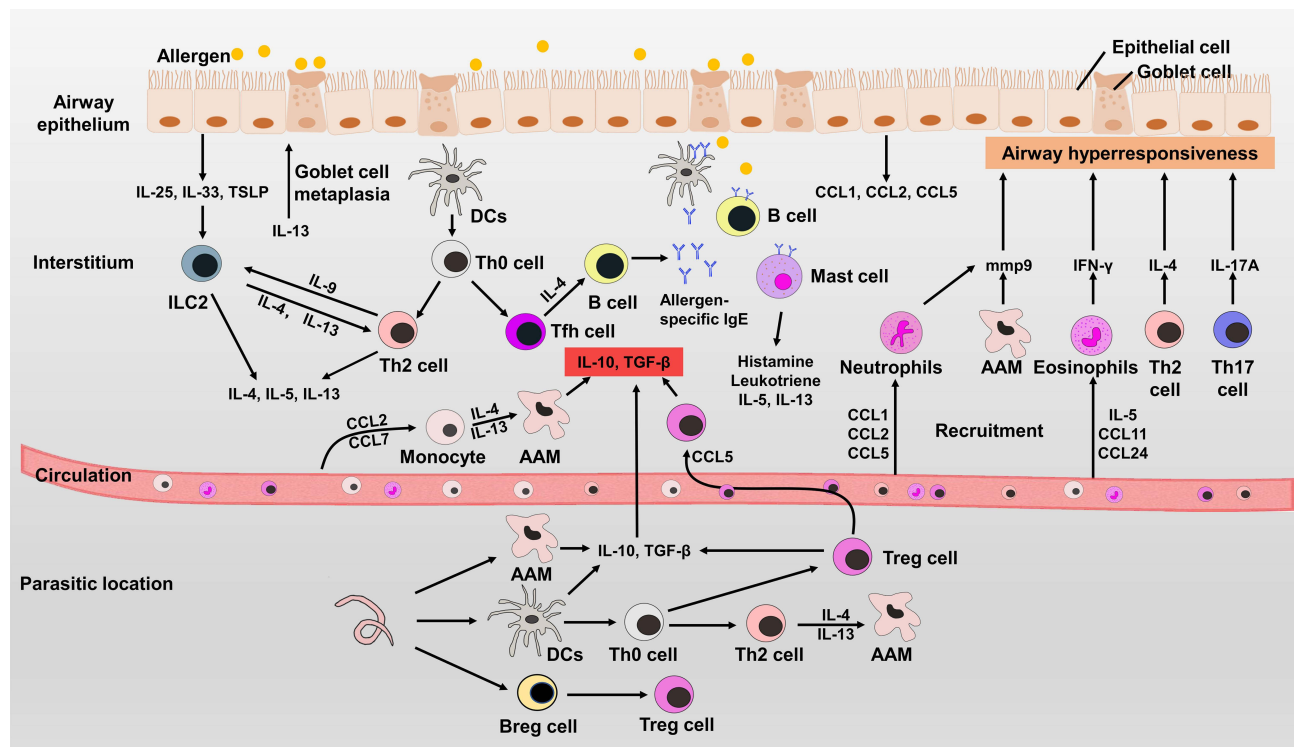


Figure 3 The pathogenesis of allergic asthma and the mechanisms of helminth therapy. When the immune system encounters allergens for the first time, airway epithelial cells activate ILC2s to induce a Th2-type immune response. Antigen presenting cells can also present allergens to Th0 cells and induce the differentiation of Th2 cells and Tfh cells. Tfh cells and IL-4 can induce B cells to produce allergen-specific IgE that binds to Fc receptors on mast cells, B cells and DCs. Eosinophils are recruited by IL-5 and release IFN- γ , which is involved in airway hyperresponsiveness. IL-17A and matrix metalloproteinase 9 also contribute to airway hyperresponsiveness. Upon subsequent exposure to allergens, immune cells can be quickly activated to cause inflammation. Helminths and helminth-derived molecules can induce the differentiation of Treg cells and anti-inflammatory cytokines in the parasitic location. Although some helminths are not exposed to lung tissue, the regulated immune cells that secrete anti-inflammatory cytokines can migrate to inflammatory tissues to suppress the inflammation in lungs.

targeting key immune effectors have been widely used in clinical applications, such as anti-IL-5 biologics and anti-IgE monoclonal antibodies.⁷⁰ However, all these therapies have drawbacks, such as side effects of glucocorticoids and impairment of the immune system caused by biological agents.^{71,72}

Advantages and Limitations of Helminth Therapy for IMIDs

As an ancient species, helminths have evolved complete mechanisms of immune evasion. The invasion of helminths causes epithelial tissue damage with the production of numerous endogenous substances.⁷³ Endogenous substances activate damage-associated molecular pattern molecules. Besides, secondary bacterial infection activates pathogen-associated molecular pattern molecules. These two processes together cause inflammation induced by the Th1-type immune response. However, ESPs released during helminth infection can induce immunosuppression and Th2-type immune response to promote tissue repair to reduce pathological damage. This immunomodulatory ability can be used to inhibit inflammation of IMIDs. Nevertheless, the abundance and composition of ESPs vary significantly at every stage of helminths development, which is consistent with the wide varieties of helminth-induced immune responses. Therefore, helminth infection is not an appropriate treatment direction due to the complex immunoregulation and safety concerns.

Helminth Therapy for IBD

At present, experimental studies have widely adopted chemical reagent-induced models of IBD in mice, such as Trinitrobenzene sulfonic acid (TNBS), dinitrobenzene sulfonic acid (DNBS), dextran sulfate sodium salt (DSS) and piroxicam. These chemical reagents can induce epithelial lesions in the colon, CD4+ T cell infiltration in the intestinal lamina propria and high levels of IFN- γ .⁷⁴ TNBS-treated mice infected with *Schistosoma* eggs could inhibit Th1-type inflammation dependent on IL-4 signaling pathway and alleviate the pathology of the colon.⁷⁵ When TNBS-treated mice

were infected with *Trichinella spiralis*, colon homogenate supernatants showed more IL-4 but less IFN- γ than control mice, which can alleviate the pathological damage caused by Th1-type inflammation in the colon.⁷⁶ The soluble molecules from the eggs of *Schistosoma mansoni* and ESPs of *Ancylostoma caninum* counteracted the detrimental effects of IFN- γ , IL-12 induced by DSS in mouse serum and significantly promoted the release of the anti-inflammatory cytokine IL-10.^{77,78} In a piroxicam-induced IL-10^{-/-} mouse model, infection with *Heligmosomoides polygyrus* promoted the production of IL-13 in the intestinal mucosa and inhibited the production of IFN- γ and IL-12 p40. Mesenteric lymph node cells in mice infected with *Heligmosomoides polygyrus* can alleviate pathological damages in the colon.⁷⁹ A clinical experiment showed that CD activity index began to decrease in partial patients when they were infected with *Necator americanus* 20 weeks later, which may be related to the increasing eosinophils in blood.¹¹ Another clinical experiment showed that symptoms were alleviated in 73% of patients after 24 weeks infection with *Trichuris suis* ova. Patients treated with immunosuppressive drugs showed a greater degree of improvement.⁸ In addition, helminth-induced Th2-type immune response can increase the production of mucus by intestinal goblet cells, which contributes to the growth of *Clostridium* bacteria but limits the growth of *Bacteroidetes*.⁸⁰ Acetate and butyrate produced by the altered gut microbiota can exert anti-inflammatory effects to protect against colitis.⁸¹ These results show that helminth therapy is a potential therapeutic direction for IBD.

Helminth Therapy for Allergic Asthma

Helminth infection can reduce the morbidity of allergic asthma. Helminth infection is often accompanied by high levels of IgE antibodies, and most antibodies are not allergen-specific and enhances tolerance of mast cells to allergens.⁸² In addition, in asymptomatic people with helminth infection, high levels of IgG4 can also inhibit IgE-mediated degranulation of effector cells.⁸³ Many studies have confirmed that infection with *Schistosoma mansoni*, *Heligmosomoides polygyrus*, and *Trichinella* can alleviate pathological changes caused by allergens, such as airway inflammation and airway hyperresponsiveness.^{84–86} In mice infected with *Schistosoma japonicum*, DCs can release a large amount of IL-10 that is required for tolerance to alleviate allergic asthma symptoms. When those DCs are adoptively transferred into recipients, the number of CD4⁺CD25⁺Foxp3⁺ T cells and CD4⁺CD25⁺IL-10⁺ T cells are increasing and allergic inflammation in the airway is suppressed.⁸⁷ IL-4, IL-13 and IL-10 can induce alternative activation of macrophages to release a large quantity of anti-inflammatory cytokines to limit the inflammatory response. In addition, *Heligmosomoides polygyrus* or *Trichinella spiralis* can inhibit the OVA-induced allergic inflammation through Treg cells.^{88,89} Unexpectedly, there were reports that helminth therapy had no obvious effect in the clinical course of allergic asthma.⁹ Infection with *Ascaris lumbricoides* increases the risk of non-allergic asthma, therefore it is necessary to evaluate the effect of the helminth loads and helminth species on the development of asthma.⁹⁰ This may be because the different compositions of ESPs at various stages of helminth infection exerted variable immune effects. In addition, another possible explanation is that helminth infection must occur prior to the development of allergic asthma, to prevent its development rather than treat it.

The Immunoregulatory Mechanisms of Identified Helminth-Derived Molecules

Helminth derivative molecules identified so far can be divided into proteins, carbohydrates, lipids, RNA and small organic molecules based on their molecular properties (Table 1). The interaction between identified helminth-derived molecules and target cells generates more stable immune effects than that between ESPs and target cells. The immune responses induced by helminth-derived molecules can be divided into two types: Th2-type immune response and immunosuppression (Figure 4). In mouse models of IBD, these molecules can alleviate the pathological damage in colon, such as the infiltration of inflammatory cells, hyperemia, ulcers, and length of colon. In mouse models of allergic asthma, these molecules can inhibit allergen-induced inflammation in lung, including the infiltration of inflammatory cells around the airway and blood vessels, alveolar wall integrity, the number of eosinophils and OVA-specific IgE.

Table 1 Classification of Identified Helminth-Derived Molecules

Molecule	Helminth	Source	Immune Cells	Immune Response	Model	Ref
Protein	IPSE/alpha-1	<i>Schistosoma mansoni</i> eggs	Basophils	Th2 immune response	-	[96]
	Thioredoxin peroxidase-2	<i>Trichinella spiralis</i>	Macrophage→ Th2 cells	Th2 immune response	-	[97]
	Omega-1	<i>Schistosoma mansoni</i> eggs	DCs→ Th2 cells	Th2 immune response	-	[102]
	Cystatin	<i>Acanthocheilonema viteae</i>	Macrophages	Immunosuppressive response	Pollen-induced allergic diseases and DSS-induced colitis	[114,115]
	Helminth defense molecules	<i>Fasciola hepatica</i>	Macrophages	Immunosuppressive response	HDM-induced model of asthma	[112,145]
	Peroxiredoxin	<i>Schistosoma mansoni</i> and <i>Fasciola hepatica</i>	Macrophages→ Th2 cells	Th2 immune response	-	[99,100]
	Serine protease	<i>Trichinella spiralis</i>	Macrophage	Immunosuppressive response	DSS- induced colitis	[110]
	Cystatin	<i>Trichinella spiralis</i>	Th2 cells and Treg cells	Inhibiting the Th1 response	TNBS- induced colitis	[98]
	Hemozoin	<i>Opisthorchis felineus</i>	Human DCs	Immunosuppressive response	-	[123]
	Cystatin	<i>Ascaris lumbricoides</i>	Treg cells	Immunosuppressive response	<i>Blomia tropicalis</i> -induced asthma and DSS-induced colitis	[124,146]
	Recombinant Sj16	<i>Schistosoma japonicum</i>	Treg cells	Immunosuppressive response	DSS- induced colitis	[140]
	SJMHE1 Peptide	<i>Schistosoma japonicum</i>	Treg cells	Immunosuppressive response	OVA model of asthma and DSS- induced colitis	[137,138]
	TGF-β mimic	<i>Heligmosomoides polygyrus</i>	CD4 ⁺ T cells	Immunosuppressive response	Allograft rejection and DSS-induced colitis	[128,129]
	Cathepsin B1 protease	<i>Schistosoma mansoni</i>	Macrophages	Inhibiting the TH1 response	-	[111]
Cystatin	<i>Schistosoma japonicum</i>	Treg cells	Immunosuppressive response	TNBS- induced colitis	[117]	

(Continued)

Table I (Continued).

Molecule	Helminth	Source	Immune Cells	Immune Response	Model	Ref
	FheCLI protease	<i>Fasciola hepatica</i>	Macrophages	Inhibiting the TH1 response	-	[111]
	FhI2	<i>Fasciola hepatica</i>	PBMCs	Immunosuppressive response	-	[106,107]
	Antigen B	<i>Echinococcus granulosus</i>	Monocyte precursors	Immunosuppressive response	-	[121]
	Antigen B	<i>Echinococcus granulosus</i>	iDCs	Th2 immune response	-	[121]
	Anti-inflammatory protein-2	<i>Ancylostoma caninum</i>	CD103 ⁺ DCs→Treg cells	Immunosuppressive response	OVA-induced allergic	[126]
	Cystatin	<i>Brugia malayi</i>	Peritoneal macrophage	Immunosuppressive response	DSS-induced colitis	[116]
	P43	<i>Trichuris muris</i>	-	Inhibiting IL-13-dependent immune responses	-	[139]
	Sm200 and SmKI-I	<i>Schistosoma mansoni</i>	Monocytes	Immunosuppressive response	Blomia tropicalis-induced models of asthma	[108]
	HpBARI	<i>Heligmosomoides polygyrus</i>	ST2-expressing cells	Immunosuppressive response	Alternaria-OVA induced asthma	[136]
	Serine protease inhibitor	<i>Trichinella spiralis</i>	Macrophages	Immunosuppressive response	TNBS- induced colitis	[109]
	Enzymatically active chitinase	<i>Trichuris suis</i>	Macrophages	Inhibiting the Th2 response	OVA induced asthma	[141]
	HpARI	<i>Heligmosomoides polygyrus</i>	Necrotic cells	Inhibiting the Th2 response	Alternaria-induced allergic	[135]
Carbohydrate	Lacto-N-fucopentaose III	<i>Schistosoma mansoni</i>	DCs→Th2 cells	Th2 immune response	-	[101]
	Lewisx	<i>Schistosoma mansoni</i> eggs	DCs	Th2 immune response	-	[104,105]
Lipid	Lysophosphatidylserine	<i>Schistosoma mansoni</i> eggs	DCs→Treg cells	Immunosuppressive response	-	[122]
RNA	miRNAs	Exosomes of <i>Heligmosomoides polygyrus</i>	-	Immunosuppressive response	Alternaria-induced allergy	[144]
	Double-stranded-RNAs	<i>Schistosoma mansoni</i> eggs	DCs	Th1 immune response	-	[147]
Small organic molecules	Succinic acid	<i>Nippostrongylus brasiliensis</i>	Intestinal tuft cells →ILC2	Th2 immune response	-	[95]

Note: - No studies have been reported.

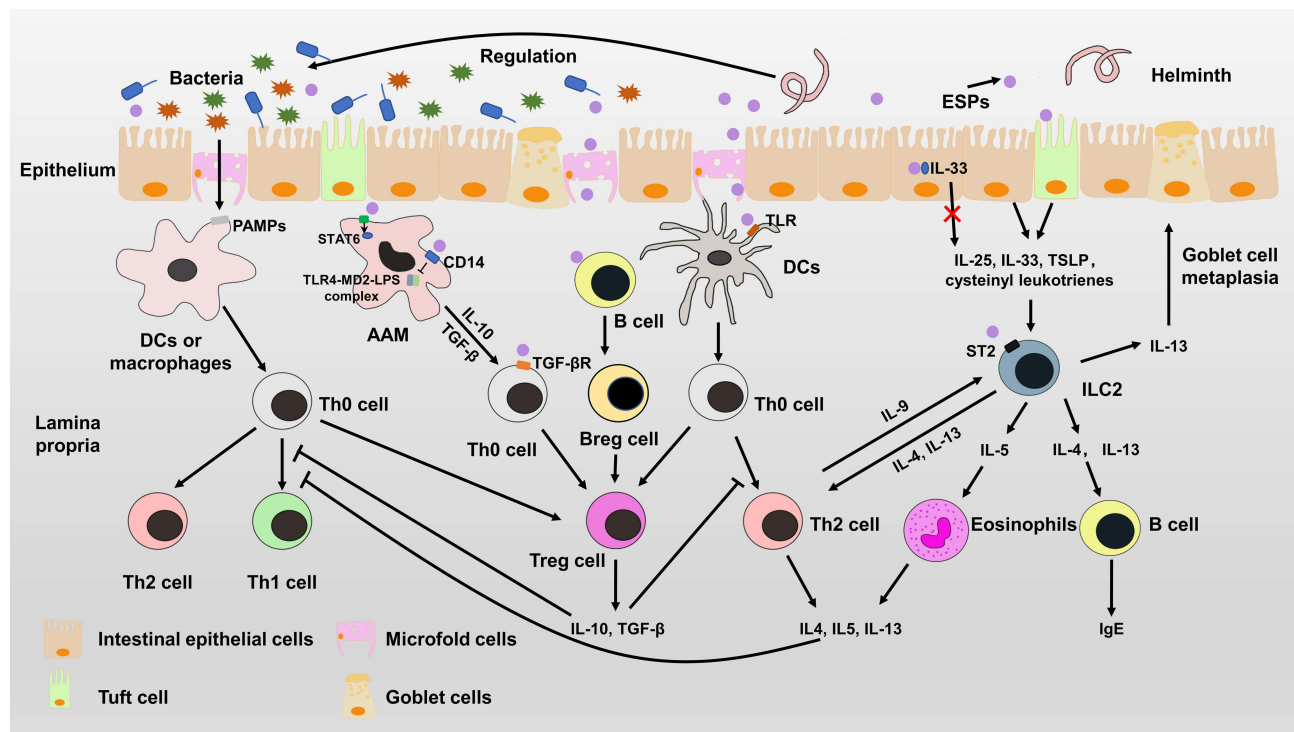


Figure 4 Immunomodulatory mechanisms of helminths. Helminths can induce intestinal epithelial cells to produce IL-25, IL-33 and TSLP, which can stimulate the proliferation of ILC2s. Activated ILC2s can secrete IL-4, IL-5 and IL-13 to expand Th2-type immune responses, which can suppress the Th1-type immune response. HPAR1 of *Heligmosomoides polygyrus* can bind to IL-33 and restrict it in necrotic cells. ESPs can induce the differentiation of Treg cells by interacting with antigen presenting cells or Th0 cells. ESPs not only induces alternative activation of macrophages (AAM) by phosphorylation of STAT6, but also inhibits the pro-inflammatory response mediated by TLR4-MD2-LPS complex. ESPs can affect the function of antigen-presenting cells to induce differentiation of Treg cells or Th2 cells. Treg cells, Breg cells and alternatively activated macrophages can secrete anti-inflammatory cytokines to suppress the Th1-type immune response and Th2-type immune response. In addition, helminths can regulate the diversity and composition of gut microbiota to alter the immune system.

Th2-Type Immune Response Induced by Identified Helminth-Derived Molecules

The initiation and development of the Th2-type immune response induced by helminths is a complex process involving multiple cells, such as mucosal epithelial cells, ILC2s and CD4⁺ T cells. Intestinal tuft cells can be stimulated by ESPs or extracts of *Trichinella spiralis* to produce IL-25.⁹¹ IL-25 can stimulate the proliferation of ILC2s in the intestinal mucosa, which releases IL-4, IL-13 and IL-5 with an increase in the number of tuft cells through positive feedback.⁹² Furthermore, intestinal tuft cells secrete cysteinyl leukotrienes during helminth infection, which cooperate with IL-25 to activate ILC2s and expand Th2-type immune response.⁹³ Activation of GATA3, STAT6 and other transcription factors related to Th2 differentiation can inhibit Th1 or Th17 differentiation as well as the production of cytokines that drive IBD development, such as IFN- γ , IL-1 β , TNF- α and IL-17.⁹⁴

It has been reported that *Nippostrongylus brasiliensis* can secrete succinic acid, which stimulates the intestinal tuft cell-ILC2 circuit and initiates the early Th2-type immune response.⁹⁵ The glycoprotein IPSE/alpha-1 in *Schistosoma mansoni* eggs depends on antigen-nonspecific IgE antibodies to induce the production of IL-4 in liver basophils, which also contribute to the early initiation of the Th2-type immune response.⁹⁶ Thioredoxin peroxidase-2 of *Trichinella spiralis* can induce alternative activation of macrophages and differentiation of naïve T cells into Th2 cells in vitro.⁹⁷ Cystatin of *Trichinella spiralis* can inhibit the Th1-type immune response by inducing production of IL-4 and Treg cells in TNBS-induced colitis.⁹⁸ Peroxiredoxin secreted by *Schistosoma mansoni* or *Fasciola hepatica* can induce the alternative activation of macrophages and the activation of naïve T cells to secrete IL-4, IL-5 and IL-13.^{99,100} Lacton-fucopentaose III of *Schistosoma mansoni* can induce the maturation of DCs via ERK/MAPK pathway and promote the differentiation of Th2 cells.¹⁰¹ Omega-1, a glycoprotein secreted by *Schistosoma mansoni* eggs, can activate DCs to induce naïve CD4⁺ T cells to differentiate toward Th2 cells in vitro independent of the IL-4 receptor signaling

pathway.¹⁰² Furthermore, C-type lectins are important transmembrane pattern recognition receptors, including C-type lectin dendritic cell-specific ICAM-3-grabbing nonintegrin (DC-sign), macrophage galactose-type lectin and mannose receptor.¹⁰³ There are many glycoconjugates in *Schistosoma mansoni* eggs, in which the carbohydrate antigen Lewisx can be combined with the DC-sign on the surface of DCs from human peripheral blood mononuclear cells.¹⁰⁴ The interaction between Lewisx and DC-sign can activate the ERK signaling pathway and contribute to DC maturation, which can induce a Th2-type immune response.¹⁰⁵

Immunosuppressive Response Induced by Identified Helminth-Derived Molecules

The immunosuppressive microenvironment induced by helminths can not only facilitate helminths to escape the host's immune response but also prevent the body from severe damage caused by excessive inflammation. Macrophages, DCs, Treg cells, Breg cells and anti-inflammatory cytokines contribute to the formation of an immunosuppressive microenvironment.

Alternatively activated macrophages, members of the innate immune cell family, play an important role in suppressing the immune response. A fatty acid binding protein (Fh12) secreted by *Fasciola hepatica* induced human peripheral blood mononuclear cells (PBMCs) to express arginase, CHI3L1 and alternatively activated macrophages released anti-inflammatory cytokines IL-10.¹⁰⁶ On the other hand, Fh12 can also target the CD14 receptor on macrophages to prevent the formation of the TLR4-MD2-LPS complex in intracellular inflammatory transduction pathways, which can directly reduce the level of pro-inflammatory cytokines.¹⁰⁷ Sm200 and SmKI-1 of *Schistosoma mansoni* can induce human PBMCs to secrete IL-10 and inhibit the production of inflammatory cytokines in *Blomia tropicalis*-induced models of asthma.¹⁰⁸ The serine protease inhibitor secreted by *Trichinella spiralis* can also induce alternative activation of peritoneal macrophages and bone marrow-derived macrophages in mice, and these alternatively activated macrophages can alleviate pathological changes in the colon caused by TNBS.¹⁰⁹ Similarly, serine protease from *Trichinella spiralis* can induce macrophages to produce IL-10 to inhibit colitis caused by DSS.¹¹⁰ The Fhce11 protease of *Fasciola hepatica* and cathepsin B1 protease of *Schistosoma mansoni*, members of the cysteine protease family, can degrade endosomal TLR3 receptors of macrophages and inhibit TRIF-dependent signaling pathways to directly suppress the development of the Th1-type immune response.¹¹¹ In addition, the molecular structure and function of helminth defense molecules in *Fasciola hepatica* are similar to mammalian antimicrobial peptide host defense peptide. Helminth defense molecules can hinder the antigenic processing and antigen presentation of macrophages to weaken the host immune response.¹¹² Cystatin secreted by *Acanthocheilonema viteae* can induce macrophages to produce a large amount of IL-10, which alleviates pathological damage in the OVA-induced allergic asthma and DSS-induced colitis models in mice.^{113,114} Further studies found that cystatin showed great therapeutic effects in both pollen-sensitized mice and PBMCs from patients with pollen allergies in vitro, which reveals its potential in the treatment of pollen-induced allergic diseases.¹¹⁵ Cystatin of *Brugia malayi* or *Schistosoma japonicum* can induce alternative activation of peritoneal macrophages and Treg cells to reduce the production of pro-inflammatory cytokines in colon tissue.^{116–118}

DCs, professional antigen-presenting cells, are the key component of the immune system connecting innate immunity and adaptive immunity. After uptake and presentation of antigens in peripheral tissues, DCs migrate to lymph nodes to drive the differentiation of naïve CD4⁺ T cells. Helminths and helminth-derived molecules can regulate the phenotype and function of DCs, including surface markers (MHC class II molecules, CD80, CD86)¹¹⁹ and cytokines (IL-12, TGF- β , IL-10).¹²⁰ It has been reported that antigen B secreted by *Echinococcus granulosus* can inhibit monocyte precursors from differentiating into immature DCs to weaken the host's immune response.¹²¹ Lysophosphatidylserine of *Schistosoma mansoni* eggs, which contains specific acyl chains, can change the function of DCs through TLR2 receptors to induce a large number of IL-10-secreting Treg cells.¹²² In addition, hemozoin of *Opisthorchis felinus* and cystatin of *Ascaris lumbricoides* can induce the secretion of IL-10 in human DCs.^{123,124}

Treg cells play an important role in maintaining the body's immune tolerance due to secrete the anti-inflammatory cytokines IL-10 and TGF- β . The number of Treg cells usually increases during helminth infection.¹²⁵ It has been reported that helminths can induce the differentiation of Treg cells through two pathways, one indirect pathway of antigen-presenting cells and the other direct pathway of helminth-derived molecules. Anti-inflammatory protein-2 of *Ancylostoma caninum* could induce the generation of Treg cells by CD103⁺ DCs to prevent or treat asthma symptoms in a mouse model.¹²⁶ The differentiation of Treg cells can be directly induced by helminths that have molecules to

replicate the biological activity or function of the transforming growth factor superfamily. For example, an activin/TGF-like molecule of *Fasciola hepatica* has a high affinity for the TGF-RII receptor in bovines.¹²⁷ A *Heligmosomoides polygyrus* TGF- β mimic can directly bind to TGF- β receptors in humans and mice, and induce differentiation of Treg cells, which alleviates pathological damage in the allograft rejection and DSS-induced colitis models in mice.^{128,129} Cell therapy using Treg cells to treat allergic asthma has been reported. Adoptive transfer of Treg cells from *Trichinella spiralis*-infected mice to OVA-treated mice showed significant anti-inflammatory effects.⁸⁹

Breg cells is a subset of B cells that can secrete IL-10 and TGF- β to regulate the immune response. Multiple studies have shown that infection with helminths can be accompanied by the proliferation of Breg cells.^{130–132} IL-10⁺ Breg cells not only induce expansion of IL-10⁺ Treg cells and maintenance of FoxP3⁺ Treg cells, but also inhibit inflammatory response in OVA model of asthma.¹³³ IPSE/alpha-1 of *Schistosoma mansoni* can induce Breg cells in mice and humans in vitro.¹³⁴

In addition, HPARI secreted by *Heligmosomoides polygyrus* can bind to IL-33 and restrict it in necrotic cells, which directly weakens allergic airway inflammation.¹³⁵ HpBARI of *Heligmosomoides polygyrus* can bind murine ST2 to prevent IL-33-ST2 interactions, which can suppress BAL and lung eosinophilia in *Alternaria*-OVA model of asthma.¹³⁶ SJMHE1 Peptide of *Schistosoma japonicum* can induce proliferation of Treg cells to suppress inflammatory response in OVA-induced model of asthma and DSS-induced model of colitis.^{137,138} P43 of *Trichuris muris* can inhibit IL-13-dependent immune responses by interacting with IL-13.¹³⁹ Recombinant Sj16 of *Schistosoma japonicum* can inhibit DSS-induced inflammation by inhibiting the PPAR- α signaling pathway.¹⁴⁰ The enzymatically active chitinase of *Trichuris suis* is similar to mouse chitinase, which can inhibit the recruitment of eosinophils in the lungs and airway hyperresponsiveness.¹⁴¹ In recent years, exosomes released by helminths, including miRNAs, RNA and proteins, represent a novel immunomodulatory mechanism.¹⁴² Exosomes released by *Schistosoma mansoni* can be internalized by DCs via DC-SIGN, and then augment DCs immune responses.¹⁴³ *Heligmosomoides polygyrus*-derived miRNAs and Y RNAs can be internalized by mouse cells via exosomes and inhibit the allergic reaction, which provides a new pathway to regulate the host's immune response.¹⁴⁴

Application of Helminth-Derived Molecules

How to appropriately harness immunoregulation by helminth-derived molecules for the treatment of epidemic IMIDs is still a difficult problem to be solved. Helminth-derived molecules are a class of heterologous antigens, which can not only regulate the immune response, but also interact with the immune system to produce side effects by virtue of their antigenicity. Therefore, it is necessary to assess the interaction between the antigen and the immune system to avoid serious side effects. In addition, with the aggravation of the disease, the immune imbalance is also constantly changing. For example, allergic asthma is triggered by the Th2-type immune response. When the symptoms are aggravated, Th1-type immune responses and Th17-type immune responses also contribute to serious pathological damage to tissues and organs. Therefore, it is necessary to assess immune indexes, such as serum cytokines, tissue cytokines, and clinical symptoms. The well-timed application of helminth-derived molecules in response to the changes in immune indexes may be a new direction of helminth therapy in the future.

Conclusion

IBD and allergic asthma are a group of heterogeneous diseases caused by immune imbalance. Helminths or helminth-derived molecules have potential therapeutic value due to the immunomodulatory ability. It is important that identified helminth-derived molecules can induce more stable and controlled immune response to correct the immune balance, including Th2-type immune response and immunosuppressive response. To date, many helminth-derived molecules have shown obvious therapeutic effects in animal models, which provides data to support clinical experiments. The future of helminth-derived molecules in the treatment of IMIDs looks bright.

Abbreviations

IMIDs, immune-mediated inflammatory diseases; IBD, inflammatory bowel disease; Th1 cells, T helper type 1 cells; Th2 cells, T helper type 2 cells; Th17 cells, T helper type 17 cells; Tfh cells, T follicular helper cells; Breg cells, B regulatory cells; Treg cells, T regulatory cells; ESPs, excretory-secretory products; Nod2, nucleotide-binding oligomerization domain 2; CARD9, caspase recruitment domain family member 9; IL-23R, interleukin-23 receptor; PTPN2, protein

tyrosine phosphatase non-receptor type 2; NF- κ B, the nuclear factor kappa-light-chain-enhancer of activated B cells; OX40L, tumor necrosis factor receptor superfamily member 4 ligand; TSLPR, thymic stromal lymphopoietin receptor; IL-12, interleukin 12; IFN- γ , interferon-gamma; TNF, tumor necrosis factor; DCs, dendritic cells; OVA, ovalbumin; TNBS, trinitrobenzene sulfonic acid; DNBS, dinitrobenzene sulfonic acid; DSS, dextran sulfate sodium salt; ILC2s, group 2 innate lymphoid cells; DC-sign, C-type lectin dendritic cell-specific ICAM-3-grabbing nonintegrin; PBMCs, peripheral blood mononuclear cells.

Consent for Publication

All the authors read the manuscript carefully and gave their consent for publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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