We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

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

C.A. Araujo¹ and M.F. Macedo-Soares²

¹Department of Immunology, St Jude Children's Research Hospital, Memphis, TN,

²Laboratory of Immunopathology, Butantan Institute, Sao Paulo, SP,

¹USA

²Brazil

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 immunomodulatory 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 immunosuppressive 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+ $\gamma\delta$ TCR+ 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 metalloproteinases 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 feeling 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 Fc ϵ RI-

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, TNF α , IL-1, VEGF) (Kumar & Sharma, 2010). Strait et al. (2003) have demonstrated that IgE-mediated anaphylaxis depends on IL-4/IL-4R α , mast cells, Fc ϵ RI, 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 Fc γ RIII 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 differentiation (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 Fc ϵ RI, 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 Fc ϵ RI, high affinity IgE receptor, and upon cross-linking of Fc ϵ RI-bound IgE with specific antigen, they release effector mediators such as histamine, leukotrienes, 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-Fc γ RIIb/Fc γ RIII antibody (against low affinity Fc γ Rs), and they secrete high amount of PAF when stimulated by IgG1-immune complexes, indicating basophils as a good candidate to trigger IgG1-mediated anaphylactic 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 cysteine 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-Fc γ RIIb/Fc γ RIII monoclonal antibodies (against low affinity Fc γ Rs) 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 Fc γ RIII-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-Fc γ RIIb/Fc γ RIII stimulates macrophages to release PAF by cross-linking Fc γ RIII on these cells and also inhibits IgG-dependent anaphylactic responses to antigen by blocking IgG-immune complex activation of macrophages through Fc γ RIII (Ujike et al., 1999; Strait et al., 2002).

2.4 Mediators involved in classical and alternative anaphylactic reactions

2.4.1 IgE and Fc ϵ RI

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 (C ϵ 1-4) (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 μ g/mL whereas IgG4 peaks at around 680 μ g/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 (Fc ϵ RI($\alpha\beta\gamma$ 2 and $\alpha\gamma$ 2), galectin-3 and Fc ϵ RII) and four receptors in mice (Fc ϵ RI($\alpha\beta\gamma$ 2 and $\alpha\gamma$ 2), galectin-3, Fc ϵ RII and Fc ϵ RIV). Most of IgE bind to high affinity IgE receptor (Fc ϵ RI) that is present in mast cells, basophils (Gould et al., 2003) and antigen-presenting cells e.g. Langerhans cells (Bieber et al., 1992). Fc ϵ RI has a central role in mediating the allergic disorders (Kinet, 1999). Cross-linking of Fc ϵ RI 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. Fc ϵ RI 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 ($K_d \sim 10^{-10}$ M). The extracellular domain of α -subunit is glycosylated which seem to be crucial to appropriate maturation during Fc ϵ RI 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 Fc ϵ RI (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 Fc γ RI, Fc γ RIIA, Fc α RI (Takai, 2005). Other variant of Fc ϵ RI 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 (Fc ϵ RII) 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, Fc γ RIV, which binds IgE-immune complexes on macrophage surface, inducing lung inflammation (Mancardi et al., 2008).

2.4.2 IgG and Fc γ RIII

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 -globulin 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 compartments. Four different types of Fc γ Rs have been identified in mice (Fc γ RI, Fc γ RIIb, Fc γ RIII, and Fc γ RIV). The human and primates Fc γ Rs have several allelic variants that codify six types of Fc γ Rs: Fc γ RI, Fc γ RIIa, Fc γ RIIc, Fc γ RIIb, Fc γ RIIIa, Fc γ IIIB.

Traditionally, these receptors belong to two different categories – they are classified in high or low affinity Fc γ Rs according IgG affinity to them, and in activating or inhibitory Fc γ Rs if the type of signaling pathway is triggered by ITAMs (immunoreceptor tyrosine-based activation motif) or ITIMs (immunoreceptor tyrosine-based inhibitory motif). Then, Fc γ RI is high affinity, activating Fc γ Rs in both mice and humans; Fc γ RIII and Fc γ RIV (in mice) and Fc γ RIIa, Fc γ RIIc, Fc γ RIIIa, Fc γ RIIb (in human) are categorized as low affinity, activating Fc γ Rs; and Fc γ RIIb is the only low affinity, inhibitory Fc γ R in mice and humans. IgGs antibodies bind with different affinity and specificity to different Fc γ Rs (Dijstelbloem et al., 2001). In general terms, monomeric IgG binds predominantly to high affinity Fc γ Rs (Fc γ RI) and IgG-immune complexes binds to low affinity Fc γ R. 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 Fc γ Rs (Fc γ RI-IV), neutrophils express mainly Fc γ RIII, Fc γ RIV and Fc γ RIIb, dendritic cells express Fc γ RI, Fc γ RIII, Fc γ RIIb, NK cells only express Fc γ RIII and B cells only have Fc γ RIIb (Nimmerjhan & Ravetch, 2008).

IgG antibodies and Fc γ RIII have been implicated in triggering alternative anaphylaxis pathway. Mice lacking mast cells, IgE or Fc ϵ RI alpha chain still develop systemic anaphylactic responses upon antigen exposure (Jacoby et al., 1984; Oettgen et al., 1994; Dombrowicz et al., 1997) whereas Fc γ R deficient mice that lack the expression of Fc γ RI and activating Fc γ (receptors Fc γ RI, Fc γ RIII, Fc γ RIV) 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-Fc γ RIIb/Fc γ RIII, Fc γ RIV monoclonal antibodies, the systemic anaphylaxis was inhibited, indicating the role of Fc γ RIII 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, rhinorrhea and conjunctival 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-4R α

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 *Trichinella 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-4R α 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 supply 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 *Schistosoma 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 (Loeffler, 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 activation, 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 eradication 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 cytotoxicity) 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* schistosomula produces a trypsin-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-activated 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 mammalian 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 differentiation (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; Goerdts 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 Initiation 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-Fc ϵ RI 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- α R 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. pahangi*. 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 immunoreactive molecules have been detected at the surface of cervical bodies, in tegument and subtegumental cells of other parasite stages of *Schistosoma 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. SmT β R1 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 subcutaneously 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-1 β , 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 hyperresponsiveness 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 metalloproteinases (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 therapeutic strategies for preventing anaphylaxis risk and recurrence.

Helminths secrete several immunomodulatory 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 immunomodulatory 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 metalloproteinase 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.

7. References

- Acevedo, N.; Sanchez, J.; Erler, A.; Mercado, D.; Briza, P.; Kennedy, M.; Fernandez, A.; Gutierrez, M.; Chua, KY; Cheong, N; Jimenez, S; Puerta, L & Caraballo, L. (2009). IgE cross-reactivity between *Ascaris* and domestic mites: the role of tropomyosin and the nematode polyprotein ABA-1. *Allergy*, Vol.64, No. 11, (November 2009), pp. 1635-1643, ISSN0105-4538
- Acevedo, N.; Erler, A.; Briza, P.; Puccio, F.; Ferreira, F. & Caraballo, L. (2011). Allergenicity of *Ascaris lumbricoides* tropomyosin and IgE sensitization among asthmatic patients in a tropical environment. *International Archives of Allergy and Immunology*, Vol.154, No.3, (September 2011), pp.195-206, ISSN1018-2438
- Actor, J.K.; Shirai, M.; Kullberg, M.C.; Buller, R.M.; Sher, A. & Berzofsky, J.A. (1993). Helminth infections results in decreased virus-specific CD8+ cytotoxic T cell and Th1 cytokine responses as well as delayed virus clearance. *Proceedings of the National Academy of Sciences USA*, Vol.90, No.3, (February 1993), pp.948-952, ISSN0027-8424
- Akdis, C.A. & Blaser, K. (2003). Histamine in the immune regulation of allergic inflammation. *Journal of Allergy and Clinical Immunology*, Vol.112, No.1, (July 2003), pp.15-22, ISSN0091-6749
- Akdis, C.A. & Simons, F.E. (2006). Histamine receptors are hot in immunopharmacology. *European Journal of Pharmacology*, Vol.533, No.1-3, (March 2006), pp.69-76, ISSN0014-2980
- Allen, J.E. & MacDonalds, A.J. (1998). Profound suppression of cellular proliferation mediated by the secretions of nematodes. *Parasite Immunology*, Vol.20, No.5, (May 1998), pp.241-247, ISSN0141-9838
- Anthony, R.M.; Rutitzky, L.I.; Urban, J.F. Jr; Stadecker, M.J. & Gause, W.C. (2007). Protective immune mechanisms in helminth infection. *Nature Reviews Immunology*, Vol.7, No.12, (December 2007), pp.975-987, ISBN1474-1733
- Araujo, C.A.; Perini, A.; Martins, M.A.; Macedo, M.S. & Macedo-Soares, M.F. (2008). PAS-1, a protein from *Ascaris suum*, modulates allergic inflammation via IL-10 and IFN-γ, but not IL-12. *Cytokine*, Vol.44, No.3, (December 2008), pp.8308-8314, ISSN1043-4666

- Arinobu, Y.; Iwasaki, H.; Gurish, M.F.; Mizuno, S.; Shigematsu, H.; Ozawa, H.; Tenen, D.G.; Austen, K.F. & Akashi, K. (2005) Developmental checkpoints of the basophils/mast cell lineages in adult murine hematopoiesis. *Proceedings of the National Academy of Science USA*, Vol.102, No.50, (December 2005), pp.18105-18110, ISSN0027-8424
- Arnold, J.N.; Wormald, M.R.; Sim, R.B.; Rudd, P.M. & Dwek R.A. (2007). The impact of glycosilation on the biological function and structure of human immunoglobulins. *Annual Reviews of Immunology*, Vol.25, (2007), pp.21-50, ISSN0732-0582
- Atochina, O.; Daly-Engel, T.; Piskorska, D.; McGuire, E. & Harn, D.A Jr. (2001). A schistosome-expressed immunomodulatory glycoconjugate expands peritoneal Gr1(+) macrophages that suppress naïve CD4(+) T cell proliferation via an IFN-gamma and nitric oxide mechanism. *Journal of Immunology*, Vol.167, No.8, (October 2001), pp.4293-4302, ISSN0022-1467
- Auriault, C.; Ouaisi, M.A.; Torpier, G.; Eisen, H.; Capron, A. (1981). Proteolytic cleavage of IgG bound to the Fc receptor of *Schistosoma mansoni* schistosomula. *Parasite Immunology*, Vol.3, No.1, (Spring 1981), pp.33-44, ISSN0141-9838
- Barrett, A.J. (1986). The cystatins: a diverse superfamily of cysteinase peptidase inhibitors. *Biomedica Biochimica Acta*, Vol.45, No.11-12, (1986), pp.1363-1374, ISSN0232-766X
- Beaven, M.A. (2009). Our perception of the mast cell from Paul Ehrlich to now. *European Journal of Immunology*, Vol.39, No.1, (January 2009), pp.11-25, ISSN0014-2980
- Belkaid, Y.; Sun, C.M. & Bouladoux, N. (2006). Parasites and immunoregulatory T cells. *Current Opinion in Immunology*, Vol.18, No.4, (August 2006), pp.406-412, ISSN0952-7915
- Bell, R.G. (1996). IgE, allergies and helminth parasites: a new perspective on an old conundrum. *Immunology and Cell Biology*, Vol.74, No.4, (August 1996), pp.337-345, ISSN0818-9641
- Benveniste, J.; Henson, P.M & Cochrane, C.G. (1972). Leukocyte dependent histamine release from rabbit platelets. The role of IgE, basophils, and a platelet-activating factor. *Journal of Experimental Medicine*, Vol.136, No.6, (December 1972), pp.1356-1377, ISSN0022-1007
- Berasain, P.; Carmona, F.; Frangione, B.; Dalton, J.P. & Goni, F. (2000). *Fasciola hepatica*: parasite-secreted proteinases degrade all human IgG subclasses: determination of the specific cleavage sites and identification of the immunoglobulin fragments produced. *Experimental Parasitology*, Vol.94, No.2, (February 2000), pp.99-110, ISSN0014-4894
- Bieber, T.; De La Salle, H.; Wollenberg, A.; Hakimi, J.; Chizzonite, R.; Ring, J.; Hanau, D. & De la Salle, C. (1992). Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (Fc epsilon RI). *Journal of Experimental Medicine*, Vol.175, No.5, (May 1992), pp.1285-1290, ISSN0022-1007
- Blackburn, C.C. & Selkirk, M.E. (1992). Inactivation of platelet-activation factor by a putative acetylhydrolase from the gastrointestinal nematode parasite *Nippostrongylus brasiliensis*. *Immunology*, Vol.75, No.1, (January 1992), pp.41-46, ISSN0019-2805
- Botturi, K.; Lacoëuille, Y.; Vervloet, D.; & Magnan A. (2010). Histamine induces Th2 activation through the histamine receptor 1 in house dust mite rhinitic but asthmatic patients. *Clinical and Experimental Allergy*, Vol.40, No.5, (May 2010), pp.755-762, ISSN0954-7894
- Bradley, J.E & Jackson, J.A. (2004). Immunity immunoregulation and the ecology of trichuris and ascariasis. *Parasite Immunology*, Vol.26, No.11-12, (November-December 2004), pp.429-441, ISSN0141-9838

- Brophy, P.M.; Patterson, L.H.; Brown, A. & Pritchard, D.I. (1995). Glutathione S-transferase (GST) expression in the human hookworm *Necator americanus*: potential roles for excretory-secretory forms of GST. *Acta Tropica*, Vol.59, No.3, (June 1995), pp.259-263, ISSN0001-706X
- Brown, S.G. (2004). Clinical features and severity grading of anaphylaxis. *Journal of Allergy and Clinical Immunology*, Vol.114, No.2, (August 2004), pp.371-376, ISSN0091-6749
- Calandra, T. & Bucala, R. (1997) Macrophage migration inhibitory factor (MIF): a glucocorticoid counter-regulator within the immune system. *Critical Reviews in Immunology*, Vol.17, No.1, (1997), pp.77-88, ISSN1040-8401
- Camerer, E.; Regard, J.B.; Cornelissen, I.; Srinivasan, Y.; Duong, D.N.; Palmer, D.; Pham, T.H.; Wong, J.S.; Pappu, R. & Coughlin, S.R. (2009). Sphingosine-1 phosphate in the plasma compartment regulates basal and inflammation-induced vascular lead in mice. *Journal of Clinical Investigation*, Vol.119, No.7, (July 2009), pp.1871-1879, ISSN0021-9738
- Caraballo, A. & Acevedo, N. (2011). Allergy in the tropics: the impact of cross-reactivity between mites and *Ascaris*. *Frontiers in Bioscience*, Vol. E3, (January 2011), pp.51-64, ISSN1093-9946
- Capron, A.; Dessaint, J.P.; Haque, A. & Capron, M. (1982). Antibody-dependent cell-mediated cytotoxicity against parasites. *Progress in Allergy*, Vol. 31, (1982), pp.234-267, ISSN0079-6034
- Cauwels, A.; Janssen, B.; Buys, E.; Sips, P. & Brouckaert, P. (2006). Anaphylactic shock depends on PI3K and eNOS-derived NO. *Journal of Clinical Investigation*, Vol.116, No.8, (August 2006), pp.2244-2251, ISSN0021-9738
- Clough, G.F.; Bennett, A.R. & Church, M.K. (1998). Effects of H1 antagonist on the cutaneous vascular response to histamine and bradykinin: a study using scanning laser Doppler imaging. *British Journal of Dermatology*, Vol.138, No.5, (May 1998), pp.806-814, ISSN0007-0963
- Conrad, D.H.; Ben-Sasson, S.Z.; Le Gros, G.; Finkelman, F.D. & Paul, W.E. (1990). Infection with *Nippostrongylus brasiliensis* or injection of anti-IgD antibodies markedly enhances Fc-receptor-mediated interleukin 4 production by non-B, non-T cells. *Journal of Experimental Medicine*, Vol.171, No.5, (May 1990), pp.1497-1508, ISSN0022-1007
- Cooper, P.J. (2009). Interactions between helminth parasites and allergy. *Current Opinion in Allergy and Clinical Immunology*, Vol.9, No.1, (February. 2009), pp.29-37, ISSN1528-4050
- Cuellar, C.; Pertequer, M.J. & de Las Heras, B. (1998). Effect of *Anisakis simplex* on nitric oxide production in J774 macrophages. *Scandinavian Journal of Infectious Diseases*, Vol.30, No.6, (1998), pp.603-606, ISSN0300-9475
- Culley, F.J.; Brown, A.; Conroy, D.M.; Sabroe, I.; Pritchard, D.I. & Williams, T.J. (2000). *Journal of Immunology*, Vol.165, No.11, (December 2000), pp.6447-6453, ISSN0022-1767
- Daeron M. (1997). Fc receptor biology. *Annual Reviews of Immunology*, Vol.15, (1997), pp.203-234, ISSN0732-0582
- Dainichi, T.; Maekawa, Y.; Ishii, K.; Zhang, T.; Nashed, B.F.; Sakai, T.; Takashima, M. & Himeno, K. (2001). Nippocystatin, a cystein protease inhibitor from *Nippostrongylus brasiliensis*, inhibits antigen processing and modulates antigen-specific immune responses. *Infeccion and Immunity*, Vol.69, No.12, (December 2001), pp.730-7386, ISSN0019-9567

- Davies, S.J.; Shoemaker, C.B. & Pearce, E.J. (1998). A divergent member of the transforming factor beta receptor family from *Schistosoma mansoni* is expressed on the parasite surface membrane. *Journal of Biological Chemistry*, Vol.273, No.18, (May 1998), pp.11234-11240, ISSN1178-6264
- De Araujo, C.A.; Perini, A.; Martins, M.A.; Macedo, M.S. & Macedo-Soares, M.F. (2010). PAS-1, an *Ascaris suum* protein, modulates allergic airway inflammation via CD8 γ TCR γ and CD4 γ CD25 γ FoxP3 γ T cells. *Scandinavian Journal of Immunology*, Vol.72, No.6, (December 2010), pp.491-503, ISSN0300-9475
- Deehan, M.R.; Harnett, M.M. & Harnett, W. (1997). A filarial nematode secreted product differentially modulates expression and activation of protein kinase C isoforms in B lymphocytes. *Journal of Immunology*, Vol.159, No.12, (December 1997), pp.6105-6111, ISSN0022-1767
- Deehan, M.R.; Goodridge, H.S.; Blair, D.; Lochnit, G.; Dennis, R.D.; Geyer, R.; Harnett, M.M. & Harnett, W. (2002). Immunomodulatory properties of *Ascaris suum* glycosphingolipids - phosphorylcholine and non-phosphorylcholine- dependent effects. *Parasite Immunology*, Vol.24, No.9-10, (September-October 2002), pp.463-469, ISSN0141-2980
- De Silva, N.R.; Brooker, S.; Hotez, P.J.; Montresor, A.; Engels, D. & Savioli, L. (2003). Soil-transmitted helminth infections: updating the global picture. *Trends of Parasitology*, Vol.19, No.12, (December 2003), pp.547-551, ISSN1471-4906
- Dijstelbloem, H.M.; van de Winkel, J.G. & Kallenberg, C.G. (2001). Inflammation in autoimmunity: receptors for IgG revisited. *Trends in Immunology*, Vol.22, No.9, (September 2001), pp.510-516, ISSN1471-4906
- Dombrowicz, D.; Flamand, V.; Miyajima, I.; Ravetch, J.V.; Galli, S.J. & Kinet, J.P. (1997) Absence of Fc epsilon RI alpha chain results in upregulation of Fc gamma RIII-dependent mast cell degranulation and anaphylaxis. Evidence of competition between Fc epsilon RI and Fc gamma RIII for limiting amounts of FcR beta and gamma chains. *Journal of Clinical Investigation*, (March 1997), Vol.99, No.5, pp.915-922, ISSN0021-9738
- Everts, B.; Perona-Wright, G.; Smits, H.H.; Hokke, C.H.; van der Ham, A.J.; Fitzsimmons, C.M.; Doenhoff, M.J.; van der Bosch, J.; Mohrs, K.; Haas, H.; Mohrs, M.; Yazdanbakhsh, M. & Schramm, G. (2009). Omega-1, a glycoprotein secreted by *Schistosoma mansoni* eggs, drives Th2 responses. *Journal of Experimental Medicine*, Vol.206, No.8, (August 2009), pp.1673-1680, ISSN0022-1007
- Ewan, P.W. (1998). ABC of Allergies-Anaphylaxis. *BMJ*, Vol.316, No.7142, (May 1998), pp.1442-1445, ISSN0958-8146
- Fallon, P.G. & Mangan, N.E. (2007). Suppression of Th2 type allergic reactions by helminth infections. *Nature Reviews Immunology*, Vol.7, (March 2007), pp. 220-230, ISSN1474-1733
- Faquim-Mauro, E.L. & Macedo, M.S. (1998). The immunosuppressive activity of *Ascaris suum* is due to high molecular weight components. *Clinical and Experimental Immunology*, Vol.114, No.2, (November 1998), pp.245-251, ISSN0009-9104
- Fernandez-Caldas, E.; Puerta, L.; Mercado, D.; Lockey, R.F. & Caraballo, L.R. (1993). Mite fauna, Der p1, Der f1 and *Blomia tropicalis* allergen levels in a tropical environment. *Clinical and Experimental Allergy*, Vol.23, No.4, (April 1993), pp.292-297, ISSN0954-7894

- Fernandez-Caldas, E.; Puerta, L.; Caraballo, L. & Lockey, R.F. (2008). Mite allergens. *Clinical Allergy and Immunology*, Vol.21, (2008), pp.161-182, ISSN1075-7910
- Ferreira, A.P.; Faquim-Mauro, E.S.; Abrahamsohn, I.A. & Macedo, M.S. (1995). Immunization with *Ascaris suum* extract impairs T cell functions in mice. *Cellular Immunology*, Vol.162, No.2, (May 1995), pp.202-210, ISSN0008-8749
- Fiebiger, E.; Tortorella, D.; Jouvin, M.H.; Kinet, J.P. & Ploegh, H.L. (2005). Cotranslational endoplasmic reticulum assembly of FcεRI controls the formation of functional IgE-binding receptors. *Journal of Experimental Medicine*, Vol.201, No.2, (January 2005), pp.267-277, ISSN0022-1007
- Finkelman, F.D.; Katona, I.M.; Urban, J.F. Jr; Holmes, J.; Ohara, J.; Tung, A.S.; Sample, J.V. & Paul, W.E. (1988). IL-4 is required to generate and sustain in vivo IgE responses. *Journal of Immunology*, Vol.141, No.7, (October 1988), pp.2335-2341, ISSN0022-1767
- Finkelman, F.D.; Holmes, J.; Urban, J.F. Jr; Paul, W.E. & Katona, I.M. (1989). T help requirements for the generation of an in vivo IgE response: a late acting form of T cell help other than IL-4 is required for IgE but not for IgG1 production. *Journal of Immunology*, Vol.142, No.2, (January 1989), pp.403-408, ISSN0022-1767
- Finkelman, F.D. (2007). Anaphylaxis: lessons from mouse models. *Journal of Allergy and Clinical Immunology*, Vol.120, No.3, (September 2007), pp.506-515, ISSN0091-6749
- Fitzsimmons, C.M.; Schramm, G.; Jones, F.M.; Chalmers, I.W.; Hoffman, K.F.; Grevelding, C.G.; Wuhrer, M.; Hokke, C.H.; Haas, H.; Doenhoff, M.J. & Dunne, D.W. (2005). *Molecular and Biochemical Parasitology*, Vol.144, No.1, (November 2005), pp.123-127, ISSN0166-6851
- Forrester, S.G.; Warfel, P.W. & Pearce, E.J. (2004). Tegumental expression of a novel type II receptor serine/threonine kinase (SmRK2) in *Schistosoma mansoni*. *Molecular and Biochemical Parasitology*, Vol.136, No.2, (August 2004), pp.149-156, ISSN0166-6851
- Fukuda, Y.; Kawashima, H.; Saito, K.; Inomata, N.; Matsui, M. & Nakanishi, T. (2000). Effect of human plasma-type platelet-activating factor acetylhydrolase in two anaphylactic shock models. *European Journal of Pharmacology*, Vol.390, No.1-2, (February 2000), pp.203-207, ISSN0021-8219
- Fukumoto, S.; Hirai, K.; Tanikata, T.; Ohmori, Y.; Stuehr, D.J. & Hamilton, T.A. (1997). Excretory/secretory products from plerocercoids of *Spirometra erinacei* reduce iNOS and chemokine mRNA levels in peritoneal macrophages stimulated with cytokines and/or LPS. *Parasite Immunology*, Vol.19, No.7, (July 1997), pp.325-332, ISSN0141-2980
- Gabrilovich, D.I. & Nagaraj, S. (2009). Myeloid-derived suppressor cells as regulators of the immune system. *Nature Reviews Immunology*, Vol.9, No.3, (March 2009), pp.162-174, ISSN1474-1733
- Galli, S.J.; Kalesnikoff, J.; Grimbaldston, M.A.; Piliponsky, A.M.; Williams, C.M. & Tsai, M. (2005). Mast cells as “tunable” effector and immunoregulatory cells: recent advances. *Annual Reviews of Immunology*, Vol.23, (2005), pp.749-786, ISSN0732-0582
- Garman, S.C.; Kinet, J.P. & Jardetzky, T.S. (1999). The crystal structure of the human high affinity IgE receptor (FcεRI α). *Annual Reviews of Immunology*, Vol.17, (1999), pp.973-976, ISSN0732-0582
- Geijtenbeek, T.B.; Krooshoop, D.J.; Bleijs, D.A.; van Vliet, S.J.; Koppel, E.A.; van Duijnhoven, G.C.; Alon, R.; Figdor, C.G. & van Kooyk, Y. (2001). DC-SIGN-ICAM-2

- interaction mediates dendritic cell trafficking. *Journal of Experimental Medicine*, Vol.193, No.6, (March 2001), pp.671-678, ISSN0022-1007
- Geha, R.S.; Helm, B. & Gould, H. (1985). Inhibition of the Prausnitz-Kustner reaction by an immunoglobulin epsilon-chain fragment synthesized in *E. coli*. *Nature*, Vol. 315, No.6020, (June 1985), pp.577-578, ISSN0028-0836
- Geissmann, F.; Manz, M.G.; Jung, S.; Sieweke, M.H.; Merad, M. & Ley, K. (2010). Development of monocytes, macrophages and dendritic cells. *Science*, Vol.327, No.5966, (February 2010), pp.656-661, ISSN0272-4634
- Ghendler, Y.; Arnon, R. & Fishelson, Z. (1994). *Schistosoma mansoni*: isolation and characterization of Smpi56, a novel serine protease inhibitor. *Experimental Parasitology*, Vol.78, No.2, (March 1994), pp.121-131, ISSN0014-4894
- Goerdts, S.; Politz, O.; Schledzewski K.; Birk, R.; Gratchev, A.; Guillot, P.; Hakiy, N.; Klembe C.D.; Dippel, E.; Kodelja, V. & Orfanos, C.E. (1999). Alternative versus classical activation of macrophages. *Pathobiology*, Vol.67, No.5-6, (1999), pp.222-226, ISSN1015-2008
- Golightly, L.K. & Greos, L.S. (2005). Second generation antihistamines: actions and efficacy in the management of allergic disorders. *Drugs*, Vol.65, No.3, (2005), pp.341-384, ISSN0012-6667
- Gomes, R.N.; Bozza, F.A.; Amancio, R.T.; Japiassu, A.M.; Vianna, R.C.; Larangeira, A.P.; Gouveia, J.M.; Bastos, M.S.; Zimmerman, G.A.; Stafforini, D.M.; Prescott, S.M.; Bozza, P.T. & Castro-Faria-Neto, H.C. (2006). Exogenous platelet-activating factor acetylhydrolase reduces mortality in mice with systemic inflammatory response syndrome and sepsis. *Shock*, Vol.26, No.1, (July 2006), pp.41-49, ISSN1073-2322
- Gomez-Escobar, N.; van der Biggelaar, A. & Maizels, R. (1997). A member of the TGF-beta receptor gene family in the parasitic nematode *Brugia parangi*. *Gene*, Vol.199, No.1-2, (October 1997), pp.101-109, ISSN0378-1119
- Gomez-Escobar, N.; Lewis, E. & Maizels, R.M. (1998). A novel member of the transforming growth factor-beta (TGF-beta) superfamily from the filarial nematodes *Brugia malayi* and *B. parangi*. *Experimental Parasitology*, Vol.88, No.3, (March 1998), pp.200-209, ISSN0014-4894
- Gomez-Escobar, N.; Gregory, W.F. & Maizels, R.M. (2000). Identification of tgh-2, a filarial nematode homolog of *Caenorhabditis elegans* daf-7 and human transforming growth factor beta, expressed in microfilarial and adult stages of *Brugia malayi*. *Infection and Immunity*, Vol.68, No.11, (November 2000), pp.6402-6410, ISSN0019-9567
- Gomez-Garcia, L.; Lopez-Marin L.M.; Saavedra, R.; Rodriguez-Sosa, M. & Terrazas, L.I. (2005). Intact glycans from cestode antigens are involved in innate activation of myeloid suppressor cells. *Parasite Immunology*, Vol.27, No.10-11, (October-November 2005), pp.395-405, ISSN0141-2980
- Gomez-Garcia, L.; Rivera-Montoya, I.; Rodriguez-Sosa, M. & Terrazas, L.I. (2006). Carbohydrate components of *Taenia crassiceps* metacestodes display Th2-adjuvant and anti-inflammatory properties when co-injected with bystander antigen. *Parasitology Research*, Vol.99, No.4, (September 2006), pp.440-448, ISSN0932-0113
- Goodridge, H.S.; Wilson, E.H.; Harnett, W.; Campbell, C.C.; Harnett, M.M. & Liew, F.Y. (2001). Modulation of macrophage cytokine production by ES-62, a secreted product of the filarial nematode *Acanthocheilonema viteae*. *Journal of Immunology*, Vol.167, No.2, (July 2001), pp.94-945, ISSN0022-1767

- Gordon S. (2003). Alternative activation of macrophages. *Nature Reviews Immunology*, Vol.3, No.1, (January 2003), pp.23-35, ISSN1474-1733
- Gould, H.J.; Sutton, B.J.; Beavil, A.J.; Beavil, R.L.; McCloskey, N.; Coker, H.A.; Fear, D. & Smuthwaite, L. (2003). The biology of IgE and the basis of allergic diseases. *Annual Reviews of Immunology*, Vol.21, (2003), pp.579-628, ISSN0732-0582
- Gould, H.J. & Sutton, B.J. (2008). IgE in allergy and asthma today. *Nature Reviews Immunology*, Vol. 8, No.3, (March 2008), pp.205-217, ISSN1474-1733
- Grencis, R.K. & Entwistle, G.M. (1997). Production of an interferon-gamma homologue by an intestinal nematode: functionally significant or interesting artifact? *Parasitology*, Vol.115, No. Suppl, (1997), pp.S101-106, ISSN0031-1820
- Hanahan, D.J. (1986). Platelet activating factor: a biologically active phosphoglyceride. *Annual Reviews of Biochemistry*, Vol.55, (1986), pp.483-509, ISSN0066-4154
- Harnett, W. & Harnett, M.M. (2001). Modulation of the host immune system by phosphorylcholine-containing glycoproteins secreted by parasitic filarial nematodes. *Biochimica et Biophysica Acta*, Vol.1539, No.1-2, (May 2001), pp.7-15, ISSN0006-3002
- Harnett W & Harnett MM. (2008). Parasitic nematode modulation of allergic disease. *Current Allergy and Asthma Reports*, Vol.8, No.5, (September 2008), pp.392-397, ISSN1529-7322
- Hartmann, S.; Kyewski, B.; Sonnenburg, B. & Lucius, R. (1997). A filarial cysteine protease inhibitor down-regulates T cell proliferation and enhances interleukin-10 production. *European Journal of Immunology*, Vol.27, No.9, (September 1997), pp.2253-2260, ISSN0014-2980
- Hartmann, S.; Schonemeyer, A.; Sonnenburg, B.; Vray, B. & Lucius, R. (2002). Cystatins of filarial nematodes up-regulate the nitric oxide production of interferon-gamma activated murine macrophages. *Parasite Immunology*, Vol.24, No.5, (May 2002), pp.253-262, ISSN0141-9838
- Hartmann, S. & Lucius, R. (2003). Modulation of host immune responses by nematode cystatins. *International Journal of Parasitology*, Vol.30, No.11, (September 2003), pp.1291-1303, ISSN0020-7519
- Hewitson, J.P.; Grainer, J.R. & Maizels, R.M. (2009). Helminth immunoregulation: the role of parasite secreted proteins in modulating host immunity. *Molecular and Biochemical Parasitology*, Vol.167, No.1, (September 2009), pp.1-11, ISSN0166-6851
- Hirata, M.; Hirata, K.; Hara, T.; Kawabuchi, M. & Fukuma, T. (2005). Expression of TGF-beta-like molecules in the life cycle of *Schistosoma japonicum*. *Parasitology Research*, Vol.95, No.6, (April 2005), pp.367-373, ISSN0932-0113
- Honda, Z.; Suzuki, T.; Kono, H.; Okada, M.; Yamamoto, T.; Ra, C.; Morita, Y. & Yamamoto, K. (2000). Sequential requirements of the N-terminal palmytoylation site and SH2 domain of Src family kinases in the initiation and progression of FcεRI signaling. *Molecular and Cellular Biology*, Vol.20, No.5, (March 2000), pp.1759-1771, ISSN0270-7306
- Hu, Z.Q.; Zhao, W.H. & Shimamura, T. (2007). Regulation of mast cell development by inflammatory factors. *Current Medicinal Chemistry*, Vol.14, No. 28, (2007), pp.3044-3050, ISSN0929-8673
- Iio, A.; Waldmann, T.A. & Strober, W. (1987). Metabolic study of human IgE: evidence for an extravascular catabolic pathway. *Journal of Immunology*, Vol.120, No.5, (May 1987), pp.1696-1701, ISSN0022-1767

- Ishii, S.; Kuwaki, T.; Nagase, T.; Maki, K.; Tashiro, F.; Sunaga, S.; Cao, W.H.; Kume, K.; Fukuchi, Y., Ikuta, K.; Miyazaki, J.; Kumada, M. & Shimizu, T. (1998). *Journal of Experimental Medicine*, Vol.187, No.11, (June 1998), pp.1779-1788, ISSN0022-1007
- Ishizaka, K. & Iszhizaka, T. (1971). Mechanism of reaginic hypersensitivity: a review. *Clinical Allergy*, Vol. 1, No.1, (March 1971), pp.9-25, ISSN0009-9090
- Ishizaka, K. & Ishizaka, T. (1976). Identification of gamma-E-antibodies as a carrier of reaginic activity. *Journal of Immunology*, Vol.99, No.6, (1976), pp.1187-1198, ISSN0022-1767
- Itami, D.M.; Oshiro, T.M.; Araújo, C.A.; Perini, A.; Martins, M.A.; Macedo, M.S. & Macedo-Soares, M.F. (2005). Modulation of murine experimental asthma by *Ascaris suum* components. *Clinical and Experimental Allergy*, Vol.35, No.7, (July 2005), pp.873-879, ISSN0954-7894
- Jacoby, W.; Cammarata, P.V.; Findlay, S. & Pincus, S.H. (1984). Anaphylaxis in mast cell-deficient mice. *Journal of Investigative Dermatology*, Vol.83, No.4, (October 1984), pp.302-304, ISSN0022-202X
- Jenkins, D.C. (1975). The influence of *Nematospiroides dubius* on subsequent *Nippostrongylus brasiliensis* infections in mice. *Parasitology*, Vol.71, No.2, (October 1975), pp.349-355, ISSN0031-1820
- Jones BL & Kearns GL. (2011). Histamine: new thoughts about a familiar mediator. *Clinical Pharmacology and Therapeutics*, Vol.89, No.2, (February 2011), pp.189-197, ISSN0009-9325
- Kane, C.M.; Cervi, L; Sun, J; McKee, A.S.; Masek, K.S.; Shapira, S.; Hunter, C.A. & Pearce, E.J. (2004). Helminth antigens modulate TLR-initiated dendritic cell activation. *Journal of Immunology*, Vol.173, No.12, (December 2004), pp.7454-7461, ISSN0022-1767
- Karasawa, K. (2006). Clinical aspects of plasma platelets-activating factor- acetylhydrolase. *Biochimica et Biophysica Acta*, Vol.1761, No.11, (November 2006), pp.1359-1372, ISSN0006-3002
- Kemp, S.F. & Lockey, R.F. (2002). Anaphylaxis: a review of causes and mechanisms. *Journal of Allergy and Clinical Immunology*, Vol. 110, No. 3, (September 2002), pp.341-348, ISSN0091-6749
- Kumar, V. & Sharma, A. (2010). Mast cells; emerging sentinel innate immune cells with diverse role in immunity. *Molecular Immunology*, Vol.48, No.1-3, (November-December 2010), pp.14-25, ISSN0161-5890
- Kimura, S; Nagata, M.; Takeuchi, M.; Takano, K. & Harada, M. (1997). Anti-granulocyte antibody suppression of active and passive anaphylactic shock in WBB6F1-W/Wv mice. *Cellular and Molecular Life Sciences*, Vol.53, No.8, (August 1997), pp.663-669, ISSN1420-682X
- Kinet, J.P. (1999). The high -affinity IgE receptor (FcεRI): from physiology to pathology. *Annual Reviews of Immunology*, Vol.17, (1999), pp.931-972, ISSN0732-0582
- Kreider, T.; Anthony, R.M.; Urban Jr, J.F. & Gause, W.C. (2007). Alternatively activated macrophages in helminth infections. *Current Opinion in Immunology*, Vol.19, No.4, (August 2007), pp.448-453, ISSN0952-7915
- Kuhn, R.; Rajewsky, K. & Muller, W. (1991). Generation and analysis of interleukin-4 deficient mice. *Science*, Vol.254, No.5032, (November 1991), pp.707-710, ISSN0272-4634

- Kunzmann, S.; Schmidt-Weber, C.; Zingg, J.M.; Azzi, A.; Kramer, B.W.; Blaser, K.; Akdis, C.A. & Speer, C.P. (2007). Connective tissue growth factor expression is regulated by histamine in lung fibroblast: potential role of histamine in airway remodeling. *Journal of Allergy and Clinical Immunology*, Vol.119, No.6, (June 2007), pp.15-22, ISSN0091-6749
- Kusmartsev, S.A.; Li, Y. & Chen, S.H. (2000). Gr-1+ myeloid cells derived from tumor-bearing mice inhibit primary T cell activation induced through CD3/CD28 costimulation. *Journal of Immunology*, Vol.165, No.2, (July 2000), pp.779-785, ISSN0022-1767
- Langlet, C.; Mazingue, C.; Dessaint, J.P. & Capron, A. (1984). Inhibition of primary and secondary IgE response by a schistosome-derived inhibitory factor. *International Archives of Allergy and Applied Immunology*, Vol.73, No.3, (1984), pp.225-230, ISSN0020-5915
- Li, H.; Burkhardt, C.; Heinrich, U.R.; Brausch, I.; Xia, N. & Forstermann, U. (2003). Histamine upregulates gene expression of endothelial nitric oxide synthase in human vascular endothelial cells. *Circulation*, Vol.107, No.18, (May 2003), pp.2348-2354, ISSN0009-7322
- Liwski, R.; Zhou, J.; McAlister, V. & Lee, T.D. (2000). Prolongation of allograft survival by *Nippostrongylus brasiliensis* is associated with decreased allospecific cytotoxic T lymphocyte activity and development of T cytotoxic cell type 2. *Transplantation*, Vol.69, No.9, (May 2000), pp.1912-1922, ISSN0041-1337
- Loffler, W. (1956). Transient lung infiltrations with blood eosinophilia. *International Archives of Allergy and Applied Immunology*, Vol.8, No.1-2, (1956), pp.54-59, ISSN0020-5915
- Loke, P.; MacDonald, A.S. & Allen, J.E. (2000). Antigen-presenting cells recruited by *Brugia malayi* induce Th2 differentiation of naïve CD4(+) T cells. *European Journal of Immunology*, Vol.30, No.4, (April 2000), pp.1127-1135, ISSN0014-2980
- Lustigman, S.; Brotman, B.; Huima, T.; Prince, A.M. & McKerrow, J.H. (1992). Molecular cloning and characterization of onchocystatin, a cysteine proteinase inhibitor of *Onchoerca volvulus*. *Journal of Biological Chemistry*, Vol.267, No.24, (August 1992), pp.17339-17146, ISSN1178-6264
- Lynch, N.R.; Medouze, L.P.F.; DiPrisco-Fuenmayor, M.C.; Verde, O.; Lopez, R.I. & Malave, C. (1984). Incidence of atopic disease in a tropical environment: partial independence from intestinal helminthiasis. *Journal of Allergy and Clinical Immunology*, Vol.73, No.2, (February 1984), pp.229-233, ISSN0091-6749
- Lynch, N.R.; Lopez, R.I.; Di Prisco-Fuenmayor, M.C.; Hagel, I.; Medouze, L.; Viana, G.; Ortega, C. & Prato, G. (1987). Allergic reactivity and socio-economic level in a tropical environment. *Clinical Allergy*, Vol.17, No.3, (May 1987), pp.199-207, ISSN0009-9090
- Lynch, N.R.; Hagel, I.; Perez, M.; DiPrisco, M.; Alvarez, N. & Rojas, E. (1992). Bronchoconstriction in helminthic infection. *International Archives of Allergy and Immunology*, Vol. 98, No.1, (1992), pp.77-79, ISSN1018-2438
- Lynch, N.R.; Palenque, M.; Hagel, I. & DiPrisco, M.C. (1997). Clinical improvement of asthma after antihelminthic treatment in a tropical situation. *American Journal of Respiratory and Critical Care*, Vol.156, No.1, (July 1997), pp.50-54, ISSN1073-449X
- MacGlashan, D. Jr. (2003). Histamine: a mediator of inflammation. *Journal of Allergy and Clinical Immunology*, Vol.112, No.4, (October 2003), pp.S53-S59, ISSN0091-6749

- Maizels, R.M.; Balic, A.; Gomez-Escobar, N.; Nair, M.; Taylor, M.D. & Allen, J.E. (2004). Helminth parasites: masters of regulation. *Immunological Reviews*, Vol.201, (October 2004), pp. 89-116, ISSN0105-2896
- Mancardi, D.A.; Iannascoli, B.; Hoos, S.; England, P.; Daeron, M. & Bruhns, P. (2008). FcγRIIb is a mouse IgE receptor that resembles macrophage FcεRI in human and promotes IgE-induced lung inflammation. *Journal of Clinical Investigation*, Vol.118, No.11, (November 2008), pp.3738-3750, ISSN0021-9738
- Manoury, B.; Gregory, W.F.; Maizels, R.M. & Watts, C. (2001). Bm-CPI-2, a cystatin homolog secreted by the filarial parasite *Brugia malayi*, inhibits class II MHC-restricted antigen processing. *Current Biology*, Vol.11, No.6, (March 2001), pp.447-451, ISSN0960-9822
- Mantovani, A.; Sica, A.; Sozzani, S.; Allavena, P.; Vechii, A. & Locati, M. (2004). The chemokine system in diverse forms of macrophage activation and polarization. *Trends in Immunology*, Vol.25, No.12, (December 2004), ISSN1471-4906
- McIntyre, T.M.; Zimmerman, G.A.; Satoh, K. & Prescott, S.M. (1985). Cultured endothelial cells synthesize both platelet-activating factor and prostacyclin in response to histamine, bradykinin, and adenosine triphosphate. *Journal of Clinical Investigation*, Vol.76, No.1, (July 1985), pp.271-280, ISSN0021-9738
- McSharry, C.; Xia, Y.; Holland, C.V. & Kennedy, M.W. (1999). Natural immunity to *Ascaris lumbricoides* with immunoglobulin E antibody to ABA-1 allergen and inflammation indicators in children. *Infection and Immunity*, Vol.67, No.2, (February 1999), pp.484-489, ISSN0019-9567
- Min, B. (2008). Basophils: what they “can do” versus what they “actually do”. *Nature Immunology*, Vol.9, No.12, (December 2008), pp.1333-1339, ISSN1529-2908
- Miyajima, I.; Dombrowicz, D.; Martin, T.R.; Ravetch, J.V.; Kinet, J.P. & Galli, S.J. (1997). Systemic anaphylaxis in the mouse can be mediated largely through IgG1 and FcγRIII. Assessment of cardiopulmonary changes, mast cell degranulation, and death associated with active or IgE- or IgG1-dependent passive anaphylaxis. *Journal of Clinical Investigation*, Vol. 99, No.5, (March 1997), pp.901-914, ISSN0021-9738
- Moyle, M.; Foster, D.L.; McGrath, D.E.; Brown, S.M.; Laroche, Y.; De Meutter, J.; Stanssens, P.; Bogowitz, C.A.; Fried, V.A. & Ely, J.A. (1994). A hookworm glycoprotein that inhibits neutrophil functions is a ligand of the integrin CD11b/CD18. *Journal of Biological Chemistry*, Vol.269, No.13, (April 1994), pp.10008-10015, ISSN1178-6264
- Mukai, K.; Matsuoka, K.; Taya, C.; Suzuki, H.; Yokozeki, H.; Nishioka, K.; Hirokawa, K.; Etori, M.; Yamashita, M.; Kubota, T.; Minegishi, Y.; Yonekawa, H.; Karasuyama, H. (2005). Basophils play a critical role in the development of IgE-mediated chronic allergic inflammation independently of T cells and mast cells. *Immunity*, Vol. 23, No. 2, (August 2005), pp.191-202, ISSN1074-7613
- Mukai, K.; Obata, K.; Tsujimura, Y. & Karasuyama, H. (2009). New insights into the roles for basophils in acute and chronic allergy. *Allergology International*, Vol.58, No.1, (March 2009), pp.11-19, ISSN1323-8930
- Nakagawa, T.; Roth, W.; Wong, P.; Nelson, A.; Farr, A.; Deussing, J.; Villadangos, J.A.; Ploegh, H.; Peters, C. & Rudensky, A.Y. (1998). Cathepsin L: critical role in li degradation and CD4 T cell selection in the thymus. *Science*, Vol.280, No.5362, (April 1998), pp.450-453, ISSN0272-4634

- Nelms, K.; Keegan, A.D.; Zamorao, J.; Ryan, J.J. & Paul, W.E. (1999). The IL-4 receptor: signaling mechanisms and biologic functions. *Annuals Reviews of Immunology*, Vol.17, (1999), pp.701-738, ISSN0732-0582
- Nigou, J.; Zelle-Rieser, C.; Gilleron, M.; Thurnher, M. & Puzo, G. (2001). Mannosylated lipoarabinomannans inhibit IL-12 production by human dendritic cells: evidence for a negative signal delivered through the mannose receptor. *Journal of Immunology*, Vol.166, No.12, (June 2001), pp.7477-7485, ISSN0022-1767
- Nimmerjahn, F. & Ravetch, J.V. (2008). Fcγ receptors as regulators of immune responses. *Nature Reviews of Immunology*, Vol.8, No.1, (January. 2008), pp.34-47, ISSN1474-1733
- O'Connor, R.A.; Jenson, J.S. & Devaney, E. (2000). No contributes to proliferative suppression in a murine model of filariasis. *Infection and Immunity*, Vol.68, No.11, (November 2000), pp.6101-6107, ISSN0019-9567
- Oettgen, H.C.; Martin, T.R.; Wynshaw-Boris, A.; Deng, C.; Drazen, J.M. & Leder, P. (1994). Active anaphylaxis in IgE-deficient mice. *Nature*, Vol.370, No.6488, (August 1994), pp.367-370, ISSN0028-0836
- Oettgen, H.C. & Geha, R.S. (1999). IgE in asthma and atopy: cellular and molecular connections. *Journal of Clinical Investigation*, Vol.104, No.7, (October 1999), pp.829-835, ISSN0021-9738
- Oh, K.; Shen, T.; Le Gros, G. & Min, B. (2007). Induction of Th2 type immunity in a mouse system reveals a novel immunoregulatory role of basophils. *Blood*, Vol. 109, No.7, (April 2007), pp.2921-2927, ISSN0006-4971
- Okano, M.; Satoskar, A.R.; Nishizaki, K. & Harn, D.A Jr. (2001). Lacto-N-fucopentaose III found on Schistosoma mansoni egg antigens functions as adjuvant for proteins by inducing Th2-type response. *Journal of Immunology*, Vol.167, No.1, (July 2001), pp.442-450, ISSN0022-1767
- Oshiro, T.M.; Rafael, A.; Enobe, C.S.; Fernandes, I. & Macedo-Soares, M.F.(2004). Comparison of different monoclonal antibodies against immunosuppressive proteins of Ascaris suum. *Brazilian Journal of Medical and Biological Research*, Vol.37, No.2, (February 2004), pp.223-226, ISSN0100-879X
- Oshiro, T.M.; Macedo, M.S. & Macedo-Soares, M.F. (2005). Anti-inflammatory activity of PAS-1, a protein component of Ascaris suum. *Inflammation Research*, Vol.54, No.1, (January 2005), pp.17-21, ISSN1023-3830
- Oshiro, T.M.; Enobe, C.S.; Araújo, C.A.; Macedo, M.S. & Macedo-Soares, M.F. (2006). PAS-1, a protein affinity purified from Ascaris suum worms, maintain the ability to modulate the immune response to a bystander antigen. *Immunology and Cell Biology*, Vol.84, No.2, (April 2006), pp.138-144, ISSN0818-9641
- Paul, W.E. (1997). Interleukin 4: signaling mechanisms and control of T cell differentiation. *Ciba Foundation Symposium*, Vol.204, (1997), pp.208-216, ISSN0300-5208
- Pastrana, D.V.; Raghavan, N.; FitzGerald, P.; Eisinger, S.W.; Metz, C.; Bucala, R.; Schleimer, R.P.; Bickel, C & Scott, A.L. (1998). Filarial nematode parasites secrete a homologue of the human cytokine macrophage migration inhibitory factor. *Infection and Immunity*, Vol.66, No.12, (December 1998), pp.5955-5963, ISSN0019-9567
- Pearce, E.J. & MacDonald A.S. (2002). The immunobiology of schistosomiasis. *Nature Reviews Immunology*, Vol.2, No.7, (July 2002), pp.499-511, ISSN1474-1733
- Pfaff, A.W.; Schulz-Key, H.; Soboslay, P.T.; Taylor, D.W.; MacLennan, K. & Hoffmann, H.W. (2002). Litomosoides sigmodontis cystatin acts as an immunomodulator during

- experimental filariasis. *International Journal of Parasitology*, Vol.32, No.2, (February 2002), pp.171-178, ISSN0020-7519
- Playfair, J.H.L. (1982). Immunity to malaria. *British Medical Bulletin*, Vol.38, No.2, (May 1982), pp.153-159, ISSN0007-1420
- Pierre, P. & Mellman, I. (1998). Developmental regulation of invariant chain proteolysis controls MHC classII trafficking in mouse dendritic cells. *Cell*, Vol.93, No.7, (June 1998), pp.1135-1145, ISSN0092-8674
- Pinckard, R.N.; Halonen, M.; Plamer, J.D.; Butler, C.; Shaw, J.O. & Henson, P.M. (1977). Intravascular aggregation and pulmonary sequestration of platelets during IgE-induced systemic anaphylaxis in the rabbit: abrogation of lethal anaphylactic shock by platelet depletion. *Journal of Immunology*, Vol. 119, No.6, (December 1977), pp. 2185-2193, ISSN0022-1767
- Potempa, J.; Korzus, E. & Travis J. (1994).The serpin superfamily of proteinase inhibitors: structure, function and regulation. *Journal of Biological Chemistry*, Vol.269, No.23, (June 1994), pp.15957-15960, ISSN1178-6264
- Poulsen, L.K. & Hummelshoj, L. (2007). Triggers of IgE switching and allergy development. *Annals of Medicine*, Vol.39, No.6, (July 2007), pp.440-456, ISSN0785-3890
- Pritchard, D.I.; Brown, A.; Kasper, G.; McElroy, P.; Loukas, A.; Hewitt, C.; Berry, C.; Füllkrug, R. & Beck, E. A hookworm allergen which strongly resembles calreticulin. *Parasite Immunology*, Vol.21, No.9, (September 1999), pp.439-450, ISSN0141-9838
- Puerta, L.; Fernandez-Caldas, E.; Lockey, R.F. & Caraballo, L.R. (1993). Mite allergy in the tropics: sensitization to six domestic mite species in Cartagena, Colombia. *Journal of Investigational Allergology and Clinical Immunology*, Vol. 3, No.4, (July-August 1993), pp.198-204, ISSN1018-9068
- Reyes, J.L. & Terrazas, L.I. (2007). The divergent roles of alternatively activated macrophages in helminthic infections. *Parasite Immunology*, Vol.29, No.12, (December 2007), pp.609-619, ISSN0141-9838
- Riese, R.J.; Wolf, P.R.; Bromme, D.; Natkin, L.R.; Villadangos, J.A.; Ploegh, H.L. & Chapman, H.A. (1996). Essential role for cathepsin S in MHC classII-associated invariant chain processing and peptide loading. *Immunity*, Vol.4, No.4, (April 1996), pp.357-366, ISSN1074-7613
- Rzepecka, J.; Lucius, R.; Dolegalska, M.; Beck, S.; Rausch, S. & Hartmann, S. (2006). Screening for immunomodulatory proteins of the intestinal parasitic nematode *Heligmosomoides polygyrus*. *Parasite Immunology*, Vol.28, No.9, (September 2006), pp.463-472, ISSN0141-9838
- Santiago, H.C.; Bennuru, S.; Boyd, A.; Eberhard, M. & Nutman, T.B. (2011). Structural and immunological cross-reactivity among filarial and mite tropomyosin: implications for the hygiene hypothesis. *Journal of Allergy and Clinical Immunology*, Vol. 127, No. 2, (February 2011), pp.479-486, ISSN0091-6749
- Schramm, G.; Mohrs, K.; Wodrich, M.; Doenhoff, M.J.; Pearce, E.J., Haas, H. & Mohrs, M. (2007). IPSE/alpha-1, a glycoprotein from *Schistosoma mansoni* eggs, induces IgE-dependent, antigen-independent IL-4 production by murine basophils in vivo. *Journal of Immunology*, Vol.178, No.10, (May 2007), pp.6023-6027, ISSN0022-1767
- Schramm, G.; Falcone, F.H.; Gronow, A.; Haisch, K.; Mamat, U.; Doenhoff, M.J.; Oliveira, G.; Galle, J.; Dahinden, C.A. & Haas, H. (2003). Molecular characterization of an

- interleukin-4-inducing factor from *Schistosoma mansoni* eggs. *Journal of Biological Chemistry*, Vol.278, No.20, (May 2003), pp.18384-18392, ISSN1178-6264
- Schönemeyer, A.; Lucius, R.; Sonnenburg, B.; Brattig, N.; Sabat, R.; Schilling, K.; Bradley, J. & Hartmann S. (2001). Modulation of human T cell responses and macrophage functions by onchocystatin, a secreted protein of the filarial nematode *Onchocerca volvulus*. *Journal of Immunology*, Vol.167, No.6, (September 2001), pp.3207-3215, ISSN0022-1767
- Scrivener, S.; Yemaneberhan, H.; Zebeñigus, M.; Tilahun, D.; Girma, S.; Ali, S.; McElroy, P.; Custovic, A.; Woodcock, A.; Pritchard, D.; Venn, A. & Britton, J. (2001). Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. *Lancet*, Vol.358, No.9292, (November 2001), pp.1493-1499, ISSN0099-5355
- Semnani, R.T.; Liu, A.Y.; Sabzevari, H.; Kubofcik, J.; Ahou, J.; Gilden, J.K. & Nutman, T.B. *Brugia malayi* microfilariae induce cell death in human dendritic cells, inhibit their ability to make IL-12 and IL-10, and reduce their capacity to activate CD4⁺ cells. *Journal of Immunology*, Vol.171, No.4, (August 2003), pp.1950-1960, ISSN0022-1767
- Shi, G.P.; Bryant, R.A.; Riese, R.; Verhelst, S.; Driessen, C.; Li, Z.; Bromme, D.; Ploegh, H.L. & Chapman, H.A. Role for cathepsin F in invariant processing and major histocompatibility complex classII peptide loading by macrophages. *Journal of Experimental Medicine*, Vol.19, No.7, (April 2000), pp.1177-1186, ISSN0022-1007
- Shimoda, K.; van Deursen, J.; Sangster, M.Y.; Sarawar, S.R.; Carson, R.T.; Tripp, R.A.; Chu, C.; Quelle, F.W.; Nosaka, T.; Vignali, D.A.; Doherty, P.C.; Grosveld, G.; Paul, W.E. & Ihle, J.N. (1996). Lack of IL-4 induced Th2 response and IgE class switching in mice with disrupted Stat6 gene. *Nature*, Vol.380, No.6575, (April 1996), pp.630-633, ISSN0028-0836
- Simons, F.E.; Frew, A.J.; Ansotegui, I.J.; Bochner, B.S.; Golden, D.B.; Finkelman, F.D.; Leung, D.Y.; Lotvall, J.; Marone, G.; Metcalfe, D.D.; Muller, U.; Rosenwasser, L.J.; Sampson, H.A.; Schwartz, L.B.; van Hage, M. & Walls, A.F. (2007). Risk assessment in anaphylaxis: current and future approaches. *Journal of Allergy and Clinical Immunology*, Vol. 120, No. 1, (July. 2007), pp.S2-24, ISSN0091-6749
- Simons, F. (2003). H1-antihistamines: more relevant than ever in the treatment of allergic disorders. *Journal of Allergy and Clinical Immunology*, Vol.112, No.4(Suppl), (October 2003), pp.S42-52, ISSN 0091-6749
- Smits, H.H.; Everts, B.; Hartgers, F.C. & Yazdanbakhsh, M. (2010). Chronic helminth infections protect against allergic diseases by active regulatory processes. *Current Allergy and Asthma Reports*, Vol.10, No.1, (January 2010), pp.3-12, ISSN1529-7322
- Soares, M.F.M.; Macedo, M.S. & Mota, I. Suppressive effect of an *Ascaris suum* extract on IgE and IgG antibody responses in mice. *Brazilian Journal of Medical and Biological Research*, Vol., No.2, (1987), pp.203-211, ISSN0100-879X
- Soares, M.F.M.; Mota, I. & Macedo, M.S. Isolation of *Ascaris suum* components which suppress IgE antibody responses. *International Archives of Allergy and Immunology*, Vol.97, No.1, (1992), pp.37-43, ISSN1871-5281
- Soares MFM & Araujo CA. Helminth products as a potential therapeutic strategy for inflammatory diseases. *Inflammation and Allergy Drug Targets*, Vol.7, No.2, (June 2008), pp.113-118, ISSN1871-5281

- Sokol, C.L.; Barton, G.M.; Farr, A.G. & Medzhitov, R. (2008). A mechanism for the initiation of allergen-induced T helper type 2 responses. *Nature Immunology*, Vol.9, No.3, (Mar 2008), pp.310-8, ISSN1529-2908
- Stafforini, D.M.; McIntyre, T.M.; Zimmermann, G.A. & Prescott, S.M. (2003). Platelet-activating factor, a pleiotrophic mediator of physiological and pathological processes. *Critical Reviews in Clinical Laboratory Sciences*, Vol.40, No.6, (2003), pp.643-672, ISSN1040-8363
- Steinfeldt, S.; Andersen, J.F.; Cannons, J.L.; Feng, C.G.; Joshi, M.; Dwyer, D.; Caspar, P.; Schwartzberg, P.L.; Sher, A. & Jankovic, D. (2009) The major component in schistosome eggs responsible for conditioning dendritic cells for Th2 polarization is a T2 ribonuclease (omega-1). *Journal of Experimental Medicine*, Vol.206, No.8, (August 2009), pp.1681-1690, ISSN0022-1007
- Stephenson, L.S.; Latham, M.C. & Ottesen, E.A. (2000). Global malnutrition. *Parasitology*, Vol.121, (2000), pp.S5-22, ISSN0031-1820
- Stewart, G.R.; Boussinesq, M.; Coulson, T.; Elson, L.; Nutman, T. & Bradley, J.E. (1999). Onchocerciasis modulates the immune response to mycobacterial antigens. *Clinical and Experimental Immunology*, Vol.117, No.3, (September 1999), pp.571-523, ISSN0009-9104
- Strait, R.T.; Morris, S.C.; Yang, M.; Qu, X.W. & Finkelman, F.D. (2002). Pathways of anaphylaxis in the mouse. *Journal of Allergy and Clinical Immunology*, Vol.109, No.4, (April 2002), pp.658-668, ISSN0091-6749
- Strait, R.T.; Morris, S.C.; Smiley, K.; Urban, J.F. Jr & Finkelman, F.D. (2003). IL-4 exacerbates anaphylaxis. *Journal of Immunology*, Vol.170, No.7, (April 2003), pp.3835-3842, ISSN0022-1767
- Sugimoto, Y.; Iba, Y.; Nakamura, Y.; Kayasuga, R. & Kamei, C. (2004). Pruritus-associated response mediated by cutaneous histamine H3 receptors. *Clinical and Experimental Allergy*, Vol.34, No.3, (March 2004), pp.456-459, ISSN0954-7894
- Swain, S.L.; Weinberg, A.D.; English, M. & Huston, G. (1990). IL-4 directs the development of Th2 like helper effectors. *Journal of Immunology*, Vol.145, No.11, (December 1990), pp.3796-3806, ISSN0022-1767
- Takai, T. (2005). Fc receptors and their role in immune regulation and autoimmunity. *Journal of Clinical Immunology*, Vol. 25, No.1, (January 2005), pp.1-18, ISSN0271-9142
- Terrazas, L.I.; Walsh, K.L.; Piskorska, D.; McGuire, E. & Harn, D.A Jr. (2001). The schistosome oligosaccharide lacto-N-neotetraose expands Gr1(+) cells that secrete anti-inflammatory cytokine and inhibit proliferation of naive CD4(+) cells: a potential mechanism for immune polarization in helminth infections. *Journal of Immunology*, Vol.167, No.9, (September 2001), pp.5412-5416, ISSN0022-1767
- Tiselius A & Kabat EA. (1939). An electrophoretic study of immune sera and purified antibody preparations. *Journal of Experimental Medicine*, Vol.69, No.1, (January 1939), pp.119-131, ISSN0022-1007
- Thurmond, R.L.; Desai, P.J.; Dunford, P.J.; Fung-Leung, W.P.; Hofstra, C.L.; Jiang, W.; Nguyen, S.; Riley, J.P.; Sun, S.; Williams, K.N.; Edwards, J.P. and Karlsson, L. (2004). A potent and selective histamine H4 receptor antagonist with anti-inflammatory properties. *Journal of Pharmacology and Experimental Therapeutics*, Vol.309, No.1, (April 2004), pp.401-413, ISSN0022-3565

- Truong, M.J.; Gruart, V.; Kusnierz, J.P.; Papin, J.P.; Loiseau, S.; Capron, A. & Capron M. (1993). Human neutrophils express immunoglobulin E (IgE)-binding proteins (Mac-2/epsilon BP) of the S-type lectin family: role in IgE-dependent activation. *Journal of Experimental Medicine*, Vol.177, No.1, (January 1993), pp.243-248, ISSN0022-1007
- Tsujimura, Y.; Obata, K.; Mukai, K.; Shindou, H.; Yoshida, M.; Nishikado, H.; Kawano, Y.; Minegishi, Y.; Shimizu, T. & Karasuyama, H. (2008). Basophils play a pivotal role in immunoglobulin-G-mediated but not immunoglobulin-E-mediated systemic anaphylaxis. *Immunity*, Vol.28, No.4, (April 2008), pp.581-589, ISSN1074-7613
- Ujike, A.; Ishikawa, Y.; Ono, M.; Yuasa, T.; Yoshino, T.; Fukumoto, M.; Ravetch, J.V. & Takai, T. (1999). Modulation of immunoglobulin(Ig)E-mediated systemic anaphylaxis by low-affinity Fc receptor for IgG. *Journal of Experimental Medicine*, Vol.189, No.10, (May 1999), pp.1573-1519, ISSN0022-1007
- Urbina, C.; Ortiz, C. & Hurtado, I. (1981). A new look at basophil in mice. *International Archives of Allergy and Applied Immunology*, Vol. 66, No.2, (1981), pp.158-160, ISSN0020-4793
- Vadas, P.; Gold, M.; Perelman, B.; Liss, G.M.; Lack, G.; Blyth, T.; Simons, F.E.; Simons, K.J.; Cass, D. & Yeung, J. (2008). Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *New England Journal of Medicine*, Vol.358, No.1, (January 2008), pp.28-35, ISSN0028-4793
- van der Kleij, D.; Latz, E.; Brouwers, J.F.; Kruize, Y.C.; Schmitz, M.; Kurt-Jones, E.A.; Espervik, T.; de Jong, E.C.; Kapsenberg, M.L.; Golenbock, D.T.; Tielens, A.G. & Yazdanbakhsh, M. (2002). A novel host-parasite lipid cross-talk. Schistosomal lyso-phosphatideylserine activates toll-like receptor 2 and affects immune polarization. *Journal of Biological Chemistry*, Vol.277, No.50, (December 2002), pp.48122-48129, ISSN1178-6264
- van Riet, E.; Hartgers, F.C. & Yazdanbakhsh, M. (2007). Chronic helminth infections induce immunomodulation: consequences and mechanisms. *Immunobiology*, Vol.212, No.6, (April 2007), pp.475-490, ISSN0175-2985
- Verity, C.K.; Loukas, A.; McManus, D.P. & Brindley, P.J. (2001). *Schistosoma japonicum* cathepsin D aspartic protease cleaves human IgG and other serum components. *Parasitology*, Vol.122, No.4, (April 2001), pp.415-421, ISSN0031-1820
- Williams, A.F. & Barclay, A.N. (1998). The immunoglobulin superfamily – domains for cell surface recognition. *Annual Reviews of Immunology*, Vol.6, (1988), pp.381-405, ISSN0732-0582
- Wilson, M.S.; Mentink-Kane, M.M.; Pesce, J.T.; Ramalingam, T.R.; Thompson, R. & Wynn, T.A. (2007). Immunopathology of schistosomiasis. *Immunology and Cell Biology*, Vol.85, No.2, (February-March. 2007), pp.148-154, ISBN0818-9641
- Winbery, S.L. & Lieberman, P.L. (2002). Histamine and antihistamines in anaphylaxis. *Clinical Allergy and Immunology*, Vol. 17, (2002), pp. 287-317, ISSN1075-7910
- Zang, X.; Yazdanbakhsh, M.; Jinag, H.; Kanost, M.R & Maizels, R.M. (1999). A novel serpin expressed by blood-borne microfilariae of the parasitic nematode *Brugia malayi* inhibits human neutrophil serine proteinase. *Blood*, Vol.94, No.4, (August 1999), pp.1418-1428, ISSN0006-4971

Allergic Diseases - Highlights in the Clinic, Mechanisms and Treatment

Edited by Prof. Celso Pereira

ISBN 978-953-51-0227-4

Hard cover, 554 pages

Publisher InTech

Published online 14, March, 2012

Published in print edition March, 2012

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

C.A. Araujo and M.F. Macedo-Soares (2012). Derived Products of Helminth in the Treatment of Inflammation, Allergic Reactions and Anaphylaxis, Allergic Diseases - Highlights in the Clinic, Mechanisms and Treatment, Prof. Celso Pereira (Ed.), ISBN: 978-953-51-0227-4, InTech, Available from:
<http://www.intechopen.com/books/allergic-diseases-highlights-in-the-clinic-mechanisms-and-treatment/anaphylaxis-an-overview-of-immune-mechanisms-and-therapeutic-strategies-using-helminth-products>

INTech
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen