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Derived Products of Helminth in the Treatment of Inflammation, Allergic Reactions and Anaphylaxis

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1. Introduction

Anaphylaxis is a life-threatening and systemic disorder that involves several organs and may lead to death. It is believed to be mostly triggered by release of mediators from activated mast cells, basophils and macrophages after allergen exposure. There are two major types of anaphylactic mechanisms: classical and alternative anaphylactic pathways. Classical anaphylactic pathway is triggered by cross-linking of IgE bound to FcεRI, high affinity IgE receptors, on mast cell and basophil surfaces to release pre-formed vasoactive amines (e.g. histamine), lipid mediators and neutral proteases from secretory granules upon allergen exposure. The alternative anaphylactic pathway is an IgE-independent mechanism and involves basophils and macrophages. Upon allergen exposure, IgG-immune complexes binds to FcγRIII, low affinity activating IgG receptor, and subsequent release PAF (platelet activating factor), but not histamine as major mediator. The understanding of immune mechanisms on triggering anaphylaxis is crucial for understanding how to manipulate the immune system to find better therapeutic interventions.

Helminth infection and their products have been demonstrated as potential therapeutic interventions in inflammatory disorders. Helminths use several imunomodulatory strategies to evade and/or modify the host immune response in order to survive in the host, including suppression or inactivation of host antigen-specific immune response. The modulation of the immune system has been considered beneficial for both host and parasites since it could avoid helminth eradication and protect the host from inflammatory responses which may damage host's tissues and organs. Several helminth immunomodulatory molecules and strategies have been identified and reported, such as eotaxin metalloproteinase, calreticulin, antioxidants and neutrophil inhibitory factor. They interfere with antigen processing and presentation, cell proliferation, cause T cell death, decrease IgE responses, reduce B cell activation and stimulate regulatory T cells. Therefore, these immunomodulatory factors can affect both the inductive and effector immune response, being suitable to modulate the inflammatory, allergic and anaphylactic responses.

Our studies have been focused in the immunossuppressive responses induced by roundworms *Ascaris suum* infection and a protein secreted by these worms named PAS-1

(protein from *Ascaris suum*). We have demonstrated that PAS-1 suppresses LPS-induced inflammation due to stimulating the secretion of IL-10 and TGF-β. Furthermore, PAS-1 was demonstrated suppressing B and T cell responses against OVA. Besides playing a down-modulatory effect in inflammatory responses induced by unrelated antigens, PAS-1 suppresses the acute and chronic lung allergic inflammation induced by APAS-3 (allergenic protein from *Ascaris suum)*. In OVA/alum lung inflammation model, PAS-1 down-modulates the lung inflammatory response due CD4+CD25+FoxP3+ cells and CD8+γδTCR+ cells, which secretes IL-10/TGF-β and IFN-γ, respectively. In chronic lung inflammation model using OVA/alum or alum/APAS-3, besides inhibiting the inflammation into the lungs, PAS-1 also inhibits the airway remodeling by decreasing the activity of metaloproteinases and the production of angiogenic factors (IL-13 and VEGF). Taken together, these findings demonstrated that PAS-1 inhibits both acute and chronic lung inflammation in mouse models.

The understanding of immune modulatory mechanisms that control anaphylactic responses is critical to investigate therapeutic interventions for anaphylactic inflammatory disorders. The purpose of this chapter is to discuss the mechanisms triggered by allergic and anaphylactic reactions and potential therapeutic strategies using helminth products.

2. Immune responses triggered by anaphylactic reactions

2.1 Concept of anaphylaxis

Anaphylaxis is a systemic and immediate hypersensitivity with multi-organ system involvement that can progress potentially to a life-threatening reaction causing thousands deaths in the world. The term anaphylaxis was named by Dr Charles Robert Richet, a Nobel laureate in Physiology or Medicine in 1913. In 1902, Richet and his colleague Paul Portier reported that dogs immunized with non-lethal dose of sea anemone venom display fatal reactions to the second injection of the venom even in small doses. Shibasaburo Kitasato and Emil von Behring had previously demonstrated that animals immunized with bacterial toxins are able to produce anti-toxins (neutralizing antibodies). Since then, this phenomenon was named **anaphylaxis,** which term is derived from the Greek words "a-" (against) and "–phylaxis" (protection).

Anaphylaxis can occur following exposure to several allergen sources including food allergens, aeroallergens, venoms, drugs and vaccination. The most common symptoms include itching, erythema and urticaria after the exposure to allergens. The most severe cases of anaphylaxis involve cardiovascular and respiratory system with drop of cardiac pressure, bronchoconstriction, laryngeal edema and shock (Brown, 2004). The gastrointestinal system may be also involved featuring vomiting, abdominal pain and diarrhea. The central nervous system can be affected leading to a felling of impending doom and lack of consciousness related to hypotension and hypoxia. Once the anaphylactic reactions occur rapidly, an effective treatment (usually epinephrine injection) may avoid the occurrence of severe symptoms (Simons et al., 2003). Thus, it is crucial to understand the molecular mechanisms involved on anaphylactic reactions for strategically managing the risk and preventing recurrence.

2.2 Types of anaphylactic reactions

Anaphylaxis occurs due to release of vasoactive and inflammatory mediators from mast cells, basophils and macrophages upon allergen exposure. When antigens cross-link FcεRI-

bound IgE or bind to IgGs, which are found as IgG-immune complexes attached to FcγRs, mainly FcγRIII, a signaling cascade is trigger to promote release of mediators which cause smooth muscle contraction and increase vascular permeability, leading to laryngeal edema (which may cause respiratory difficulty), hypotension, urticaria, abdominal muscular contraction, diarrhea (Ewan, 1998). It is reported that anaphylactic reactions in rodent models are induced by two different pathways: classical and alternative anaphylactic pathways (Figure 1).

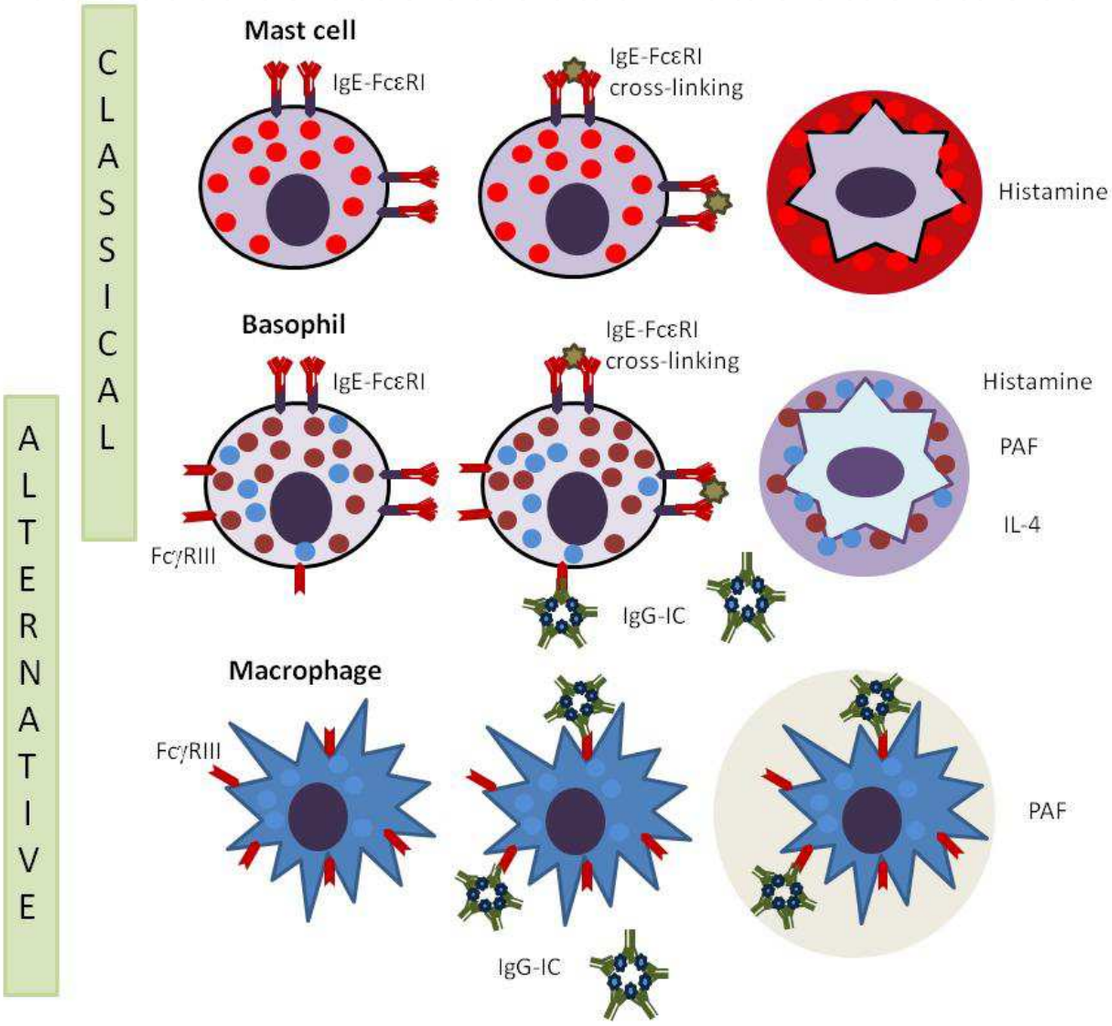


Fig. 1. Classical and alternative anaphylactic pathways. In the classical anaphylactic pathway, cross-linking among IgE-bound FcεRI and specific antigen leads to mast cell and basophil degranulation and secretion of histamine as major mediator. In the alternative anaphylactic pathway, IgG-immune complexes bind to FcγRIII on basophil and macrophage surfaces, triggering the secretion of PAF as major mediator. Basophils also secrete IL-4 that is crucial for IgE class-switching.

Classical anaphylactic pathway is triggered by cross-linking of antigen and antigen-specific IgE bound to FcεRI on mast cell and basophil surfaces, which stimulates these cells to

degranulate and release histamine, serotonin, lipid mediators (such as leukotrienes) and cytokines (such as IL-4, TNFα, IL-1, VEGF) (Kumar & Sharma, 2010). Strait et al. (2003) have demonstrated that IgE-mediated anaphylaxis depends on IL-4/IL-4Rα, mast cells, FcεRI, IgE, histamine and H1 receptor but does not depend on macrophages, serotonin and leukotrienes. Alternative anaphylactic pathway is triggered by IgG-immune complexes bound to FcγRIII on basophils and macrophages, causing release of PAF (Mukai et al., 2009).

2.3 Cells involved in anaphylactic reactions

2.3.1 Mast cells

Mast cells were identified by Paul Ehrlich in 1879 (reviewed in Beaven, 2009) as cells present in connective tissues that reacts metachromatically with aniline dyes. He named them *Mastzellen* due the presence of granules that he believed to have a nutritional role on this cell type (the word *mast* denotes fattening in German). Mast cells are generated from bone marrow immature cells that migrate to skin and intestine and differentiate into connective tissue mast cells and mucosal mast cells, respectively (Arinobu et al., 2005; Galli et al., 2005). Stem cell factor (SCF or c-kit ligand) and c-kit play an important role in the growth and differentiation of mast cells, which express c-kit constitutively at all stages of differentiaton (Hu et al., 2007). They serve as important effector cells of the innate immune system along with other cell types (i.e. macrophages, dendritic cells, neutrophils, NK cells).

In anaphylactic reactions, mast cells are the effector cells in triggering the classical anaphylactic pathways. They express constitutively FcεRI, high affinity IgE receptor, which are usually bound to monomeric IgE upon antigen exposure. This receptor-IgE complex is cross-linked with multivalent antigens that consequently stimulate the release of effector mediators such as histamine, lipid mediators, and cytokines, which are pre-formed and stored in secretory granules of mast cells (Kumar & Sharma, 2010; Kemp & Lockey, 2002). These mediators act on many cellular types, including vascular endothelial cells and bronchial smooth muscle, inducing anaphylactic manifestations such as hypotension and dyspnea (Winbery & Lieberman, 2002).

2.3.2 Basophils

Similarly to mast cells, basophils were identified as cells that present metachromatic granules in the cytoplasm. Unlike human, mouse basophils are exceptionally rare (Urbina et al., 1981). They are the least common circulating cells that comprise less than 1% of total circulating granulocytes and are not normally present in tissues although are recruited to inflammatory sites. Basophils may contribute to IgE-mediated allergic inflammation and IgG1-mediated systemic anaphylaxis (Mukai et al., 2005; Tsujimura et al, 2008). They arise from bone marrow progenitors and complete their terminal differentiation in bone marrow (Arinobu et al., 2005).

Basophils constitutively express FcεRI, high affinity IgE receptor, and upon cross-linking of FcεRI-bound IgE with specific antigen, they release effector mediators such as histamine, leucotrienes, PAF and Th2 cytokines (IL-4, IL-5, IL-13) and TSLP (thymic stromal lymphopoietin) in response to protease allergens, causing immediate type hypersensitivity (Min, 2008). Mukai et al. (2009) have reported basophils as one of the major players in the IgG- but not IgE-mediated systemic anaphylaxis although basophils may function as initiator of allergic inflammation. Experiments from Tsujimura et al. (2008) demonstrated that mice passively transferred with anti-PenicillinV (PenV) monoclonal IgG1 antibody and challenged with PenV-conjugated BSA as allergen presented high drop of body temperature

in both mast cell sufficient or deficient mice. They found that mainly basophils captured IgG1-immune complexes (they possessed highest amount of allergen per cell in comparison with other cell types), the binding was greatly inhibited by treatment with anti-FcγRIIb/FcγRIII antibody (against low affinity FcγRs), and they secrete high amount of PAF when stimulated by IgG1-immune complexes, indicating basophils as a good candidate to trigger IgG1-mediated anaphylatic reactions.
Besides their function as effector cells in IgG1-mediated anaphylaxis, basophils play a crucial role as early secretor of IL-4 that is essential to the development of anaphylactic reactions due to promoting class-switching to IgE. Sokol et al. (2008) have demonstrated that basophils are crucial for the initiation of Th2 cells in response to papain, a cystein protease, which activity is commonly found in most allergenic proteins. In addition, other findings reported that naïve CD4+ T cells stimulated with peptide-pulsed DCs could develop into Th2 cells when co-cultured with basophils from wild type mice but not IL-4-deficient mice (Oh et al, 2007), enforcing the role of basophils as early source of IL-4 in the immune responses.

2.3.3 Macrophages

Macrophages are long lived cells that function as a first line of defense in the body. These cells serve as early detector of invading pathogens through PAMPs, as antigen-presenting cells which initiate the immune responses, as effector cytotoxic cells to kill directly pathogens and also they play a role as regulatory and suppressor cells in parasitic infections and tumor-bearing hosts (Gordon, 2003). They arise from monocytes which are released in the blood stream and migrate to tissues to differentiate in macrophages or dendritic cells according to the stem cell factors milieu (Geissmann et al., 2010).
Macrophages have been involved in the development of IgG-dependent anaphylactic pathway (Oettgen et al., 1994; Miyajima et al., 1997; Strait et al., 2002). Passive immunization with allergen-specific monoclonal IgG1 antibody induce systemic anaphylaxis upon allergen exposure but this effect can be neutralized by treatment with anti-FcγRIIb/FcγRIII monoclonal antibodies (against low affinity FcγRs) and after depletion of macrophages with gadolinium (Strait et al, 2002), indicating the participation of macrophages in triggering IgG1-mediated anaphylactic reactions. Although platelets and neutrophils have been implicated in IgG-dependent anaphylaxis (Pinckard et al., 1977; Kimura et al., 1997), Strait et al. (2002) found in their studies that the techniques used for platelets and neutrophil depletion may inhibit IgE-independent anaphylaxis by producing immune complexes that desensitize macrophages, mimicking these cells as contributors of FcγRIII-dependent anaphylaxis.
Macrophages along with basophils also contribute to IgG-mediated anaphylaxis by releasing PAF upon antigen exposure. It has been demonstrated that the injection of anti-FcγRIIb/FcγRIII stimulates macrophages to release PAF by cross-linking FcγRIII on these cells and also inhibits IgG-dependent anaphylactic responses to antigen by blocking IgG-immune complex activation of macrophages through FcγRIII (Ujike et al., 1999; Strait et al., 2002).

2.4 Mediators involved in classical and alternative anaphylactic reactions

2.4.1 IgE and FcεRI

Ishizaka & Ishizaka (1976) discovered a new class of antibodies capable of transferring sensitivity to allergens. IgE antibodies are considered major players in allergic disorders such as anaphylaxis, asthma, atopic dermatitis, food allergy (Oettgen & Geha, 1999). It is considered the only antibody involved in classical anaphylactic reactions. It is also

associated with protective immunity to parasitic infections (Capron et al., 1982). IgE consists of two identical heavy chains and two light chains with variable (V) and constant (C) regions and no hinge region which makes IgE to be less flexible. The ε-heavy chains contain one variable heavy chain and four constant region domains (Cε1-4) (Williams & Barclay, 1988) and are highly glycosylated (Arnold et al., 2007). IgE is the less abundant antibody class in serum with normal concentration of 50-200 ng/mL in nonallergic individuals (Gould et al., 2003). Even during helminth infections or allergic reactions, human serum IgE levels are lower than serum IgG levels; IgG peaks at around 30 μg/mL whereas IgG4 peaks at around 680 μg/mL (Bell, 1996). IgE has the shortest half-life of all immunoglobulins. Its half-life is about 3 days in serum (Iio et al., 1987), 16 hours on cells in suspension (Ishizaka & Ishizaka, 1971) and 2 weeks in tissues when is receptor-bound on cell surfaces (Geha et al., 1985). Its production requires class-switching from IgM, often via IgG to IgE by somatic recombination of germline genes in B cells", which depends on Th2 cytokines (IL-4/IL-13) and CD40 ligation (Poulsen & Hummelshoj, 2007).

It has been identified three IgE receptors in human (FcεRI(αβγ2 and αγ2), galectin-3 and FcεRII) and four receptors in mice (FcεRI(αβγ2 and αγ2), galectin-3, FcεRII and FcεRIV). Most of IgE bind to high affinity IgE receptor (FcεRI) that is present in mast cells, basophils (Gould et al., 2003) and antigen-presenting cells e.g. Langerhans cells (Bieber et al., 1992). FcεRI has a central role in mediating the allergic disorders (Kinet, 1999). Cross-linking of FcεRI associated to IgE with specific antigens induces the release of preformed mediators, newly formed lipid mediators and de novo synthesis of cytokines that potentially mediate anaphylactic reactions or prolonged allergic inflammation. FcεRI shares a common oligomeric structure, comprising a ligand binding immunoglobulin-like α-subunit associated to a β-subunit and two γ-subunits (Daeron, 1997). It binds stably monomeric IgE on mast cell surface (Kd ~ 10^{-10} M). The extracellular domain of α-subunit is glycosilated which seem to be crucial to appropriate maturation during FcεRI traffic through endoplasmic reticulum (Fiebiger et al., 2005) although is not required for monomeric IgE binding (Garman et al., 1999). The β- and γ-subunits bear ITAM (immunoreceptor tyrosine-based activation motif) that is phosphorylated in tyrosine residues by Lyn after cross-linking of FcεRI (Honda et al., 2000). The β-subunit possesses four transmembrane domains and the C-terminal domain has an ITAM motif. The γ-subunit belongs to T cell receptor (TCR) (gene family and is associated to Fc receptors including FcγRI, FcγRIIA, FcαRI (Takai, 2005). Other variant of FcεRI is constituted only by three chains (one α-subunit and two γ-subunits) that are expressed in monocytes, macrophages and neutrophils (Gould & Sutton, 2008). The low affinity IgE receptor (FcεRII) or CD23 is expressed in several cell types including B cells, activated T cells, monocytes, eosinophils, platelets, follicular dendritic cells, and thymic epithelial cells. CD23 facilitates the antigen presentation to T cells upon binding to IgE-antigen complex and also plays a role as negative regulator of IgE production (Gould & Sutton, 2008). Another IgE receptor is galectin-3 or ε-binding protein, which has been reported to be involved in neutrophil activation (Truong et al., 1993). In mice, it has been found a fourth type of IgE receptor, FcγRIV, which binds IgE-immune complexes on macrophage surface, inducing lung inflammation (Mancardi et al., 2008).

2.4.2 IgG and FcγRIII

IgG antibodies were identified by Tiselius and Kabat in 1939. They immunized rabbits with ovalbumin and fractionated the immune serum by electrophoresis into albumin, α-globulin,

β-globulin and γ-globluin fractions. The fact that this rabbit serum binds to ovalbumin γ-globulin fraction named the immune factor present in rabbit sera as immunoglobulin(Ig) or IgG (Tiselius & Kabat, 1939). Classically, there are four types of IgG subclasses in humans (IgG1-IgG4) and mice (IgG1, IgG2a, IgG2b, and IgG3). They are the most predominant antibody isotype (70-75% of total IgG) in the blood and extravascular compartiments. Four different types of FcγRs have been identified in mice (FcγRI, FcγRIIb, FcγRIII, and FcγRIV). The human and primates FcγRs have several allelic variants that codify six types of FcγRs: FcγRI, FcγRIIa, FcγRIIc, FcγRIIb, FcγRIIIa, FcγIIIb.

Traditionally, these receptors belong to two different categories – they are classified in high or low affinity FcγRs according IgG affinity to them, and in activating or inhibitory FcγRs if the type of signaling pathway is triggered by ITAMs (immunoreceptor tyrosine-based activation motif) or ITIMs (immunoreceptor tyrosine-based inhibitory motif). Then, FcγRI is high affinity, activating FcγRs in both mice and humans; FcγRIII and FcγRIV (in mice) and FcγRIIa, FcγRIIc, FcγRIIIa, FcγRIIIb (in human) are categorized as low affinity, activating FcγRs; and FcγRIIb is the only low affinity, inhibitory FcγR in mice and humans. IgGs antibodies bind with different affinity and specificity to different FcγRs (Dijstelbloem et al., 2001). In general terms, monomeric IgG binds predominantly to high affinity FcγRs (FcγRI) and IgG-immune complexes binds to low affinity FcγR. These receptors are widely expressed in haematopoietic cells (except T cells), endothelial cells, osteoclasts, and mesangial cells. In mice, monocytes and macrophages express all activating and inhibitory FcγRs (FcγRI-IV), neutrophils express mainly FcγRIII, FcγRIV and FcγRIIb, dendritic cells express FcγRI, FcγRIII, FcγRIIb, NK cells only express FcγRIII and B cells only have FcγRIIb (Nimmerjhan & Ravetch, 2008).

IgG antibodies and FcγRIII have been implicated in triggering alternative anaphylaxis pathway. Mice lacking mast cells, IgE or FcεRI alpha chain still develop systemic anaphylactic responses upon antigen exposure (Jacoby et al., 1984; Oettgen et al., 1994; Dombrowicz et al., 1997) whereas FcRγ deficient mice that lack the expression of Fc(RI and activating Fcγ (receptors FcγRI, FcγRIII, FcγRIV) have no apparent signal of systemic anaphylaxis (Miyajima et al., 1997). Furthermore, it has been found that mice passively transferred with allergen-specific monoclonal IgG, particularly monoclonal IgG1, developed systemic anaphylaxis upon allergen exposure; when these mice were pre-treated with anti-FcγRIIb/FcγRIII, FcγRIV monoclonal antibodies, the systemic anaphylaxis was inhibited, indicating the role of FcγRIII in IgG-mediated anaphylaxis (Strait et al., 2002).

2.4.3 Histamine and H1 receptor

Histamine is an autacoid, also referred as 2-(1H-imidazol-4-yl)ethanamine, that modulates the cellular function in several tissues including dermis, small intestine, stomach, lungs and brain (Jones & Kearns, 2011). Its synthesis depends on histidine decarboxylase (HDC) that removes of carboxylic acid residue on the histidine side chain in the Golgi apparatus. It is stored basically in mast cells and basophils although it has been demonstrated that other cell types (e.g. neutrophils, lymphocytes, monocytes, dendritic cells, platelets, gastric cells and brain histaminergic cells) express HDC (MacGlashan, 2003). The release of histamine occurs in response to cross-link of antigen-specific IgE on mast cells and basophils surfaces upon antigen exposure during systemic anaphylaxis and the early phase of allergic responses. Large quantities of histamine (10^{-5} to 10^{-3} mol/L) are released within 30 minutes after allergen exposure (Simons, 2003). Histamine and other released mediators such as

leukotrienes and prostaglandins produce the acute symptoms including pruritus of nasal mucosa, eyes, skin and increased vascular permeability, vasodilatation and edema resulting in nasal congestion, rhinorrea and conjuntival edema and erythema (Clough et al., 1998). Histamine can cause bronchoconstriction due to mucus accumulation by activated globet cells in the lung (Golightly & Greos, 2005) and may be involved in airway remodeling (Kunzmann et al, 2007). Histamine is responsible for mast cell activation by stimulating the secretion of cytokines and chemokines from T and B lymphocytes which up-regulates adhesion molecules in epithelial cells (Akdis & Blaser, 2003).

Histamine binds to four major receptors (H1, H2, H3 and H4) which belong to G-protein seven transmembrane receptor family. H1 receptor has been widely discussed in anaphylactic disorders. Histamine binds to H1R that activates inositol-1, 4, 5 pathway, mobilizing intracellular calcium which induces the vascular endothelium to release nitric oxide and stimulate guanyl cyclase to increase the production of cyclic GMP in vascular endothelial cells. This cascade promotes vasodilatation, erythema, vascular permeability and edema (Li et al, 2003). Activation of H1R produces direct effect in bronchial smooth muscle leading to bronchoconstriction. H1 and H2 receptors are overexpressed in patients with asthma in contrast to patients with rhinitis only (Botturi et al, 2010). The H2 receptor is expressed on gastric mucosa, vascular smooth muscle, brain, adipocytes and immune cells. Activation of H2 results in relaxation of smooth muscle in the airway and vasculature (Akdis & Simons, 2006). The stimulation of H3 receptor is been involved in pruritus (Sugimoto et al, 2004) and H4 receptor may play a role in inflammatory processes by inducing chemotaxis and calcium influx in bone marrow-derived and tracheal mast cells migration from connective tissue toward epithelium (Thurmond et al, 2004).

2.4.4 Platelet activation factor (PAF)

The term PAF was first used to describe the factors that aggregate and activate platelets (Benveniste et al., 1972). PAF is a potent proinflammatory phospholipid synthesized from the cleavage of glycerophospholipids by phospholipase A2 that binds to PAF receptor, a G-protein coupled seven-transmembrane receptor. It is active at concentration as low as 10^{-12}M (Stafforini et al, 2003). Since its discovery, pleiotropic effects of PAF have been demonstrated, including its role in bronchoconstriction, hypotension, vascular permeability, chemotaxis, degranulation of eosinophils and neutrophils (Hanahan, 1986). PAF is released from mast cells, basophils and macrophages upon antigen stimulation in human and experimental anaphylactic reactions (Vadas et al., 2008; Finkelman, 2007). Histamine, which can be secreted by mast cells and basophils, effectors cells in classical anaphylactic pathway, is a potent agonist for PAF synthesis by human endothelial cells (McIntyre et al., 1985). Circulating levels of PAF are controlled by the activity of PAF acetylhydrolase, enzyme that rapidly degrades PAF, making its half-life very short; it ranges from 3 to 13 minutes (Karasawa, 2006).

Vadas et al. (2008) have found that PAF levels positively correlate with the severity of anaphylaxis and may be pivotal for anaphylaxis outcome. Serum PAF levels is significantly elevated in allergic patients with severe anaphylaxis than those with milder manifestations of anaphylaxis. PAF has been identified as relevant vascular leak mediator in anaphylaxis (Camerer et al., 2009). The deletion of PAF receptor impairs anaphylactic responses in genetically manipulated mice (Ishii et al., 1998). In addition, recombinant PAF acetylhydrolase is protective and reduces mortality in experimental models of anaphylaxis (Fukuda et al., 2000; Gomes et al., 2006). Furthermore, PAF stimulate NO (nitric oxide) production by enhancing the activity of NOS (constitutive nitric oxide synthase), instead of

iNOS (inducible nitric oxide synthase), which relaxes vascular smooth muscle, leading to hypotension and death (Cauwels et al., 2006).

2.4.5 IL-4 and IL-4Ralpha

IL-4 is a pleiotropic type I cytokine, recognized as signature cytokine of Th2 immune responses (Swain et al., 1990). It is produced by Th2 CD4+ T cells, basophils, mast cells, eosinophils and CD1-restricted NKT cells upon stimulation (Paul, 1997). IL-4 binds to IL-4 receptor, which is a heterodimer of IL-4 receptor α chain and common γ chain, resulting in phosphorylation of STAT6 (signal transducer and activator of transcription 6) (Nelms et al., 1999).

IL-4 exacerbates anaphylaxis through a direct effect on mast cell and basophils or through enhancing antibody production. Strait et al. (2003) have demonstrated that IL-4R signaling increase the responsiveness of mast cell- and macrophage-secreted mediators such as histamine, PAF, serotonin and leukotriene C4. IL-4 increases anaphylactic responses in a mouse model infected with *Thrichinella spiralis* by increasing histamine and PAF, but also enhances anaphylaxis at doses lower than those produced by helminth infections (Conrad et al., 1990). The contribution of IL-4/IL-4Rα in the anaphylaxis is also associated to their role in antibody production. IL-4 promotes class-switching to IgE antibodies (Finkelman et al., 1988) but it does not seem crucial to IgG1 production since high IgG1 levels is found in mice treated with anti-IL-4, and in IL-4 or STAT-6 deficient mice (Finkelman et al., 1989; Kuhn et al., 1991; Shimoda et al., 1996).

3. Helminth infections as predisposed factors to allergic and anaphylactic reactions

Helminths are known to cause widespread infections, mainly in tropical and subtropical areas in the developing world where the water suply and sanitation conditions are not adequate (De Silva et al., 2003). Although they did not cause high mortality, they tend to cause chronic infections in populations that live in endemic area, leading to iron-deficiency anemia and malnourishment and interfering with physical and mental growth in children (Stephenson et al., 2000).

The immune response against helminth infections is associated with high production of IgE levels and tissue infiltration of eosinophils, mast cells and Th2 cells which secrete IL-4, -5 and -13 (Fallon & Mangan, 2007). Th2 immune responses are believed to mediate protective immunity against these parasites (Anthony et al., 2007). Certain parasites such as *Schistosome mansoni* produce a strong Th2 immune response that is correlated with the formation of Th2 granuloma around schistosoma eggs (Wilson et al., 2007).

Several studies have demonstrated that helminth infection may increase allergic inflammation. Individuals exposed to helminthes for a short time often have allergic-like manifestations (Cooper, 2009). Lynch and collaborators (Lynch et al., 1984, 1987, 1992, 1997) have shown that the intensity of helminth transmission determines the effect of helminth infection on allergic reactivity - in high income urban areas where the transmission is low, the allergic reactivity is high whereas in urban and rural areas where people are chronically infected by helminthes, the allergic reactivity is low. Geohelminth parasite with pulmonary larval stages, such as *Ascaris lumbricoides, Necator americanus, Ancylostoma duodenale* and *Strongyloides stercoralis,* are found to cause Loeffler's syndrome which is characterized by eosinophilic infiltrate into the lungs after parasitic infection (Loefller, 1959).

Corroborating with Lynch's studies, it has been reported high association between dust mites and parasitic diseases in tropical allergies (Caraballo & Acevedo, 2011). Mites are important source of allergens in tropical areas (Fernandez-Caldas et al., 1993, 2008). The warm temperatures and high humidity facilitate the proliferation of dust mites such as *Blomia tropicalis* and *Dermatophagoides pteronyssinus* (Puerta et al., 1993). Likewise, nematodes are highly prevalent in tropical areas. *Ascaris lumbricoides* is the most prevalent, affecting around 1.5 million people worldwide (McSharry et al., 1999) by oral contamination with embryonated eggs that differentiate in migratory larvae, compromising intestine, liver, and lungs (Bradley & Jackson, 2004). Cross-reactivity between mites and *Ascaris* could explain why there is a positive correlation between allergies caused by dust mites and nematode infections in tropical areas. Acevedo et al. (2009) found cross-reactivity of specific IgE and tropomyosin from *B. tropicalis*, *D. pteronyssinus* and *A. lumbricoides* in asthmatic patients. It is postulated that high prevalence of specific IgE to mites in a tropical environment may be influenced by cross-reactivity with *Ascaris* spp. allergens (Acevedo et al., 2011). Another study also suggested that nematode infections may induce reactivity to tropomyosin in atopic individuals. Santiago et al. (2011) have demonstrated that there is 72% of amino acid identity between tropomyosin from *D. pteronyssinus* (Der p10) and *Onchocerca volvulus* in sera from *O. volvulus*-infected and non-infected atopic individuals and the prevalence of Der p10-specific IgE and IgG was increased in *O. volvulus*-infected individuals. Besides *Ascaris* infection, HDM (house dust mite) sensitization is strongly associated to wheeze symptoms in individuals from urban areas than in rural areas that had *Trichuris* infection (Scrivener et al., 2001).

Cooper (2009) and Smits et al. (2010) have listed four factors that may determine the effect of helminthic infections in promoting allergic responses (Figure 2): 1) **Timing** - periodic helminth infections in adult age (acute infections) may induce allergic manifestations whereas long-lasting helminthic infections in early age (childhood) (chronic infections) may suppress allergic inflammation due to inducing an immunomodulatory environment. 2) **Intensity of infection** – light parasite burden may induce allergic manifestations and heavy parasite burdens may induce down-modulation of allergic symptoms. 3) **Host genetics** – atopic individuals may be more likely to develop allergic manifestations than non-atopic individuals. 4) **Parasite** – different helminthes have different effects on atopy and allergies, parasites with larvae stages in the lung and skin than in other organs/tissues may be more predisposed to allergic manifestations.

4. Helminths and their products as anti-inflammatory modulators for allergic and anaphylactic disorders

Despite inducing strong Th2 and being considered predisposing factor to allergic manifestations, helminth infections can induce suppression of allergic diseases. Smits et al. (2010) related that chronic helminth infections may protect against allergic diseases by stimulating regulatory B and T cells and modulating dendritic cell functions. The immunosuppressive effect of helminthes and their products in the immune response have been widely reported in the literature (Smits et al., 2010; Hewitson et al., 2009; Soares & Araujo, 2008; Harnett & Harnett, 2008; Maizels et al., 2004). Helminth molecules can degrade some host molecules such as eotaxin and antibodies, inhibit the formation of reactive oxygen and nitrogen intermediates, interfere with macrophage activaction, down-modulate the antigen presentation by dendritic cell and macrophages, and mimic cytokines such as IFN-γ, TGF-β and MIF.

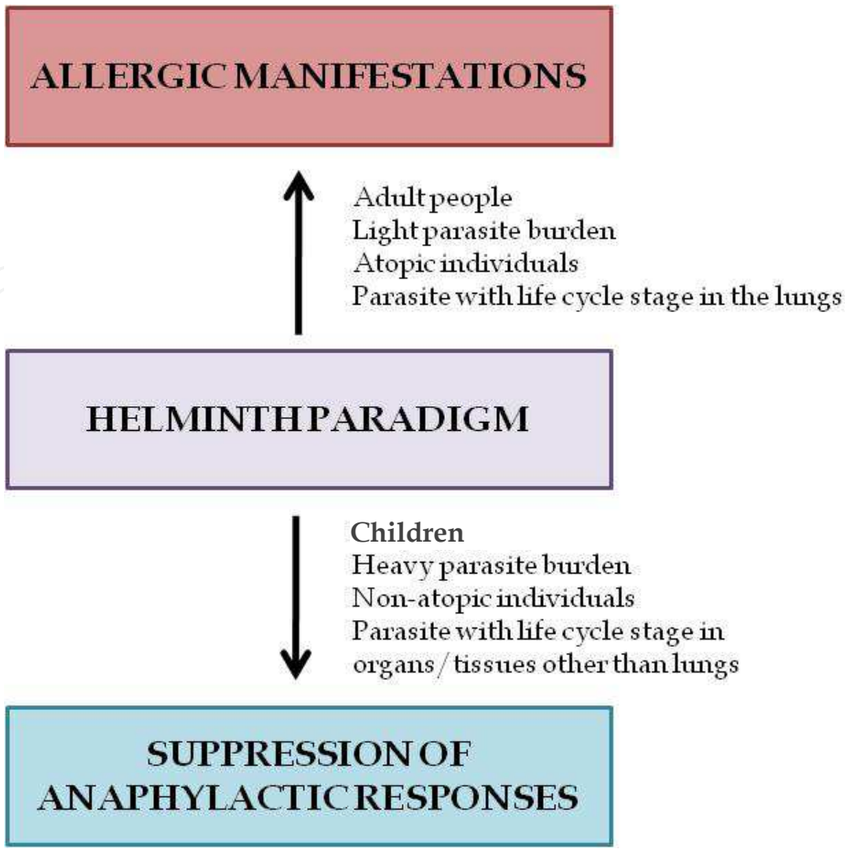


Fig. 2. Helminth paradigm. Helminthes can stimulate allergic manifestations or suppress inflammatory/anaphylactic responses depending on time and intensity of the infection, host genetic background and parasite life cycle.

Helminth infections can impair immune response toward heterologous antigen (Stewart et al., 1999), allografts (Liwski et al., 2000), viral infections (Actor et al., 1993) and other helminth infections (Jenkins, 1975). Helminths employ several immunomodulatory strategies in order to evade and/or modify the host immune response and, consequently, perpetuate their survival in the host (Playfair, 1982), including inactivation and/or modulation of the host protective immune response. The immunomodulation has been considered beneficial both to the host and the parasites since it could avoid helminth erradication and protect the host from inflammatory responses that may damage the host´s tissue (van Riet et al., 2007).

It has been identified several immunomodulatory molecules and strategies by which the helminths evade the host immune system, permitting that the parasites subvert the host protective responses. Some of these molecules include eotaxin metalloproteinase (Culley et al., 2000), calreticulin (Pritchard et al., 1999), antioxidants (Brophy et al., 1995) and neutrophil inhibitory factor (Moyle et al., 1994). They can interfere with antigen processing and presentation (Dainichi et al., 2001), cell proliferation (Allen & MacDonalds, 1998), cause T cell death (Semnani et al., 2003), decrease IgE responses (Langlet et al., 1984), reduce B cell activation (Deehan et al., 1997) and stimulate regulatory T cells (Belkaid et al., 2006). In this section, we will discuss about some helminth products and their immunomodulatory effect in the immune system (Figure 3).

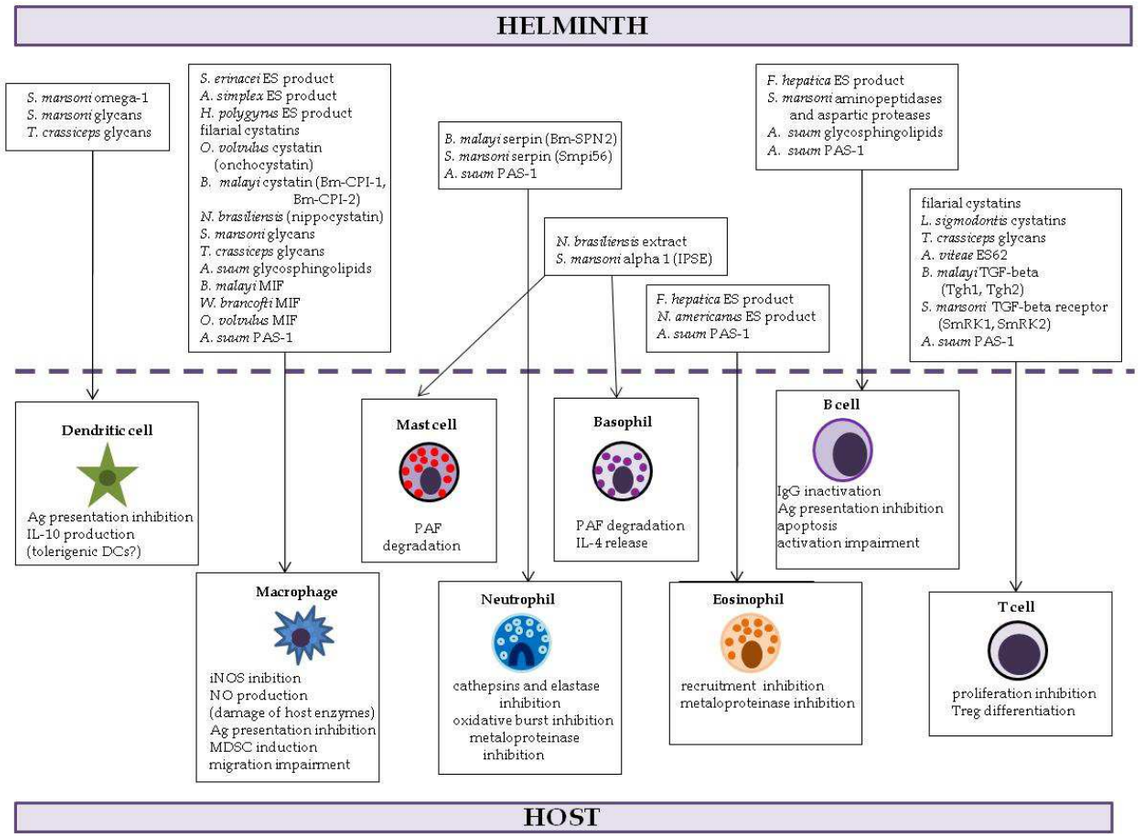


Fig. 3. Some immunosuppressive products secreted by helminthes that may be used as therapeutic strategies for anaphylactic disorders. Helminth can secrete molecules that possess down-modulatory effect on the host's immune system. The upper panel show some molecules secreted by helminthes and the lower panel show the cell targets of the helminth-secreted products. Abs, antibodies; Ag, antigen; ES, excretory/secretory products; MIF, macrophage-migration inhibition factor; MDSC, myeloid-derived suppressor cells; NO, nitric oxide; iNOS, inducible nitric oxide synthase; PAF, platelets-activating factor; PAS-1, protein from *Ascaris suum*; Treg, regulatory T cells.

4.1 Helminth products and their strategies to immunomodulate the host immune responses

4.1.1 Cleavage of host immune system molecules

It has been described several helminth defense mechanisms that can block host immune system by cleaving immune factors. The adult stage of *Nippostrongylus brasiliensis* releases in *in vitro* culture a product with acetylhydrolase activity that promotes cleavage of platelet-activating factor (PAF), promoting bronchoconstriction and increasing vascular permeability (Blackburn & Selkirk, 1992). Excretory/secretory (ES) products from hookworm *Necator americanus* cleave eotaxin (Culley et al., 2000), and in this way inhibit the recruitment of eosinophils, pivotal cells in development of the late phase of allergic responses.

Helminth serpins can also interfere in the immune response by cleaving immune factors. Serpins are an extensive family of serine proteinase inhibitors which regulate a wide variety

of proteinase-dependent physiological functions, such as blood coagulation, fibrinolysis, activation of complement, and the inflammatory response (Potempa et al., 1994). A serpin produced by microfilarial stage of *Brugia malayi*, Bm-SPN-2, inhibits the enzymatic activity of serine proteinases, cathepsin G and elastase from human neutrophils (Zang et al., 1999). In addition, Smpi56, a serpin from *Schistosoma mansoni*, inhibits the neutrophil elastase (Ghendler et al., 1994), protecting the parasite from activated neutrophils during inflammation.

Besides promoting the cleavage of PAF, eotaxin and inactivation of neutrophil enzymes, helminth products also can cleave host antibody. Antibody cleavage is critical for the parasite evasion because it inhibits ADCC (antibody-dependent cell cytotoxity) and promotes IgG degradation, which blocks FcγR-mediated cytokine release. For instance, ES products from *Fasciola hepatica* cleave all human IgG subclasses at the hinge region (Berasain et al., 2000). In addition, *S. mansoni* schitosomula produces a trypsine-like proteinase or aminopeptidase that cleave Fab fragment when Fc receptor of the worm binds IgG (Auriault et al., 1981). Recombinant schistosome aspartic proteases from *S. japonicum* cleave specifically human IgG, suggesting that these proteases may play a role in the degradation of host serum proteins ingested as part of the schistosome bloodmeal (Verity et al., 2001).

4.1.2 Modulation of nitric oxide production

Nitric oxide (NO) is a potent microbicidal agent that plays a role in host defense against parasites. This effect has been demonstrated toward several helminthes. It has been found that ES products from parasites such as *Spirometra erinacei* (Fukumoto et al., 1997), *Anisakis simplex* (Cuellar et al., 1998), *Heligmosomoides polygyrus* (Rzepecka et al., 2006) suppress the expression of iNOS in LPS-activated macrophages in a dose dependent manner. However, filarial nematode cystatins (Hartmann et al., 2002) up-regulate NO production from IFN-γ-activacted macrophages. In spite of the susceptibility of parasites to NO, its stimulation in the host by helminth products is critical to promote nitration and oxidation of host´s molecules and damage several biological processes. Moreover, in filariasis murine model NO production was associated with suppression of T cell proliferation (O'Connor et al., 2000), suggesting that the secretion of NO is linked to microfilariae killing and T cell response inhibition.

4.1.3 Interference with antigen presentation and T cell responses

Helminth cystatins are thought to be the most important molecules that interfere with antigen presentation. Cystatins constitute a family of cysteine protease inhibitors that are widely distributed and play essential roles in a spectrum of physiological processes (Barrett, 1986). Nematode cystatins could lead to severe changes in antigen processing and inhibit efficient generation of peptide-MHC class II molecule, decreasing the antigen presentation by APC. These molecules target cysteine proteases such as cathepsins, which play a role in two catalytic processes (Hartmann & Lucius, 2003). First, cysteine proteases degrade proteins within the endosomal-lysosomal compartment of APC. Second, cysteine proteases are involved in the cleavage of the MHC class II-associated invariant chain, which leads to the formation of MHC molecules associated to CLIP (class II-associated invariant chain peptide). Then, synthesized CLIP molecules allow the binding of peptides to MHC class II molecules to promote antigen presentation. The invariant chain cleavage is promoted by cathepsins S in B cells and dendritic cells (Riese et al., 1996), cathepsins L in thymus epithelial cells (Nakagawa et al., 1998) and cathepsin F in macrophages (Shi et al., 2000).

Nematode cystatins are homologous to mamalian cystatin C, which are highly expressed by immature dendritic cells and are down-regulated during dendritic cells maturation process to permit the transport of MHC II molecules to cell surface. Parasite cystatins maintain dendritic cells in immature state, preventing the antigen presentation by these cells and also down-regulate *in vitro* cellular proliferation (Pierre & Mellman, 1998). The first described parasite cystatin was onchocystatin, derived from *Onchocerca volvulus* (Lustigman et al., 1992), that down-regulates the HLA-DR expression by human monocytes after 72 hours of co-culture (Hartman et al., 1997). *Brugia malayi* nematodes secrete two homologues cystatins (Schonemeyer et al., 2001; Manoury et al., 2001): Bm-CPI-1, which is selectively expressed by L2 and L3 stage into the mosquito vector and Bm-CPI-2, which is constitutively expressed during the parasite life and interferes with two classes of proteases in the MHC class II antigen presentation: cathepsins B, L and S and asparagine endopeptidase. Also, Bm-CPI-2 blocks the presentation of peptide derived from tetanus toxoid by human B cells. Nippocystatin, a cysteine protease inhibitor found in ES products from *N. brasiliensis*, modulate the antigen processing and interfere with antigen presentation due to inhibiting multiple cysteine protease activities found in endosomes/lysosomes of B cells (Dainichi et al., 2001). In addition, *Litomosoides sigmodontis* cystatins upregulate the production of tumor necrosis factor alpha (TNF-α) and decrease antigen-specific proliferation of spleen cells in mice (Pfaff et al., 2002). Besides inhibiting proteases from MHC classe II pathway, cystatins can also down-modulate T cell proliferation and up-regulate IL-10 production (Hartmann et al., 1997; Schonemeyer et al., 2001). ES62, a phosphorylcholine-bearing filarial product, secreted by *Acanthocheilonema viteae*, desensitizes LPS-stimulated mouse peritoneal macrophages to produce IFN-γ (Goodridge et al., 2001). ES-62 also reduces lymphocyte proliferation and stimulates anti-inflammatory properties (Harnett & Harnett, 2001). Phosphorylcholine(PC)-containing glycosphingolipids from *Ascaris suum* are immunomodulatory molecules due to the fact that they inhibit BCR-mediated B cell proliferation by causing apoptosis, inhibit LPS-induced activation of B cells by decreasing Erk phosphorylation, modulate IL-12p40 production in LPS/IFN-γ-induced peritoneal macrophages (Deehan et al., 2002) indicating the PC moiety is important to induce the immunomodulatory effect. In addition, lysophosphatidylserine from *S. mansoni* can specifically target the immune system via TLR-2, interacts to dendritic cells and induce IL-10-producing regulatory T cells involved in immunosuppression (van der Kleij et al., 2002).

4.1.4 Stimulation of myeloid-derived suppressor cells

Several carbohydrate components derived from helminthes also modulate the immune response by stimulating myeloid-derived suppressor cells (MDSC) (Reyes & Terazas, 2007) These cells are a heterogeneous population of cells that express CD11b and Gr-1 and consists of early myeloid progenitors and immature myeloid cells (macrophages, granulocytes and dendritic cells) at different stages of differentitation (Gabrilovich & Nagaraj, 2009). The basic concept about suppressor cells is based on the findings of Gordon's group who observed a direct in vitro effect of IL-4 on the expression of mannose receptor in macrophages (reviewed in Gordon, 2003). This observations lead to macrophages being categorized in classically-activated (CA) macrophages which are NO- and IFN-γ-dependent (Kusmartsev et al., 2000) and alternatively-activated (AA) macrophages which are IL-4- or IL-13-dependent (Kreider et al., 2007; Goerdt et al., 1999). In this regard, Mantovani et al. (2004) proposed that macrophages can be polarized in

inflammatory (M1) or anti-inflammatory (M2) conditions. Besides, M2 macrophages can be classified into subpopulations M2a (which are AA macrophages) and M2b (which are IL-10-secreting cells upon immune complex activation), and M3c (which are IL-10-induced deactivated macrophages). All these type of macrophages (and other suppressor cells) can be found in several different of immunological situations, including tumors, autoimmunity, intracellular pathogen infections, helminthic infections.

Two glycans derived from *Schistosoma* eggs, lacto-N-fucopentaose III and lacto-N-neotetraose, have been related to induce IL-10 production, suppressing T cell proliferation (Terrazas et al., 2001). Soluble egg antigens (SEA) from *S. mansoni*, which are rich in lacto-N-fucopentaose III, suppress the LPS-induced inflammation by inducing Th2 responses (Pearce & MacDonald, 2002), by enhancing production of IL-10 and impairing dendritic cell (DC) activation. This latter property is due to the fact that SEA inhibit MyD88-independent, but not dependent-, pathways which result in IL-10 production (Kane et al., 2004), suggesting that SEA regulate multiple signaling pathways downstream and may target the initiation signaling in DC. The suppression of DC activation could be through the ligation of mannose receptor or DC-SIGN (DC-specific intercellular adhesion molecule-grabbing non-integrin) that results in inhibition of DC to secrete IL-12 in response to TLR ligands (Nigou et al., 2001). DC-SIGN ligation leads to IL-10 production, which has been implicated in suppression of DC function (Geijtenbeek et al., 2001). It has been found that lacto-N-fucopentaose III presents an anti-inflammatory effect due to inducing Th2 response and functioning as an adjuvant (Okano et al., 2001). High levels of IL-4, IL-5, IL-10, but not IFN-γ, are secreted by nasal lymphocytes from mouse immunized with human serum albumin conjugated to lacto-N-fucopentaose III. Lacto-N-fucopentaose III is also able to expand peritoneal macrophages that bear Gr1+ marker and act as suppressor cells, inhibiting CD4+ T cell proliferation via NO- and IFN-γ-dependent mechanisms (Atochina et al., 2001).

Carbohydrate components from *Taenia crassiceps* also favor Th2 responses, stimulating IgG1 and polyclonal IgE responses, IL-4, IL-5, IL-10 production to a bystander antigen and are critical to induce gene expression in AA macrophages (Gomes-Garcia et al., 2006), indicating that these components enhance Th2 responses as an adjuvant and trigger anti-inflammatory responses by stimulating AA macrophages. Glycans from *Taenia crassiceps* in their conformational structure recruit F4/80+ Gr1+ peritoneal exudate cells and suppresses proliferation of CD90+ cells (T cells) via cell-to-cell contact, not via IFN-γ and NO (Gomes-Garcia et al., 2005). Moreover, *T. crassiceps* glycans did not activate F4/80+ Gr1+ cells (M2a macrophages) through TLR-4 as has been proposed to synthetic and natural glycoconjugates (Terrazas et al., 2001; Atochina et al., 2001). In addition, the treatment of intact glycans with sodium periodate, which removes glycosilation, decrease M2a macrophages indicating that intact glycans are essential to recruit F4/80+ Gr1+ cells.

4.1.5 Inititation of Th2 immune responses

S. mansoni eggs secrete two proteins that have been implicated in Th2 differentiation: alpha-1 and omega-1. Alpha-1 is a dimer that cross-link IgE-FcεRI complex on basophils, in an antigen-dependent manner, hence being named IL-4 inducing principle of schistosoma eggs (IPSE). It induces the degranulation of mouse and human basophils and releases of IL-4 release (Schramm et al., 2003, 2007), initiating Th2 differentiation. Omega-1 is a ribonuclease also secreted by schistosoma eggs which is necessary to egg transit into the host tissues (Fitzsimmons et al., 2005). It is believed to be involved in Th2 responses by conditioning

human monocyte-derived dendritic cells to drive Th2 polarization (Everts et al., 2009; Steinfelder et al., 2009).

4.1.6 Mimicry of cytokines and other mediators

Helminthes can produce homologous proteins to immune system mediators/receptors, such as TGF-β, IFN-γ, TNF-αR and histamine that play a role in regulating anti-parasite responses. Parasite-encoded TGF-β molecules have been characterized in filarial nematodes *Brugia malayi* and *B. pahrangi.* They are two TGF-β homologues that show to be differentially regulated during the filarial life cycle: tgh-1 in *Brugia malayi* and *B. pahangi* (Gomez-Escobar et al., 1997), and tgh-2 in *B. malayi* (Gomes-Escobar et al., 2000). Tgh-1 molecule is required for filarial development within the human host (Gomes-Escobar et al., 1998) and Tgh-2 is predominantly expressed in adult stages and binds to the human TGF-β receptor (Hirata et al., 2005), mimicking human TGF-β and stimulating regulatory responses in the host. In addition to *Brugia* species, TGF-β immunorective molecules have been detected at the surface of cervical bodies, in tegument and subtegumental cells of other parasite stages of S*chistosoma japonicum*, during the whole life cycle (eggs, cercariae, schistosomula and adult worms), although being distinctly regulated at each developmental stage (Davies et al., 1998).

Besides TGF-β homologues, TGF-β receptor homologues have also been described in *Brugia* and *Schistosoma* species. SmTβR1 or SmRK1, a homologue of type I TGF-β receptor and a type of TGF-β family of receptor serine/threonine kinase, have been shown in *Schistosoma mansoni* surface following its entry into the mammalian host (Forrester et al., 2004). In addition to expressing SmRK1, *S. mansoni* expresses another type I TGF-β receptor, SmRK2, from schistosomula and adult stages and it is located predominantly to the tegumental surface of parasite (Grencis & Entwistle, 1997). Type I TGF-β receptor (Bp-trk-1) has been also isolated from the filarial parasitic nematode *Brugia pahangi* in the three main stages of its life cycle: microfilariae, infective larvae and adults; although the ligand remains unknown, it may likely act as a receptor for host TGF-β rather than for parasite ligands (Gomes-Escobar et al., 2000).

Helminths also produce homologues that mimic IFN-γ. *Trichuris muris*-derived molecules share cross reactive epitopes with the host IFN-γ. Moreover, these molecules can be shown to bind to IFN-γ receptor and induce change in lymphoid cells similar to those induced by murine IFN-γ (Calandra & Bucala, 1997). Thus, it possible that the host immune system produces IL-4 to expulse the worms, the IFN-γ homologue production may perpetuate the parasite survival into the host.

Other types of molecules that mimic the host cytokines are macrophage-migration inhibition factors (MIFs), which are produced by several nematodes. Mammalian MIFs are small proteins produced by non-haematopoietic cells that act as pro-inflammatory cytokines and induce TNF production by macrophages in acute settings, such as septic shock (Pastrana et al, 1998). The first MIF homologue to be characterized from a nematode was BM-MIF-1 identified in the filarial parasite *Brugia malayi*, but *Wuchereria bancrofti* and *O. volvulus* also encode MIF family proteins (Reyes & Terrazas, 2007). It may play multiple roles in host-parasite interaction due being located in several tissue types and being found in both cell-associated and secreted forms. Possibly, helminthes may secrete MIF molecules down-modulate the inflammatory response, mainly by stimulating myeloid-derived suppressor

cells that has been found to play down-regulatory functions in helminth infections, such as T cell proliferation inhibition and IL-10 and TGF-β release.

5. PAS-1, an anti-inflammatory protein from *Ascaris suum*

Our research group has been investigating the effect of *Ascaris suum* infection and secreted products in the inflammatory response. We have been demonstrated that components from *Ascaris suum* body extract modulate the antibody response and the cell-mediated response in mice. Soares et al. (1987) have demonstrated that, besides inhibiting the IgE production, *A. suum* extract suppresses the IgG1 and IgG2a antibody production. Ferreira et al. (1995) have shown that DBA/2 mice immunized subcutaneouly with OVA + *A. suum* extract and challenged with OVA in the footpad present suppression of immediate (3 hour after challenge) and late (24 hours after challenge) type IV hypersensitivity reaction. The isolation of protein fractions from *A. suum* extract by Sephacryl S-300 gel filtration chromatography yields three peaks (PI, PII, and PIII). PI is constituted by high weight components that suppress anti-OVA IgE antibody production in mice immunized with OVA + PI (Soares et al., 1992; Faquim-Mauro & Macedo, 1998). Thus, the suppressive effect observed in *A. suum* extract is due to high molecular weight components. PI protein fraction was used to obtain the monoclonal antibody MAIP-1, which recognizes one of the suppressive components in the *A. suum* extract; it is a 200-kDa-protein named PAS-1 (protein from *Ascaris suum*) (Oshiro et al., 2004).

PAS-1 suppresses the LPS-induced leukocyte migration and pro-inflammatory (IL-1β, IL-6 and TNF-α) cytokines production in air pouches exudates and macrophage culture supernatant; moreover, it stimulates the production of IL-10 and TGF-β (Oshiro et al., 2005), indicating that the modulatory effect of PAS-1 in LPS-induced inflammation is likely due to these two cytokine. Furthermore, PAS-1 was demonstrated modulating the humoral and cellular immune response against OVA. It inhibits the production of IgM, IgG1, IgG2a, IgE and anaphylactic IgG1 toward T-dependent but not T-independent, antigens and anti-OVA type IV hypersensitivity reaction in mouse footpad injected with carrageenan (Oshiro et al., 2006), suggesting that PAS-1 suppresses B and T cell responses.

PAS-1 also down-modulates antibody production, Th2 cytokine secretion, cellular recruitment and airway hyperesponsiveness induced by APAS-3, allergenic protein from *A. suum* (Itami et al., 2005). We have demonstrated that regulatory T CD4+CD25+ cells and T CD8+ cells secrete IL-10/TGF-β and IFN-γ, respectively and they are involved in the mechanisms by which PAS-1 down-modulate the acute lung allergic inflammation in mice since OVA-induced inflammation is reverted when PAS-1-primed regulatory T CD4+CD25+ cells or T CD8+ cells are adoptively transferred to OVA-immunized mice (Araujo et al., 2008; De Araujo et al., 2010). Besides playing an immunosuppressive role in the acute lung inflammation, we recently found that PAS-1 decreases the airway remodeling and angiogenesis in a mouse chronic lung inflammation model induced by OVA or APAS-3 by inhibiting metaloproteinases (MMP-2, MMP-9, ADAM-33) and angiogenic factors (VEGF and IL-13) (Araujo et al., manuscript in preparation).

6. Conclusion

In conclusion, anaphylaxis is a life-threatening and systemic disorder that involves two different pathways: classical anaphylactic pathway which is IgE-dependent mechanism

triggered by IgE-FcεRI signaling on mast cell and basophils to secrete histamine, and alternative anaphylactic pathway which is IgG-dependent triggered by IgG-immune complex bound to FcγRIII on basophils and macrophages to secrete PAF. The understanding of molecular and cellular mechanisms involved in the anaphylactic disorders is crucial to investigate terapeuthic strategies for preventing anaphylaxis risk and recurrence.

Helminths secrete several immmunomodulatory factors that can modulate inflammatory response. Some helminth products can cleave host molecules, such as chemokines, antibodies, and enzymes; modulate the NO production; interfere with antigen presentation and T cell responses by down-modulating DC functions; mimic cytokines such as IFN-γ and TGF-β and MIF. Other potent immunodulatory molecule from helminth is PAS-1, a protein from *A. suum*, that down-modulate acute inflammatory responses and chronic lung allergic inflammation, decreasing IgG1 and IgE production, eosinophil infiltrate, and Th2 cytokines and interfering with metaloproteinase activity and production of angiogenic factors. Thus, due to their capacity to induce immunomodulation, these helminth products may be useful for therapeutic interventions in inflammatory, allergic and anaphylactic disorders.

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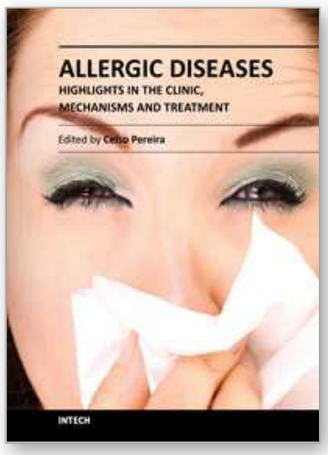
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