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Parasite-Derived Proteins Inhibit Allergic Specific Th2 Response

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1. Introduction

The prevalence of allergic disease and asthma has increased dramatically during the last 30-40 years. Atopic disorders comprise a range of allergic diseases including asthma, anaphylaxis, allergic rhinitis, and atopic dermatitis; these diseases have been seen a precipitous increase in the last four decades. Intriguingly, geographic regions with a high helminth infection burden tend to have a lower incidence of asthma (1). The effects of parasitic infections on the incidence of allergic disease has been receiving increased attention from researchers of late, with studies conducted in Ethiopia and Gabon demonstrating that parasitic infestation is associated with reduced atopic sensitization and dust mite skin test sensitivity (2-4). Children treated repeatedly for *Trichuris trichiura* and *Ascaris lumbricoides* exhibited increased dust-mite skin responses as compared with children that had not been treated for asymptomatic soil-associated helminthic infections (5). Several molecules from helminthes induce pronounced Th2 responses in a manner similar to that seen in cases of full-blown parasitic infection. Excretory-secretory (ES) glycoproteins isolated from the rodent nematode, *Nippostrongylus brasiliensis*, have been shown to evidence Th2-promoting activity on dendrite cells, however, the exact nature of the molecules involved in *N. brasiliensis* ES proteins remain to be clearly elucidated. This activity is heat-labile and protease-sensitive, thereby suggesting that the active component is proteinaceous in nature (6). Also, in schistosomiasis, the soluble extract of *Schistosoma mansoni* eggs (SEA) was shown to induce SEA-specific Th2 responses when injected into mice (7), and SEA was also demonstrated to condition human dendrite cells (DCs) to polarize Th response in a Th2 direction *in vitro* (8). When exposed to Th2 cytokines, these molecules can also activate host CD4+CD25+Foxp3⁺ T cells (regulatory T cells, T_{reg}) which subsequently release IL-10 and tumor growth factor β (TGF- β), which may be functionally involved in the suppression of the level of Th2 cytokines IL-4, IL-5, and IL-13. These parasites can establish a chronic infection, which highlights important issues (9), in that the presence of these metabolically active pathogens indicates that the immune system is being relentlessly challenged with foreign antigens; this continuous immune reactivity, if uncontrolled, could eventuate severe pathology. In addition, these pathogens may have developed evolutionary strategies by which they may evade the immune system for long-term survival in an immunocompetent host (10).

In order to ascertain, then, whether parasitic infections can reduce allergic reactions and whether their infective stage influences the immune system of the host, we have mimicked

chronic infection conditions in our experiment via treatment with parasite-derived proteins for one month prior to allergen treatment. We attempted to determine whether or not these parasite-derived proteins suppressed allergy-specific Th2 reactions.

2. Immunization of parasite derived proteins inhibits allergic specific Th2 response

Long-lived parasites are highly accomplished practitioners of immune evasion and manipulation, utilizing strategies honed during their long co-evolutionary interaction with the mammalian immune system (10, 11). How is the host affected by these parasitic strategies? Although many hypotheses have been advanced, until the present time there has been little evidence to support these theories. Th2 host response as the result of parasitic infection was apparent, although this is the result of parasitic strategies to escape from the host immune system or the result of a human protective system associated with parasitic infection. Additionally, we could readily detect Th2 responses in allergic patients. Thus, until now, there has been considerable controversy regarding the relationship between parasites and allergic reactions; particularly, whether parasites can evoke some allergic-specific response or can reduce allergen-specific responses (12-14).

We have attempted to determine whether parasite-derived proteins can accelerate or reduce asthma symptoms in accordance with the treatment period (15). We have mimicked chronic infection conditions in our experiment via treatment with parasite (*Toxascaris leonina* adult worm)-derived proteins [ES protein (TI-ES) and total proteins (TI-TP)] for one month prior to the administration of allergen treatment. We mentioned this group as Immunized group; also Challenged with OVA group were mentioned which were administrated TI-ES and TI-TP at the same challenge days in airway allergic reaction procedure. As results, the immunized TI-ES and TI-TP groups evidenced a thinning of the bronchial epithelial and muscle layer, a disruption and shedding of the epithelial cells, a reduction in the number of goblet cells as compared to the OVA-challenged groups (Fig. 1). When the airway functions of these mice were monitored, we detected that the Penh values by methacholine treatment (from 2.5 mg/ml to 25 mg/ml) were significantly higher in the OVA-inhalation mice than those of TI-TP and TI-ES immunized group (Fig. 2A). The numbers of most inflammatory cells (macrophages, eosinophils, lymphocytes and neutrophils) in the BAL fluids were significantly increased in all of the OVA-challenged groups (Fig. 2B & 2C). The administration of TI-ES and TI-TP prior to asthma induction (immunized group) and the TI-ES and TI-TP with OVA challenge (challenged with OVA groups) evidenced inhibited recruitment of inflammatory cells into the airway (Fig. 2B & 2C). In particular, neutrophils and lymphocytes were significantly reduced by the parasite proteins at any administration time (p value < 0.05). The total number of eosinophils of the immunized and OVA-challenged group were slightly reduced; however, this reduction was not statistically significant (P value > 0.05).

Although some articles have previously asserted that nematodes can induce allergic reactions during their larval migration period (16, 17), many articles have reported that parasitic infections, particularly chronic parasitism, help to reduce host allergic reactions and to modulate host immune responses (14, 18, 19). We have determined that immunization with *T. leonina* adult worm ES and total proteins induces a down-regulation of asthma-associated cytokines, including IL-4 and IL-5, in the bronchial alveolar lavage (BAL) fluids (Fig. 3). However, these proteins did not significantly influence allergic airway

inflammation response as the result of simultaneous OVA challenge, as compared to the immunization method. In particular, the TI-ES treatment with OVA challenge group exhibited more severe lung inflammation than was observed in the immunized group. We believe that certain allergens or proteases might be included in the ES proteins, and parasitic proteases have also been identified as allergens (20-23). Sokol *et al.* previously suggested that a host-derived sensor of proteolytic activity might involve cleavage via parasite or allergic proteases. This sensor, once cleaved, activates the cells of the innate immune system to induce a Th2 response (13).

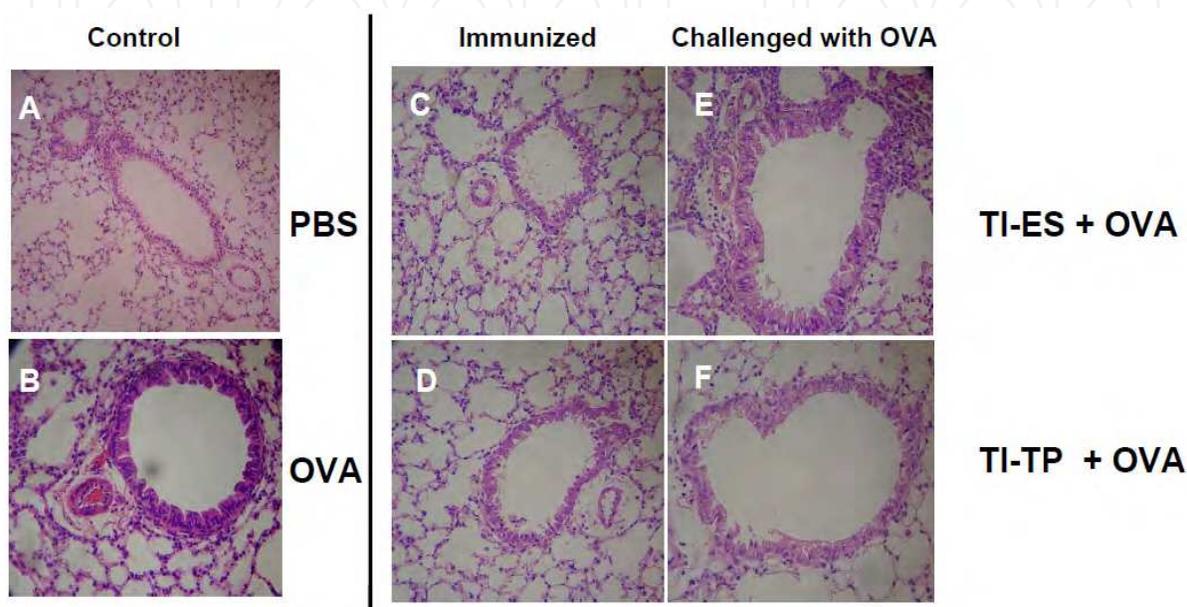


Fig. 1. Histological findings of airway inflammation in ova-challenged control mice and the effect of immunization and challenge with OVA groups. Female and 6 weeks of age mice were induced airway allergic reaction using intraperitoneally (I.P.) sensitizing with 75 ug of ovalbumin (OVA, Sigma, Grade V) and 2 mg of aluminium hydroxide gel, on days 0 and 7. One week after the final sensitization, the mice were intra nasal challenged with 50 ug of OVA on 4 consecutive days (days 13, 14, 19, and 20). We mentioned “Immunized group” that were injected by I.P. with 100 ul of 10 ug/ml *Toxascaris leonina* excretory-secretory (TI-ES) and *T. leonina* total protein (TI-TP), respectively, on 7 and 14 days before airway allergic reaction procedure. Also “Challenged with OVA” group were mentioned which were injected by I.P. with 100 ul of 10 ug/ml of TI-ES and TI-TP respectively at the same challenge days in airway allergic reaction procedure. The negative control group was challenged with PBS (I.N.) on the same challenge day in airway allergic reaction procedure. A; PBS-treated, B-F; OVA+ alum-treated (induced asthma), (C) immunized TI-ES protein, (D) immunized TI-TP, (E) TI-ES protein treatment with OVA challenge, (F) TI-TP protein with OVA challenge.

IL-4 has been demonstrated to regulate isotype class switching in B cells to IgE synthesis, and IL-5 stimulates eosinophil growth, activates these cells, and prolongs eosinophil survival. *T. leonina*-derived proteins could inhibit increases in the levels of IL-4 and IL-5 from OVA challenge. In particular, the level of IL-4 in the BAL fluid in the immunized group was almost half of that observed in the OVA-only challenge group. This result was consistent with the results regarding the IgE concentration in the blood (15). Although levels of the IL-5 cytokine of *T. leonina* ES and total protein-immunized mice were lower than those observed in asthma

control mice, this effect was not remarkable. Also, the total number of eosinophils was not substantially reduced as the result of immunization. Eosinophils and IgE proved vitally important in allergy-induced Th2 response; additionally, the elevation of the numbers of these cells and IgE levels were identified as specific responses to parasite infection and this response was shown to be elicited only by treatment with parasite total proteins (24, 25).

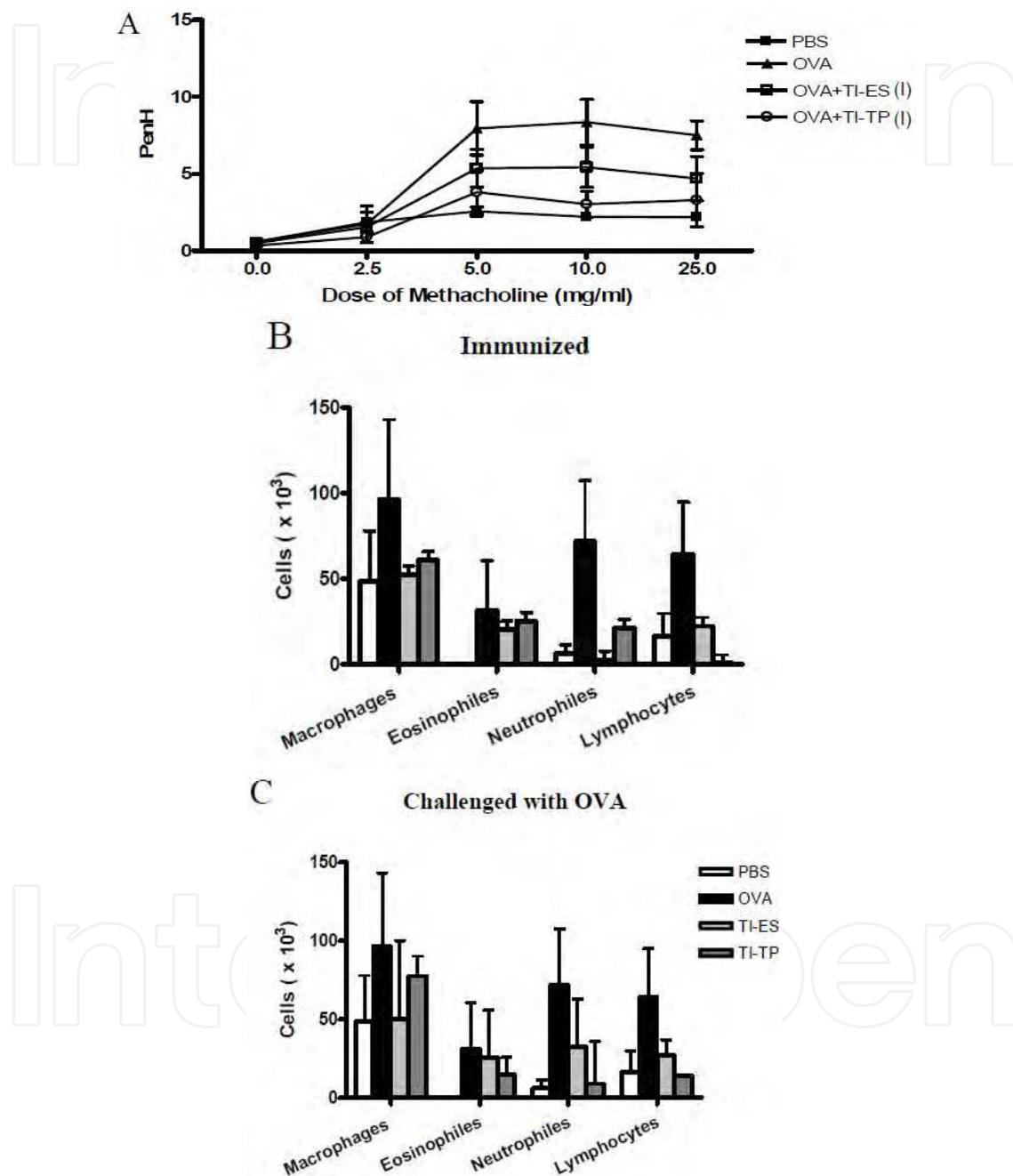


Fig. 2. Airway hyperresponsiveness measurements and comparison of differential cell counts obtained via airway inflammation in ova-sensitized PBS mice and the effects in immunized and OVA-challenged groups. Total protein of *T. leonina* immunization group [TI-TP (I)] has lower penh value than those of OVA challenge group (A). The numbers of inflammatory cells were significantly lower in the parasite-derived protein-treated mice (B & C). The data were expressed as the means \pm SD of individual mice.

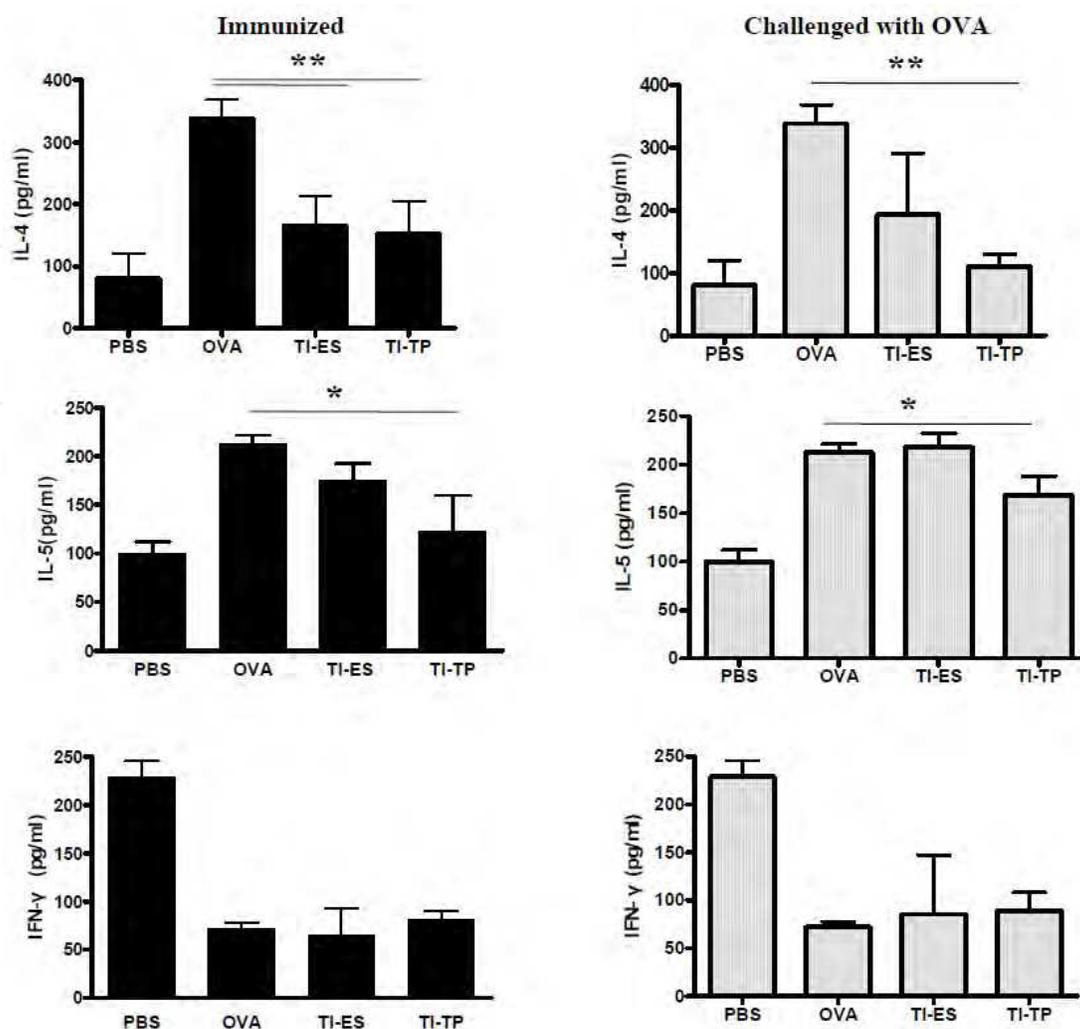


Fig. 3. Th1 and Th2 cytokines levels in the BAL fluids of TI-ES and TI-TP treated mice. The levels of all Th2 cytokines of the immunized group were contrasted with those of the OVA-challenged control mice. The data were expressed as the means \pm SD of individual mice (* ; p value <0.05, **; p value <0.01).

How does helminth infection protect against allergy? Many hypotheses have been advanced thus far regarding this theme. One of these hypotheses is that non-specific IgE generated as the result of helminthic infection may inhibit allergen-specific IgE binding sites on mast cells or basophils. Although Jarrett suggested in 1980 that parasite-induced 'nonspecific' IgE does not protect against host allergic reactions (26). However, other scientists have suggested that nonspecific IgE can modulate host immune responses, as in the case of insulin-dependent diabetes, as well as Th2 response by allergens (25, 27-29). The other hypothesis states that helminth parasites stimulate the production of immunoregulatory mediators, which are likely to perform a function in the maintenance of the chronicity of infection, with no marked induction of pathology. In particular, elevated IL-10 levels have been associated previously with protection against allergic diseases in helminth-infected African children (4). Helminth infections can induce T_{reg} cells from hosts, and these cells secrete IL-10 and suppress the proliferation of other CD4⁺ T cells (30-32). We also found that parasite proteins could also induce the IL-10 cytokine, particularly in the TI-TP immunized group (Fig. 4).

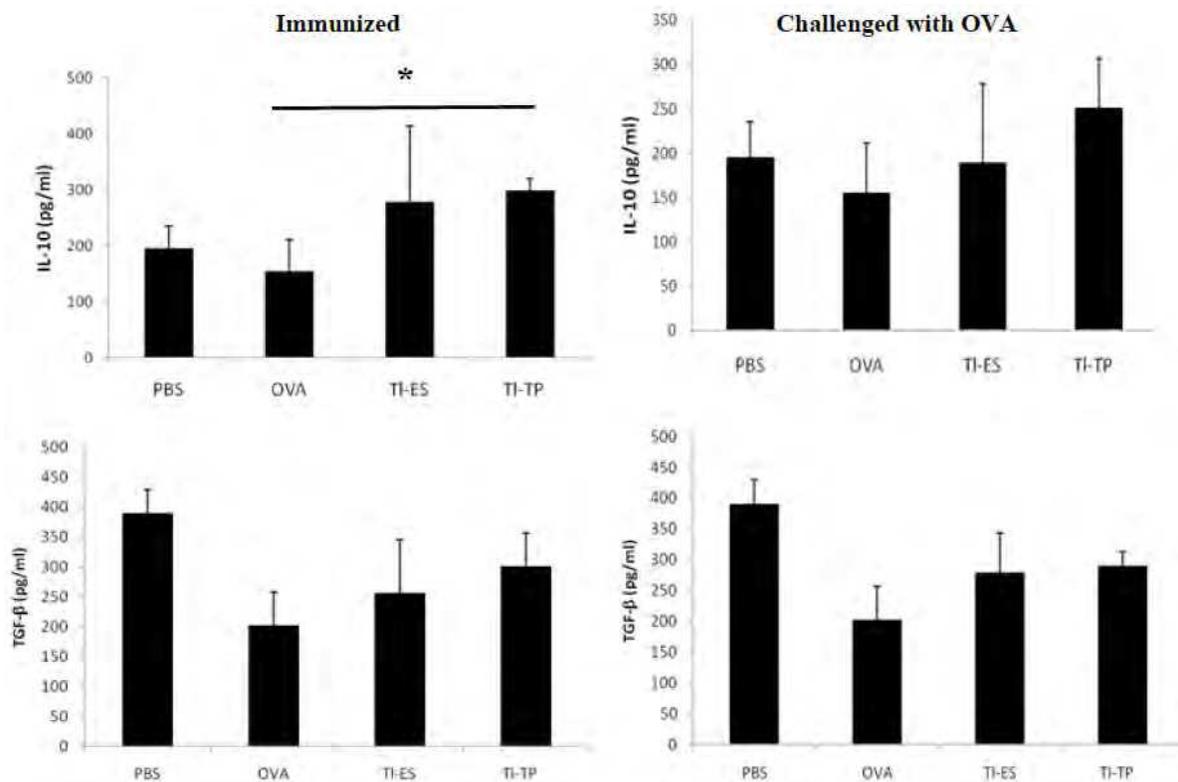


Fig. 4. T_{reg} cell related cytokines levels in the BAL fluids of TI-ES and TI-TP treated mice. The data were expressed as the means \pm SD of individual mice (* ; p value <0.05, **; p value <0.01).

Finally, the data presented herein demonstrate that *T. leonina*-derived proteins may perform a crucial function in resistance against Th2 immune responses. We suggested that this inhibition may be related to the IL-10 cytokine, which was induced by parasite proteins. Further steps are currently being taken in an effort to gain a greater understanding of the molecular basis of immune evasion by nematodes. Thus, we are attempting to gain new insights into the immune regulation strategies of nematodes, and the growing number of new strategies employed by parasites to exert their marked down-regulatory effects.

3. Macrophage migration inhibitory factor homologues of parasite suppress Th2 response in allergic airway inflammation model via T_{reg} cell recruitment

A number of parasite-derived proteins, glycoconjugates, and small lipid moieties have been demonstrated to perform known or hypothesized functions in immune interference. Other researchers have already isolated several other immune downregulatory molecules from parasites, and these molecules have been identified as mammal cytokine homologues, protease inhibitors, abundant larval transcript antigens, glyco-networks, and venom allergen-like proteins (33-39). The cytokine network is a crucial component of host defense against pathogens. It is not, therefore, surprising to find that one of the immune evasion strategies utilized by infectious organisms is the generation of mammalian cytokine homologues, including TGF- β and the macrophage migration inhibitory factor (MIF) (40, 41).

MIF was described initially as one of the earliest cytokines to be derived from activated T-cells, and was believed to prevent the random migration of macrophages (42). MIF has also been demonstrated to be generated abundantly by monocytes/macrophages and to function in an autocrine/paracrine manner in the upregulation and sustenance of the activation of diverse cell types (43). The profile of the activities of MIF, both *in vivo* and *in vitro*, is reflective of a role for MIF in the pathogenesis of a variety of inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, and psoriasis (44). MIF performs a crucial function in airway inflammation and airway hyper-responsiveness in asthma (45).

Recently, several MIF homologues have been isolated from parasitic nematodes. Two types of MIF homologues have thus far been identified in nematodes (34). The type 1 MIF homologues bear a greater amino acid similarity with the mammalian MIFs than do the type 2 MIF homologues (46). The type 1 MIF homologues isolated from *Brugia malayi* (Bm-MIF1) induce eosinophil recruitment, and alternatively activated macrophage recruitment *in vivo* when injected into the peritoneal cavities of mice. Mutation of the conserved proline residue induces the abrogation of this activity (47). This ability of parasite MIF homologues was similar to those of mammalian MIF. However, recently Cho et al. reported that hookworm MIF (structurally type 2 MIF) functions differently from mammalian MIF (48, 49).

We have cloned another type 2 MIF homologue (As-MIF) from *Anisakis simplex* (whale worm) 3rd stage larva, which causes anisakidosis in humans (50). Recombinant As-MIF (rAs-MIF) proved highly effective with regard to the inhibition of goblet cell hyperplasia and inflammatory responses in the airways of OVA-induced asthma model mice (Fig. 5). Increasing concentrations of rAs-MIF induced an increase in the anti-inflammatory effects on asthma model mice. Additionally, the function of rAs-MIF was antagonized as compared to the function of host MIF (59).

How does As-MIF suppress allergy responses in mice? There have been many reports demonstrating that Th2-type effector responses may be regulated by T_{reg} cells (51-53). Additionally, nematode infections can induce and expand naturally occurring T_{reg} cells in both humans and mice (4, 54), thereby suggesting a role for these T_{reg} cells in the helminth-induced modulation of inflammatory diseases (55, 56). In particular, the clinical symptoms of allergic airway inflammation in the mouse model was clearly modulated by T_{reg} cell mediated immune suppression, which was itself activated by helminth infection or antigen treatment (57, 58). We could determine the increase in T_{reg} cells as the result of rAs-MIF treatment in OVA-alum asthma-induced mice (Fig. 6).

IL-10 and TGF- β were produced primarily by T_{reg} cells, and they are known to suppress immune response effects. The IL-10 and TGF- β levels measured in BALFs from rAs-MIF-treated asthma-induced mice were higher than those of the asthma-induced mice; the IL-10 and TGF- β levels occurred in accordance with their treated concentrations (59). The helminthic parasites stimulate the production of immunoregulatory mediators, which likely perform a function in the maintenance of the chronicity of infection, without any marked induction of pathology. In particular, elevated IL-10 levels have been associated with responses against allergic diseases in helminth-infected individuals (4). Also, Nagler-Anderson *et al.* showed that in mice sensitized with peanut plus cholera toxin, anti-IL-10 treatment abrogated the ability of helminths to protect against allergic symptoms and to downregulate allergen-specific IgE. IL-10, which is referred to as the cytokine synthesis inhibitory factor, is an anti-inflammatory cytokine, which is capable of inhibiting the

synthesis of pro-inflammatory cytokines (60). The IL-10 requirement is critical to several important human diseases, including schistosomiasis, wherein marked increases in host morbidity and mortality are observed when IL-10 levels are low or absent (61). In cases of murine *S. mansoni* infection, IL-10 attenuates the hepatocyte damage induced by the eggs of the parasite. IL-10 is also essential for the maintenance of non-lethal chronic infections, in addition to the inhibition of inappropriate immune responses in experimental models (62). TGF- β 1 is also a strong candidate for immune suppression by T_{reg} cells from helminth-infected mice, and has already been recognized to alleviate experimental airway allergy symptoms (63) and to instruct peripheral T cells to develop their regulatory capacities (64). Thus, the inhibition of asthma response by rAs-MIF may be associated with the principal T_{reg} cell-associated downregulatory cytokines, including TGF- β 1 and IL-10.

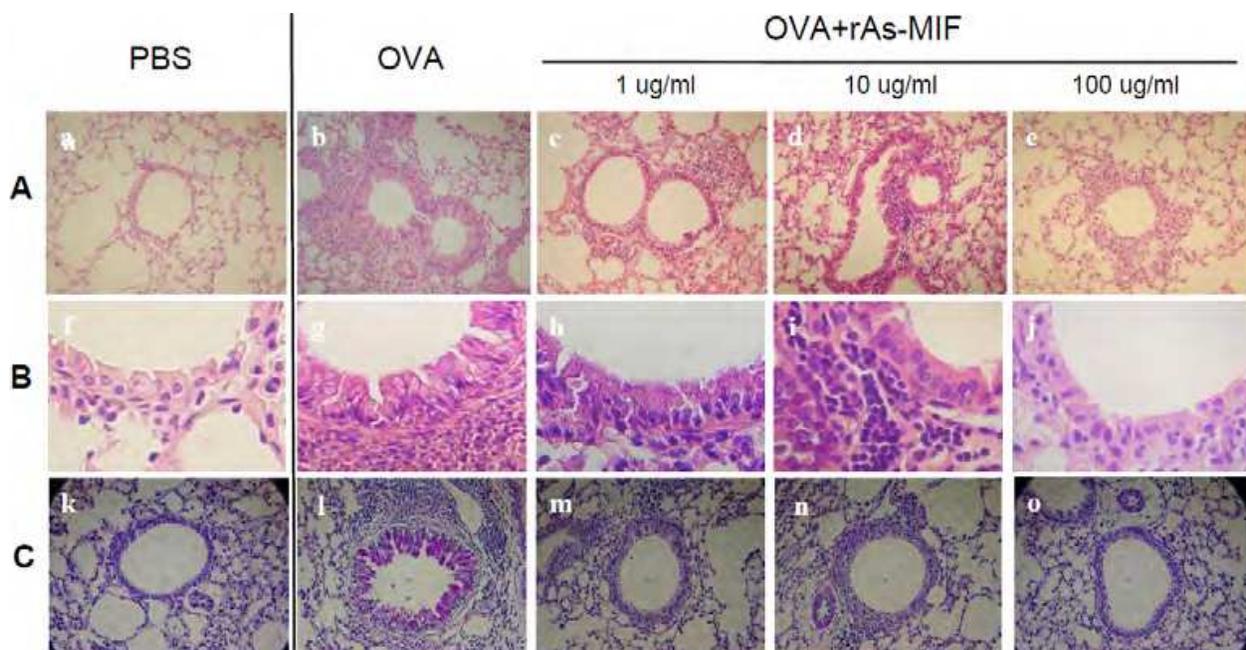


Fig. 5. Histologic appearance of lungs after challenge with PBS, OVA, and rAs-MIF by concentration (H-E stain). (A; x 100, B; x 600; C; PAS stain), C; **a, f, and k**; phosphate-buffered saline (PBS) treated, **b-e, g-j, and l-o**; OVA plus alum-treated (induced asthma), **c, h and m**; challenged with 1 μ g/ml rAs-MIF, **d, i, and n**; challenged with 10 μ g/ml rAs-MIF. **e, j, and o**; challenged with 100 μ g/ml rAs-MIF. In asthma-induced mice, a massive peri-bronchial infiltration with immune-related cells and hyperplasia of bronchial epithelial cells were observed. Upon challenge with 1 μ g/ml rAs-MIF treatment (**c, h and m**), asthma-induced mice evidenced thinner bronchial epithelial cells than were observed in the asthma-induced mice (**b, g, and l**). Mice challenged with treatment with 10 and 100 μ g/ml rAs-MIF evidenced thinner than normal bronchial epithelial cells and decreased numbers of immune-related cells. Goblet cells and immune-related cells in the airway walls of mice exposed to PBS, OVA and OVA challenge with 1, 10, and 100 μ g/ml rAs-MIF. In asthma-induced mice (**g**), a massive peri-bronchial infiltration of inflammatory cells and hyperplasia of bronchial epithelial cells were detected. However, goblet cell hyperplasia was reduced in the bronchial epithelial cells of the rAs-MIF-treated mice (**h-j**).

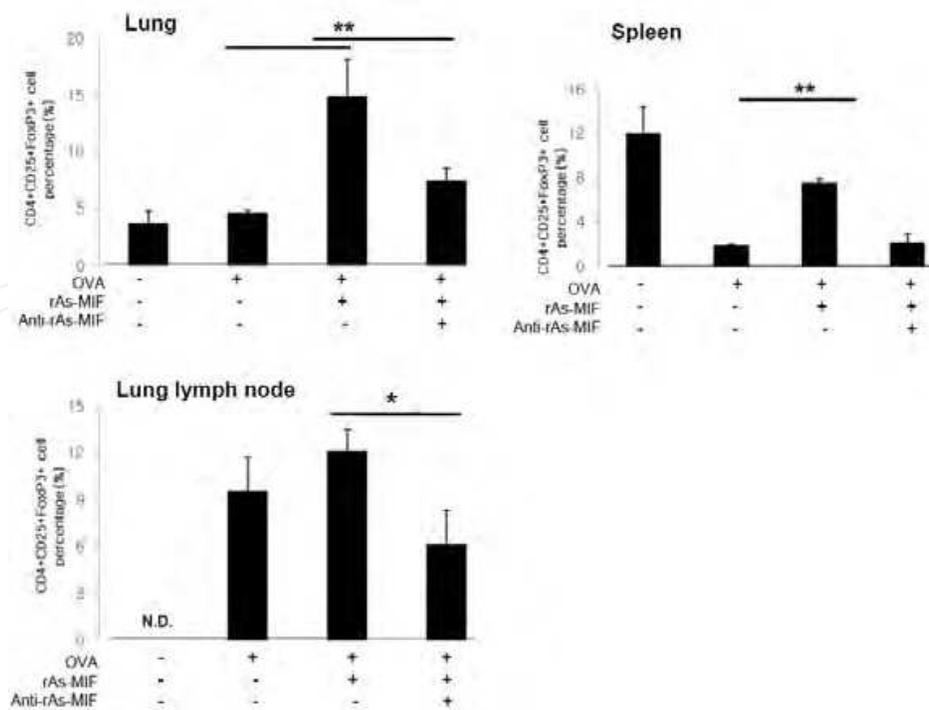


Fig. 6. T_{reg} cell production could be induced by rAs-MIF treatment. T_{reg} cell populations in the lungs and spleen were significantly increased by rAs-MIF treatment, but this effect was inhibited by rAnti-As-MIF. (*, $p < 0.05$, **; $p < 0.01$, $n = 5$ mice per group, 3 independent experiments).

4. Conclusion

We showed that parasite derived proteins may perform a crucial function in resistance against allergic airway inflammation via IL-10 cytokine induction and Treg cell recruitment. Parasites regulate or suppress their host immune response, maintaining their parasitism for a prolonged period, using unknown molecules. As-MIF might be one of the molecules that affect host immune regulation. The further characterization of parasite derived proteins might ultimately result in the design of novel therapeutic intervention strategies for the treatment of asthma.

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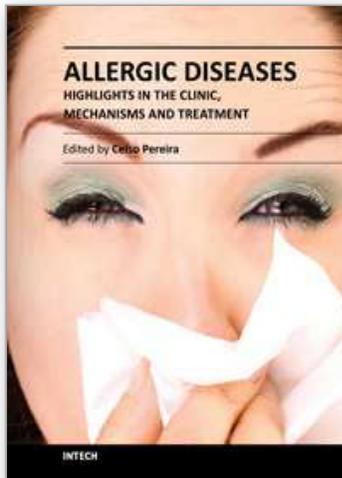
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The present Edition "Allergic diseases - highlights in the clinic, mechanisms and treatment" aims to present some recent aspects related to one of the most prevalent daily clinical expression disease. The effort of a group of outstanding experts from many countries reflects a set of scientific studies very promising for a better clinical care and also to the treatment and control of the allergy. This book provides a valuable reference text in several topics of the clinical allergy and basic issues related to the immune system response. The inflammatory reaction understanding in allergic disease is clearly evidenced, as well as new strategies for further researches.

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