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Review

Environment and T regulatory cells in allergy

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ABSTRACT

The central role of T regulatory cells in the responses against harmless environmental antigens has been confirmed by many studies. Impaired T regulatory cell function is implicated in many pathological conditions, particularly allergic diseases. The “hygiene hypothesis” suggests that infections and infestations may play a protective role for allergy, whereas environmental pollutants favor the development of allergic diseases. Developing countries suffer from a variety of infections and are also facing an increasing diffusion of environmental pollutants. In these countries allergies increase in relation to the spreading use of xenobiotics (pesticides, herbicides, pollution, etc.) with a rate similar to those of developed countries, overcoming the protective effects of infections. We review here the main mechanisms of non-self tolerance, with particular regard to relations between T regulatory cell activity, infections and infestations such as helminthiasis, and exposure to environmental xenobiotics with relevant diffusion in developing countries.

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1. Introduction

The development of immune responses, including allergic reactions, is orchestrated by the activity of CD4 T helper (Th) cell subpopulations and their cytokine products. In the mature immune response, two phenotypes of Th cell, designated Th1 and Th2, predominate and are distinguished by the function of the cytokines they secrete (O'Garra and Vieira, 2004; Romagnani et al., 2000). While both populations secrete interleukin (IL)-3 and granulocyte/macro-

phage-colony stimulating factor (GM-CSF), only Th1 cells express interferon (IFN)- γ , IL-2, and tumor necrosis factor (TNF)- α , and only Th2 cells express IL-4, IL-5, IL-6, and IL-13. The existence of functional subpopulations of Th cells provides a mechanism for the development of different qualities of immune responses, depending upon the nature of the challenge to the host (Mosmann and Sad, 1996). A further T cell subset able to induce tolerance against non-dangerous agents has been identified: the T regulatory (Treg) cell, producing IL-10 and TGF- β (Blaser et al., 2006). By this point of view, tolerance is not a mere absence of immune reaction, but requires the specific activity of cells and proteins (Shevac, 2000; Maloy and Powrie, 2001; Coutinho et al., 2001; Sakaguchi, 2004; Sakaguchi et al., 1995).

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Tregs can be distinguished in:

- Naturally occurring CD4⁺ CD25⁺ Treg, thymus derived, expressing a transcriptional regulator (FoxP3 gene), are implicated in counteracting the development of autoimmune diseases (Sakaguchi, 2005). Neonatal thymectomy leads to the development of autoimmune diseases due to natural Treg cell deficiency (Asano et al., 1996). These cells represent 5% to 10% of TCD4⁺ cells in peripheral blood and express the surface IL-2 receptor α chain (CD25), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4 or CD152), glucocorticoid-induced TNF receptor family-related gene (GITR), OX40 (CD134) and L-selectin (CD62L) (Read et al., 2000; Shimizu et al., 2002; O'Garra and Vieira, 2004; Thompson and Powrie, 2004). In peripheral blood, natural Tregs are represented by a large number of T CD4⁺ CD25^{high}, due to the presence of IL-2 and TGF- β positive cells which express high levels of CD25; and a smaller number of CD25^{low} cells, which probably, represent natural Tregs, undergoing homeostatic proliferation or tissue infiltration (Fontenot et al., 2005; Wan and Flavell, 2005). However, not all authors agree on the real Treg activity of these last cells proliferating (CD25^{low}) subpopulations that may be a reservoir for active Tregs (Khaidukov and Litvinov, 2005). Both cell populations are regulatory and immunosuppressive and express FoxP3.
- Inducible or adaptive CD4⁺ CD25⁺ Tregs, that can be divided in Tr1 and Th3, derived from conventional CD4⁺ T cells in periphery after encounter of foreign or self-antigens in the presence of specific signals such as IL-10 and TGF- β . These cells induce suppression through production of IL-10 (Tr1) and TGF- β (Th3) (O'Garra and Vieira, 2004).
- CD8⁺ Tregs, that have been studied less than the CD4⁺ Treg compartment are not yet fully phenotypically characterized. There are two classes of CD8⁺ Tregs according to the expression of CD28, but the phenotype of these cells seems to be much more complex, including both CD8-positive and -negative cells (Mills, 2004). CD8 Tregs are found in the thymus of healthy individuals, appear to express molecules similar to those expressed by CD4⁺ Tregs and have similar suppressor capacity (Cosmi et al., 2003). In the peripheral blood of healthy subjects CD8⁺ Tregs express the integrin CD103 (Uss et al., 2006).
- NK Tregs and dendritic cells, specialized components of the innate immune system, may influence maturation of other compartments (Fernandez et al., 1999; Cooper et al., 2004; Moretta, 2002). Dendritic cells regulate the intensity of the cytolytic effects of NK cells on tumors, virus-, bacteria- or parasite-infected cells. NK cells exert negative regulatory effects that contribute to immune homeostasis. If the ratio NK/DC is low (1:5), the interaction leads to a greater production of cytokines by DC cells (IL-12 or TNF- α); while at high NK/DC ratio (5:1 or higher?) the inhibitory effects of NK cells kill immature DC cells and inhibit cytokine production (Zitvogel, 2002; Moretta et al., 2003).

1.1. T regulatory cells in healthy subjects

A peripheral T cell repertoire to all allergens that recognizes the same T cell epitopes as allergic patients exists also in healthy individuals (Carballido et al., 1992; Ebner et al., 1995; Akdis et al., 2004). Accordingly, both induction and maintenance of peripheral tolerance to allergens appear to be active mechanisms of regulation. Allergen-specific T cells constitute less than 0.1% of CD4⁺ T cells and can be classified as Th1, Th2, and Treg cells, according to their cytokine production, IFN- γ , IL-4, and IL-10, respectively (Akdis et al., 2004). In allergic patients Th2 is the dominant subset of T cells, whereas specific Tregs represent the main subset against common environmental allergens in healthy people. Treg cells may act both by cytokine production and by cell–cell contact signals, as programmed death-1,

glucocorticoid-induced TNF receptor, membrane TGF- β , and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) (Robinson et al., 2004; Akdis et al., 2004). In allergic and healthy subjects all 3 allergen-specific T cell subsets that coexist and change in dominant subset, especially in the ratio between specific Tregs and Th2 cells, might determine the development of healthy or allergic immune responses.

Treg cells contribute to the control of allergen-specific immune responses in 5 major ways:

1. *suppression of antigen-presenting cells that support the generation of effector Th2 and Th1 cells.* IL-10 down-regulates the expression of MHC class II and of costimulatory molecules on monocytes/macrophages and dendritic cells (DC) (Moore et al., 2001; Waal Malefyt et al., 1991; Willems et al., 1994; Buelens et al., 1995; Ding et al., 1993; Groux et al., 1999), thus suppressing Ag-induced immune response. In allergic patients treated by specific immunotherapy (SIT), induced-Treg cells appear to modify both antigen-presenting cell and T cell responses (Larchè et al., 2006).
2. *suppression of Th2 and Th1 cells.* Treg cells abolish allergen-induced proliferation of Th1 and Th2 cells, as well as their cytokine production (Larchè, 2007) through multiple suppressor mechanisms, including IL-10 and transforming growth factor- β (TGF- β), as secreted cytokines, and various surface molecules, such as cytotoxic T-lymphocyte antigen 4 and programmed death-1. IL-10, in particular, inhibits CD28 tyrosine phosphorylation, preventing the binding of phosphatidylinositol 3-kinase p85 and consequently inhibiting the CD28 signalling pathway (Taylor et al., 2006; Larchè et al., 2006). It is interesting that Tregs exist and regulate T cell responses already early in life (being identified in cord blood) depending on the atopic phenotype of the mother (Schaub et al., 2009) and can exert protective properties against allergic diseases (Smith et al., 2008). Furthermore, peripheral blood T cells isolated from allergic patients treated by SIT are able to suppress allergen-specific proliferation and response of pretreatment T cells in an IL-10-dependent and TGF- β -dependent way. In fact, antibodies neutralizing these cytokines abrogate T cell suppression (Larchè et al., 2006).
3. *regulatory function on B cells by suppression of allergen-specific IgE and induction of IgG4, IgA, or both.* Treg cells can negatively regulate T cell-dependent B-cell antibody production in mice at the level of germinal centers (Lim et al., 2004). IL-10 has two major effects on B cells: it decreases ϵ -transcript expression and therefore IgE production, and enhances g4 transcript expression and IL-4-induced IgG4 production (Jeannin et al., 1998; M. Akdis et al., 1998). In sera of healthy individuals antibody response to allergens, as Der p 1, is characterized by specific IgA and IgG4 levels, small amounts of IgG1 and almost undetectable IgEs (Jutel et al., 2003). In allergic patients, a significant increase in specific IgA, IgG1, and IgG4 levels is observed after specific immunotherapy SIT (Jutel et al., 2003). The increase of specific IgA and IgG4 levels in serum coincides with increased TGF- β and IL-10 levels, respectively (C.A. Akdis et al., 1998; Sonoda et al., 2009). These findings suggest a regulatory function, in addition to the well-known suppressor function of Treg cells.
4. *suppression of mast cells, basophils, and eosinophils.* Effector cells of allergic inflammation, such as mast cells, basophils, and eosinophils, require T cell cytokines for priming, survival and activity (Walker et al., 1991), which are not efficiently provided by Treg-suppressed Th2 cells. Treg cells, in fact, modulate the thresholds for mast cell and basophil activation and decrease IgE-mediated histamine release (Treter and Luqman, 2000; Shim et al., 2003). In addition, through IL-10, Tregs reduce pro-inflammatory cytokine release from mast cells (Marshall et al., 1996), down-regulate eosinophil function and activity and suppress IL-5 production by resting Th0 and Th2 cells (Schandane et al., 1994).

5. *interaction with resident tissue cells and remodeling.* Tregs may not always be responsible for beneficial effects, in fact, several studies have shown that they could favor chronicity of infections and tumor tolerance. Treg cytokines, TGF- β in particular, are potent regulators of fibroblast and myofibroblast function and control the production of several extracellular matrix proteins, including collagens, proteoglycans, and tenascin (Duvernelle et al., 2003). In allergic asthma, remodeling includes deposition of several extracellular matrix proteins in the basement membrane and bronchial mucosa, increase in airway smooth muscle mass, goblet-cell hyperplasia, and new blood vessel formation (Davies et al., 2003; Tulic and Hamid, 2006). The thickening of the subepithelial lamina reticularis in bronchial asthma has been related to an increase in fibroblasts in correlation with TGF- β expression (Hoshino et al., 1998). There is clear evidence that lamina reticularis thickening starts very early, even at the time of first diagnosis (Laitinen et al., 1993), suggesting that a barrier between activated epithelium or mucosal allergens and inner tissues (ie, immune system cells) may contribute to down-regulate allergen-induced inflammatory responses. Taken together, increased subepithelial lamina reticularis thickness and mucosal IgA production against allergens could be promoted by Treg cells, in the attempt to decrease the amount of allergen exposure and favor immunologic ignorance.

1.2. Infections and xenobiotics influence Treg activity and allergy

Treg cell numbers, expression and function are impaired during allergic sensitization (Cosmi et al., 2004; Bellinghausen et al., 2005; Grindebacke et al., 2004). This can be contributed by many conditions that can interfere with or favor subsequent allergic sensitization. Environmental factors, such as infections and xenobiotics, may have a crucial effect in these changes and should be taken into account in studies of allergies in heavily exposed people.

It is well-known that microbial exposure is a protective factor for the onset of allergies (Braun-Fahrlander et al., 2002) and that the increase in Tregs could be the key factor for preventing the allergy onset (Schaub et al., 2009).

Injury from perinatal air pollution exposure could also be responsible for the increased proportion of unsusceptible individuals who, because of their exposure to pollutants during the susceptibility window and because of epigenetic alterations due to environmental factors, will become susceptible. Different cis-regulatory elements at the Foxp3 locus are subjected to epigenetic modification in different subsets of CD4+ T cells and that regulates Foxp3 expression (Lal and Bromberg, 2009; Polansky et al., 2010). Epigenetic alterations could also transfer this susceptibility to future generations, leading to individuals developing asthma not only at 4 years of age but ≥ 20 years later.

Sub-Saharan African countries presently face an increasing diffusion of environmental pollutants while still suffering from a great variety of chronic infections. In these countries allergic pathologies increase in relation to the spreading use of xenobiotics (pesticides, herbicides, pollutants, etc.) at rates similar to those of developed countries. Seemingly, these substances overcome the protective effects of infections and, in particular, of helminthic infestations, that may play a protective role against allergy by enhancing T regulatory activity.

1.3. Tregs, infections and allergy

The characteristic response against helminths includes expansion of Th2 cells (Quinnell et al., 2004; Jackson et al., 2004a,b; Turner et al., 2003), with the production of IL-4, IL-5, IL-9, IL-13, IL-21, IL-25 and IL-33 (Pesce et al., 2006; Fallon et al., 2006; Schmitz et al., 2005; Bancroft et al., 1998). This induces a cascade of effector mechanisms,

potentially including IgE isotype-switched B-cell responses, mast cells, eosinophils, basophils and increased permeability, smooth muscle contractility and mucus production in gut epithelia. The other recurring immunological characteristic of helminth infections is that, despite significant responses, for example vigorous antibody responses and eosinophilia, which may or may not be effective, it often determines a marked systemic suppression of innate and adaptive immunity (Babu et al., 2006; Wilson and Maizels, 2004a,b). This may be linked to expansions of regulatory CD4+ CD25+ T cells producing the TGF- β and/or IL-10 and perhaps other suppressor T cell subsets (Jiang and Chess, 2004), including CD8+ T cells with cytokine independent suppressive activity (Metwali et al., 2006).

All organisms should be able to perfectly control their immune system under any combination of infectious challenges or antigenic stimuli, and have been selected to perform optimally within the set of conditions encountered by their ancestors. In humans, as in other mammals, one of these conditions is arguably exposure to a diverse community of helminths. Because helminth infection is, and (probably) has been, so ubiquitous, mammalian immune systems may have been selected to anticipate that they would suffer chronic exposure to large-bodied Th2/Treg-inducing pathogens. In other words, there would have been selection for immunoregulatory systems that work well in the context of helminth infection. However, there would rarely have been selection for immunoregulatory systems that work optimally when helminths are absent (the situation seen in modern human populations). The absence of parasitic worms and their strong Th2/Treg-inducing influences may therefore uncover flaws in immunoregulatory networks that were previously hidden from selection (Maizels, 2007; Cooke et al., 1999). Such scenario might explain the links between increased susceptibility to microbial pathogens and helminth-infected populations in the developing world and justify the dramatic increases in allergy and autoimmune conditions in Western countries. This hypothesis is also supported by the protective effect of helminth infection, or helminth-derived products, in laboratory models of allergy and autoimmunity (Cooke et al., 1999; McInnes et al., 2003).

The gut is the environment in which there is the most delicate balance between tolerance to commensal bacteria and food products and ability to maintain immune responses against ingested pathogens: by removing or altering the gut flora, the capacity and type of response to pathogens can change. For example, the susceptibility to develop infections with *Giardia lamblia* (Singer and Nash, 2000) and *Leishmania* varies with the change of intestinal flora (Oliveira et al., 1999, 2005).

1.3.1. Chronic infections

The role of Tregs has been mainly documented in the context of chronic infections (Moore et al., 2001). Through IL-10 they can inhibit both Th1 and Th2 responses to many pathogens in experimental models (Hoffmann et al., 2000; Gazzinelli et al., 1992; Li et al., 1999) and in human infectious diseases such as tuberculosis, malaria, hepatitis C, filariasis, leishmaniasis, and schistosomiasis (MacDonald et al., 2002; Plebanski et al., 1999; Boussiotis et al., 2000; Mahanty et al., 1997; Carvalho et al., 1994; King et al., 1996; Yazdanbakhsh et al., 2002).

A large number of microbes must establish long-term interactions with their host in order to sustain their transmission and/or reproduction. During this coexistence, the pathogen must avoid elimination by the host immune response and sustain its life cycle, while at the same time delaying or preventing host destruction, and should therefore dictate an immune response appropriate to insure survival. For instance, microbial pathogens have been shown to induce a large array of regulatory cells to insure their own survival (Belkaid, 2007; Wohlfert and Belkaid, 2008) and the host must generate a controlled immune response that recognizes and controls microbial expansion while limiting collateral damage to self-tissues

that may result from an exuberant immune response. A remarkable example of this control is illustrated by the fact that the outcome of malaria is determined, in part, by the balance of pro-inflammatory and regulatory immune responses. Failure to develop an effective pro-inflammatory response can lead to unrestricted replication of the infectious agent, whilst failure to regulate this response leads to the development of a severe immunopathology (Couper et al., 2008). Tregs, being able to control the intensity of effector responses, have been shown to play a major role in the control of host–microbial interactions.

The role of Tregs in favoring the survival of the parasite and the host is clearly shown also in experimental models. During infection of mice with *Toxoplasma gondii*, IL-10 production by T cells is the key regulator of effector-cell responses, as IL-10-deficient mice can control parasite number, but they succumb to lethal immunopathology driven by unrestrained effector-cell responses (Gazzinelli et al., 1996).

The overall outcome of an helminthic infection may therefore be an environment with down-regulated pro-inflammatory responsiveness, activated damage repair mechanisms and a tightly controlled development of Th2 anti-parasite effector responses.

Th2 mediators are important in defense against metazoan parasites, and also in damage repair (Diaz and Allen, 2007). It is intuitive that these two roles might be evolutionarily linked. In fact, worm infections are likely to produce high levels of local tissue damage associated with the feeding and migratory activities of the parasites. There may also be a requirement for the host to physically 'wall off' dangerous motile stages by fibrotic reactions within tissues. It thus seems plausible that, during evolution, anti-worm mediators may have been 'grafted' onto the control networks that regulate wound repair and tissue remodeling. Mechanisms involved in wound healing and responses to helminths are not totally overlapping, of course, as the latter also involve genuine effector mechanisms (IgE, mast cells and eosinophils) not usually implicated in wound repair, and themselves capable of generating immunopathology.

Despite the fact that elevated IgE and effector cells are characteristic of allergic sensitization, an inverse association between chronic helminth infection and overt allergic responsiveness has been observed in humans (Yazdanbakhsh et al., 2001). Furthermore, the available data favor an effect mediated by regulation of effector-phase mechanisms, with the proto-allergic IgE response remaining intact in infected patients. Seminal work by Van den Biggelaar (van den Biggelaar et al., 2000) compared 520 Gabonese schoolchildren (5–14 years) for skin-prick test (SPT) responses to standard allergens, in relation to parasitological data for *Schistosoma haematobium* and filarial nematode infection. Children with urinary schistosomiasis had a lower prevalence of skin reactivity to house dust mite compared to those free of infection. A critical point is that infected children were strongly sensitized to house dust mite allergen (judged by specific IgE) but had lower overt skin reactivity. The proposition that helminths down-regulate the effector phase was supported by the negative correlation between SPT scores and parasite-specific IL-10 response.

Selassie et al. (2000) studied 153 Ethiopians from 17 to 67 years of age, measuring specific IgE for *Necator*, *Ascaris*, and Der p 1, as well as parasite loads, total IgE, and bronchial hyperreactivity. They found that asthma correlated positively with levels of Der p 1-specific IgE, but inversely to infection with *Ascaris* and/or *Necator*. As with other studies, the presence of Der p 1-specific IgE was not affected by infection status, again implying that helminth infection does not alter the generation of atopy, but rather its translation into asthma.

A higher incidence of allergic reactivity has been reported in residents of low helminth-transmission areas compared to those living in areas with high-transmission intensities. When children were antihelminth-treated, they showed increased allergen-specific IgE and SPT-manifested skin allergy (Lynch et al., 1993). Thus, not

only infection does repress atopy, but removal of helminth infection results in the reappearance or introduction of allergic reactivity.

It is clear that despite IgE sensitization to aeroallergens, helminth-infected individuals are somehow protected from mast cell degranulation and inflammation.

The majority of the available studies supports these general conclusions. For example, a large study (693 adults) in rural and urban areas of Gambia by Nyan et al. (2001) reported an inverse association between skin-test reactivity and the presence of intestinal helminth (*Ascaris* or hookworm) infection. Scrivener's work (2001) in rural Ethiopians argues indeed that in high intensity infections, Der p 1 sensitization rates remain high among non-atopics, again suggesting that only effector phases are downmodulated by parasitism. These authors propose that the higher allergy incidence in urban Ethiopians (measured as wheeze) is due at least in part to loss of the protective effect of helminth infection. There is also evidence of activation of suppressive mechanisms with ablation of both sensitization and effector mechanisms. In fact, Bashir et al. (2002) observed that allergic responses to a food allergen from peanut were downmodulated by infection with the gastrointestinal nematode *H. polygyrus*, with inhibition of both allergen-specific IgE and IL-13, while this effect was reversed in animals treated with anti-IL-10.

1.3.2. Acute infections

Not all studies of helminth-allergy interactions and experimental helminth infections have concluded with an inverse association. In fact, under conditions of existing elevated IL-4 and IL-5 and consequent IgE and localized eosinophilia, an incoming wave of helminth larvae migrating through the respiratory system could exacerbate airway hyperresponsiveness (Silveira et al., 2002; Negrao-Correa et al., 2003). Lynch et al. (1997) reported that clinical improvement of asthma could be achieved with anti-helminthic (albendazole) treatment for a year, compared with untreated controls. Thus, there are contexts in which helminth infection can actually exacerbate allergic symptoms. In humans, a key difference may exist between acute and chronic helminth infections, and the extent to which the allergic state pre-exists at the time of parasite invasion.

Wang et al. (2001) infected mice with two doses of the human parasite *Strongyloides stercoralis*, which produces a short-lived tissue infection. Mice sensitized to ovalbumin (OVA) shortly after the second infection showed greatly reduced allergen-specific IgE production and eotaxin secretion than mice pre-sensitized with the same antigen.

Furthermore, in patients with acute leishmaniasis the levels of Foxp3 mRNA transcripts were significantly lower than those observed in patients with chronic leishmaniasis (Bourreau et al., 2009).

After acute *Clonorchis sinensis* infection familial cases of food allergy have been reported (Ciprandi et al., 2008). In these patients, helminth infection could have caused an increased permeability of allergenic molecules through the enteric wall, with a transient disturbance of immune tolerance and consequent sensitization. In fact, the processing of luminal antigens, normally exposed only at the apical surface, might have a different immunologic outcome when these antigens gain access to the basolateral surface of the enterocytes via leaky tight junctions. An antigen normally tolerated or eliciting no significant responses when processed apically, may become immunogenic after processing from the basolateral membrane. Furthermore, during inflammation, the enterocytes express the costimulatory molecules CD80 (B7-1) or CD86 (B7-2) (Snoeck et al., 2005), thus functioning under pathologic conditions as professional APC and stimulating mucosal CD4+ T cell responses. This response may lead to allergy to food proteins in patients with acute helminthic infection characterized by evident IgE response and low regulatory T cell activity, while patients with high regulatory cell activity during chronic helminthic infections are protected from allergy (Maizels and Yazdanbakhsh, 2003). Quite possibly occasional or short-lived

infections may be more pro-allergic, whereas frequent or chronic infections may build up sufficiently to generate a suppressive effect (Hagel et al., 2004).

1.4. T regulatory cells and xenobiotics

In these last decades there has been a significant increase in the prevalence of allergies in many countries, in particular in developing ones, and there is an increasing concern about the association of allergic disease with indoor air quality and environmental atmospheric pollution.

Although the role played by outdoor pollutants in allergic sensitization of the airways has yet to be clarified, a body of evidence suggests that urbanization, with its high levels of vehicle emissions, and a westernized lifestyle are linked to the rising frequency of respiratory diseases observed in most industrialized countries. First of all it has been demonstrated that asthmatics are at increased risk of developing asthma exacerbations with exposure to ozone, nitrogen dioxide, sulphur dioxide and inhalable particulate matter (Bayram et al., 2001). However, it is not easy to evaluate the impact of air pollution on the timing of asthma exacerbations and on the prevalence of asthma in general (D'Amato et al., 2005). The main question is that, in the absence of adequate and specific markers of exposure, effect and susceptibility, the linear dose and effect model, and the concomitant pollutant concentration and disease occurrence relationship cannot explain the complexity of the phenomenon of host–particle interactions. In particular, initial cell alterations (e.g., oxidative stress, DNA adduct formation) rarely turn into permanent tissue damage and evident disease because of host repair and defence mechanisms (Cetta et al., 2010).

Against this background there is a need to address the toxicological, occupational and public health problems associated with the possibility that some chemicals are able to cause allergic sensitization (ability of some chemicals to cause allergic sensitization), in particular the respiratory tract, and occupational asthma. Many chemicals seem to be able not only to induce sensitization, but also to favor sensitization to environmental allergens by inducing a Th2 cytokine pattern secretion by T lymphocytes, so favoring a shift in immunoglobulin production from IgG to IgE. Moreover, chemicals, in particular those emitted from oil combustion, can influence the activity of Treg cells, that, as shown above, are key factors in influencing tolerance/reaction against foreign substances.

In developing countries, both people living in rural areas and in cities are increasing their exposure to chemicals, in particular those linked to agriculture (pesticides and herbicides) and urban pollution, due in particular to gasoline combustion.

This will be discussed here in relation to T reg cell activity and allergy.

1.4.1. Treg, urban pollution and allergy in Africa

Sub-Saharan African cities experience increased urbanization and motorization, consequently air pollution, particularly from vehicles, is worsening and is becoming a major environmental and health concern. Low income levels have been an incentive to import older used vehicles in recent years, to use cheap two-wheelers and cheap fuel, and to postpone vehicle maintenance. Such conditions multiply many times the emissions per kilometer traveled, as do slow speeds due to low investment in road maintenance and traffic management. Moreover, public transportation is undersupplied and unaffordable for many residents. Walking is still a major transportation mode in African cities, exposing the poorest to hours of breathing highly polluted air. Forty percent of urban trips are made on foot and sidewalks are often missing or in disrepair. The many roadside vendors, mostly women, are exposed throughout the day.

The most important pollutants emitted from gasoline and diesel combustion are linked to the increase of allergic diseases. Various

studies addressed the evaluation of the effects of such compounds on allergic diseases both from the epidemiological point of view and by *in vivo* and *in vitro* experiments. In particular sulfur dioxide (Houssaini et al., 2007; Wang et al., 2008; Mortimer et al., 2008; Wang and Pinkerton, 2007), lead (Stepanova, 2003) (Africa is the last regions where motorized vehicles continue to use almost exclusively leaded gasoline), nitrogen oxides (van Amsterdam et al., 2004; Mortimer et al., 2008; Wang and Pinkerton, 2007), carbon monoxide (Whetzel et al., 2007; Mortimer et al., 2008; Wang and Pinkerton, 2007) hydrocarbons (Al-Daghri, 2008; Mizutani et al., 2007) and diesel exhaust particles (DEP) (Dávila et al., 2007; Bartra et al., 2007; Salvi, 2007; D'Amato et al., 2005; Diaz-Sanchez et al., 1997), have been found to favor allergic diseases and to induce immunological effects that are typical of allergic conditions, namely prevalence of Th2 cytokine producing lymphocytes, increase in the releasability of mast cells and in the activation of inflammatory cells.

In particular, a series of epidemiological studies demonstrated that diesel pollution might be involved in the exacerbation and amplification of allergic diseases and suggested a link between increase in the prevalence of allergic diseases and atmospheric DEP levels (Diaz-Sanchez et al., 2003). DEPs are known to modulate the production of cytokines associated with acute and chronic respiratory symptoms and allergic respiratory disease, favoring the recruitment of TH2 cells both in allergic subjects and in non atopics (Senechal et al., 2003). In fact, Chang et al. (2006) demonstrated the adjuvant activity of DEP in inducing IgE production and promoting Th2 differentiation, which enhances allergic inflammation, from cells of non-allergic subjects. DEP significantly suppressed IFN- γ mRNA and protein production, while did not affect IL-4 or IL-5 mRNA and protein levels. The suppressive effect of DEP on IFN- γ mRNA expression was more potent than that of dexamethasone (McHugh et al., 2002). Moreover, DEP significantly suppressed IL-10 mRNA expression and production by stimulated T cells. In peripheral blood mononuclear cells (PBMCs) primed with LPS and exposed, concurrently or after 24 h, to DEP, IL-10 production was inhibited by 50% (Pacheco et al., 2001; Fai Chan et al., 2006) through the oxidative stress produced by DEP itself (Chang et al., 2006; Nel et al., 1998; Hiura et al., 1999; Sagai et al., 1993; Whitekus et al., 2002; Li et al., 2000). In fact, the suppression of cytokine production in DEP-treated T cells is recovered by NAC (Chang et al., 2006), a precursor of L-cysteine and reduced glutathione, that is a source of sulfhydryl groups in cells and scavenger of free radicals, as it interacts with ROS such as OH and H₂O₂ (Zafarullah et al., 2003).

However, the action of DEP on IL-10 production in different human studies conducted on healthy subjects is contradictory, as some studies find a decrease (Ohtani et al., 2005), other no changes (Stenfors et al., 2004). These differences probably reflect the cell types studied and the amount of DEP applied in cell cultures. In fact, the maximal inhibition of IL-10 in LPS-primed human PBMCs occurred only at low doses of DEP, lower than 30 ng/ml (Pacheco et al., 2001; Yoshino and Sagai, 1999). On the other end, only low DEP doses (50 $\pm$ 200 pg/ml) induced an increase in IL-6 and IL-8 production by TNF- α primed human bronchial epithelial cells (Steerenberg et al., 1998). Similar results were observed for production of TGF- β (a cytokine of the Treg pattern), inhibited at doses similar to those required for IL-10 (Pacheco et al., 2001). Data reported in the literature are consistent with evidence that DEP binds to NFkB sites in cytokine promoter regions, and may exert inhibitory as well as stimulatory effects directly on gene transcription.

Altogether, these results suggest that diesel pollution participates in the genesis of allergic reactions by favoring TH2-mediated responses through a reduction of Th1 cytokines, with a prevalence of the Th2 pattern, in concomitance with decreased Treg activity. Through these modifications, diesel exhaust exposure might shift the

immune response in non-atopic individuals toward an allergic pattern and might contribute to the increased prevalence of allergic disorders. Tolerance is an important mechanism through which the immune system can maintain non-responsiveness to common environmental antigens, therefore a fall in Treg activity induced by DEP during exposure to allergen would permit an inflammatory response that otherwise would be inhibited.

1.4.2. Tregs, pesticides and allergy

Pesticides are designed to interfere with living species, and are necessarily characterized by variable levels of toxicity. Epidemiological evidence from Western countries indicates that the prevalence of diseases associated with alterations in the immune response, such as asthma, certain autoimmune diseases and cancer, are increasing to such an extent that it cannot be attributed to improved diagnostics alone (Martin et al., 2009; Tanaka et al., 2007). There is some concern that this trend could be at least partially attributable to new or modified patterns of exposures to chemicals, including pesticides (Corsini et al., 2008). However, available data are inadequate to draw firm conclusions on the immunotoxic risk associated with pesticide exposure. In fact, the studies on the effects of pesticides on the human immune system have several limitations, including limited data on exposure levels, heterogeneity of the applied methods and difficulties in assessing the significance of observed slight changes and in the interpretation of findings.

The immunotoxicity of different organophosphorus (OP) pesticides was reported in different animals and in humans: malathion in chicken and mice (Rishi and Garg, 1993; Kakkar et al., 1996; Relford et al., 1989), diazinon in mice and rats, fish (*Tilapia nilotica*) and humans (Alluwaimi et al., 2001; Abd-Elnessaer, 1995; Barnett et al., 1980; Khalaf-Allah, 1999), parathion in rabbits (Castro et al., 1994), carbaryl and bromfeninfos in mice (Kakkar et al., 1996; Czuminiska, 1988), trichlorfon and dichlorvos in fish (carp) (Dunier et al., 1991), formothion in rats (Gushkin et al., 1991), quinalphos in mice and monocrotophos in goats (Jha et al., 1990).

The immunotoxicity of OP pesticides in mammals could exert direct or indirect effects on the immune system, being usually associated with immunosuppression, autoimmunity or allergy (Stiller-Winkler et al., 1999; Galloway and Handy, 2003).

Few works addressed the effects of pesticides on Tregs in humans and in animals. These showed different results, some with a decrease in all studied cytokines, others with an increase in Treg pattern cytokines production, and the most recent ones with IL10 inhibition along with a decrease or an increase in Th1 cytokine release.

A significant reduction of IL-2, IL-4, IL-10 and IFN- γ in mice intoxicated with permithrin, dimethoate and diazinon has been shown by Alluwaimi and Hussein (2007). In mice exposed to pirimiphos-methyl, other authors reported a slight increase in IL10, overwhelmed by a dramatic increase in inflammatory cytokines (IL-2, IL-4, IL-6, IFN- γ) and decreased T cell proliferation induced by Con A (Kim et al., 2007). The authors concluded that pesticides may induce allergic responses by relatively enhancing Th2-derived cytokines and, additionally, contribute to chronic inflammation by attracting macrophages through IFN- γ .

Predominant Th2 stimulation by pesticides was demonstrated by studying cytokine level in lymphocytes subpopulation (CD4+, CD8+, CD4 + CD25+ and B cells). Significant increase of IL-10 in B cells and CD4+ cells and decrease of IFN- γ in CD4+ cells was found, as transient upregulation of type 2 cytokines negatively down-regulated IFN- γ in B cells (Alluwaimi and Hussein, 2007).

Associations between exposures to OP pesticides and prevalence of Th2 cytokine pattern were found in children living in agricultural settings (Duramad et al., 2006) and in adults and children there were associations between OP pesticide exposure and self-reported exacerbation or onset of respiratory disorders (Hoppin et al., 2002; Salam et al., 2004; Zhang et al., 2002). Salam et al. (2004) reported

that exposure to herbicides and pesticides in the first year of life was associated with higher odds of asthma in children. In adult agricultural workers, the investigation of serum, cellular and functional immune parameters suggested that intermittent exposure to the pesticide propanil resulted in a modest immunomodulatory effect, with a statistically significant increase in IgG1 plasma levels, a trend in the increase of IL-6 production and a clear reduction of IL-10 and IFN- γ release, associated with a decreased IFN/IL-4 ratio (Corsini et al., 2007). The effect on cytokine production was also confirmed *in vitro*, where dose dependent production of IL-2, IL-10 and IFN by continuous treatment of peripheral blood leukocytes has been demonstrated (Corsini et al., 2007). The authors concluded that propanil is potentially acting as an adjuvant on innate immune mechanisms, which, by altering Th1/Th2 cytokine production, enhances humoral immune responses (Corsini et al., 2007). Consistently with animal data (Zhao et al., 1998), other authors reported that propanil was able to modulate PHA-induced IL-2 and IFN- γ production and inhibited IL-10 production. Both Zhao et al. (1998) and Corsini et al. (2007) concluded that these experimental evidences may have implications for a potential role of this class of compounds in autoimmune or allergic diseases.

2. Conclusions

An ideal organism should be able to perfectly control its immune system under any combination of infectious challenges and antigenic stimuli. However, organisms are not perfect and have been selected to perform optimally within the set of conditions encountered by their ancestors. In humans, one of these conditions was arguably, and in many areas still is, exposure to a diverse community of helminth parasites. The relationship between helminths and vertebrates is ancient and can be traced back to when nematodes invaded primitive tetrapods (Anderson, 1995) and the ancestral platyhelminths (Littlewood et al., 1999) first appeared in fishes prior to the colonization of land. Because helminth infection is and (probably) has been so ubiquitous, mammalian immune systems may have been selected to anticipate that they would suffer chronic exposure to large-bodied Th2/Treg-inducing pathogens. In other words, there would have been selection for immunoregulatory systems that work well in the context of worm infection and there would rarely have been selection for immunoregulatory systems that work optimally when worms are absent, the situation seen in modern human populations (Maizels, 2007; Cooke et al., 1999). Such a scenario might explain the dramatic increases in allergy and autoimmune conditions in Western countries and is supported by the protective effect of helminth infection in laboratory models of allergy and autoimmunity and in areas of the world, like African countries, where helminth infections are still endemic in humans (Cooke et al., 1999; McInnes et al., 2003). However, at present Sub-Saharan Africa is facing an unprecedented diffusion of environmental pollutants, mainly due to the uncontrolled diffusion of xenobiotics (pesticides, herbicides, urban and traffic pollution, etc.). Chemicals linked to agriculture (pesticides and herbicides) and pollutants from gasoline and diesel combustion may have effects similar to those exerted by helminths with regard to stimulation of Th2 immune reactions, with production of IL4, IL13, IL5, inhibition of IFN- γ , increased production of IgE, increased releasability of mast cells and activation of inflammatory cells like eosinophils. However, differently from helminths, these pollutants induce a decrease in the activity of T regulatory cells. From an epidemiological point of view this condition favors the development of allergic diseases, overcoming the protective effects of infections. Consistently with this, allergies are seem to be increasing in Sub-Saharan Africa at rates similar to those of developed countries.

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