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Antigen mimicry between infectious agents and self or environmental antigens may lead to long-term regulation of inflammation

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THE PAST INFLUENCES THE PRESENT: INFECTIONS INDUCE AN IMMUNOLOGICAL STATE THAT CONTROLS THE DEVELOPMENT OF ALLERGY, ATOPY, AND AUTOIMMUNE DISEASES

To account for the increasing prevalences of allergic and autoimmune diseases in populations that partake of good hygiene conditions, and, therefore, are less exposed to pathogens, the hygiene hypothesis proposes that infections favor the long-lasting control of types I and IV hypersensitivity reactions (1). This effect has been ascribed to interleukin (IL-)10 production (2–4). However, type I hypersensitivity can still be kept in check well after the infection has subsided (5), and past infections may protect against the development of autoimmunity (4, 6).

In one study, 613 individuals from two African villages with different prevalences of schistosomiasis caused by *Schistosoma haematobium* were investigated for the presence of circulating anti-nuclear autoantibodies (ANA). ANA levels were lower in the most heavily infected individuals in the low schistosomiasis-prevalence village, although no statistically significant differences among differently infected groups was reported. A statistically significant, but small mean difference of about 3 IU between treated and untreated individuals was observed, a fact that allows one to conclude that ongoing *S. haematobium* infections inhibit the production of ANA. However, at least two pieces of evidence in that study convincingly argue in favor of a stronger effect of past infections in determining ANA levels. Firstly, uninfected individuals' ANA levels in the high infection-prevalence village were similar to heavily infected individuals' ANA levels in the low infection-prevalence area. Past infections of uninfected individuals, in the high prevalence area, could account for this finding. Secondly, much lower intensities of infection were observed in more than 22-year-old individuals (mean of approximately 2.5 eggs per 10 mL of urine) than in younger individuals (means ranging from 17.0 to 75.0 eggs per 10 mL of urine) (4). It is very likely, therefore, that the prevalence of infection is also much lower in older individuals, who have been, nevertheless, exposed during a longer time interval than the younger individuals to the parasite. Despite this, no difference in ANA levels among the different age groups were observed, suggesting that past infections down-regulated ANA formation in the older group.

The findings mentioned above provide indirect evidence for the persistence of an expanded population of regulatory cells in the absence of stimulation of the immune system by pathogen-derived antigens. The strength of the immune regulation, however, may increase with the continuous presence of the pathogen or of its antigens. For instance, the prevention of diabetes in NOD mice by the injection of *Trypanosoma cruzi* extract depends on repeated extract injections (Mengel J. et al., unpublished data). It is also reasonable to assume that different diseases may require distinct levels of immune regulation in order to be controlled.

DO AUTOREACTIVE AND ALLERGEN-REACTIVE IMMUNE REGULATORY CELLS PLAY A ROLE IN MAINTAINING AN INFECTION-TRIGGERED IMMUNE MODULATORY STATE?

It is proposed herein a mechanism by which past infections would result in a persistent downregulation of immune-mediated inflammatory reactions. This mechanism would entail the stimulation of autoreactive FoxP3$^+$ or FoxP3$^-$ regulatory T (Treg) cells or IL-10 – producing B (B10) cells, or bystander stimulation of these cells (7, 8), during immune responses against complex microorganisms. Some of the thousands of foreign epitopes would crossreact with self and lead to the expansion of autoreactive regulatory cells (9). Regulatory cells have indeed been shown to expand during infections (10–13), although it has not been described whether they crossreact with autoantigens. The crossreactive regulatory

cells would then be constantly activated by autoantigens, even after the infectious agent had been eliminated. This view agrees with reported evidence that the establishment of peripheral tolerance requires the continuous presence of antigen (14), which, of course, is the case with non-sequestered autoantigens.

What has been proposed above for autoreactive lymphocytes could well also take place with lymphocytes that recognize ubiquitous foreign antigens. For instance, unless very strict control measures are adopted, most individuals are recurrently exposed to aeroallergens through the respiratory mucosa, in many cases in almost the same degree that they are exposed to autoantigens (15). Moreover, anti-house dust mite antibodies have been shown to crossreact with *Ascaris lumbricoides* aqueous extracts (16). One could, therefore, also propose that mite allergens would maintain mite allergen-reactive regulatory cells, initially activated by crossreactive *A. lumbricoides* antigens, in an active state (**Figure 1**). Alternatively, pathogen-derived antigens could induce the activation of bystander allergen-specific regulatory cells.

The regulatory cells would act mainly by means of secreted IL-10 and TGF-beta. These cytokines, which have been associated with the control of both autoimmunity (4, 17, 18) and allergic diseases (19), can act by directly inhibiting cytokine synthesis and proliferation of effector lymphocytes (20, 21), by deviating the differentiation of naïve T cells to inducible CD25$^+$ regulatory T (iTreg) cells or to Tr1 cells (22, 23), or by conferring a tolerogenic profile to dendritic cells (tolDCs; 19). The tolDCs, in their turn, would induce the development of Tr1 and B10 cells, further intensifying the immune regulatory character of the environment (24) (**Figure 1**). Another interesting possibility would concern an IL-10- and TGF-beta-induced switching on

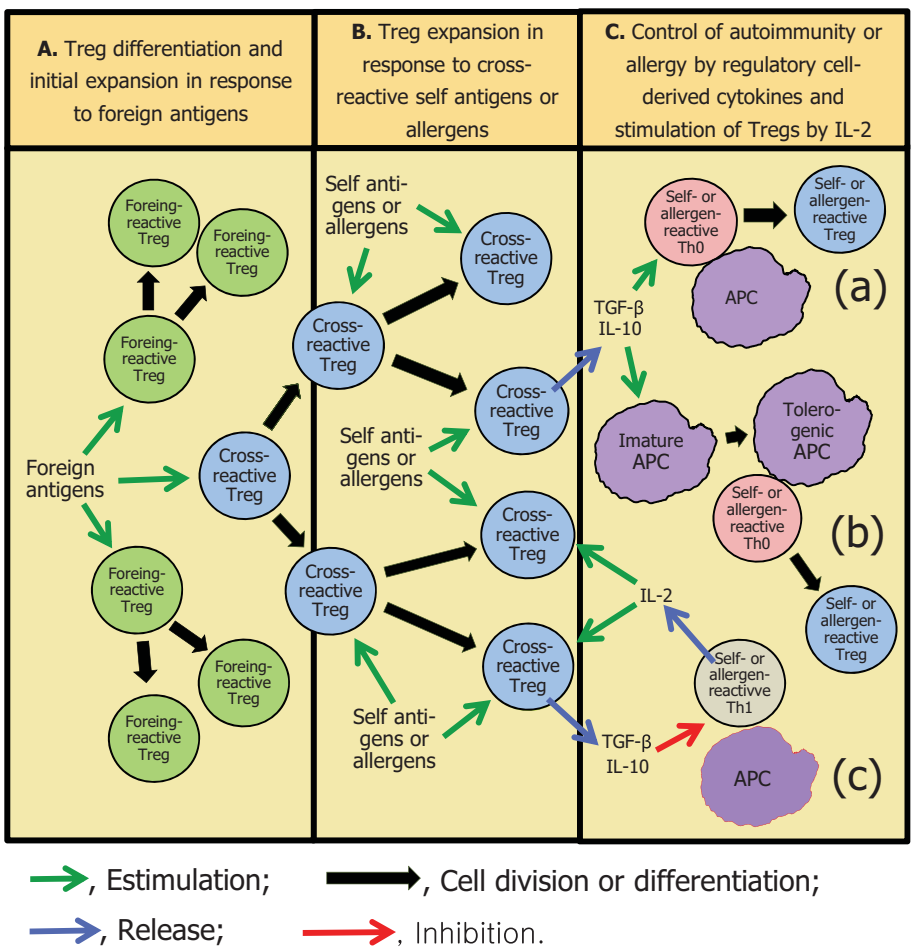

FIGURE 1 | A possible mechanism for the maintenance of an infection-triggered immune regulatory environment. (A) Foreign, pathogen-derived antigens would activate and initially expand regulatory T cells (Treg) that crossreact with self-antigens and allergens, as well as pathogen-specific regulatory cells. **(B)** Self-antigens or common allergens would further expand and activate the crossreactive Treg cells. **(C)** Regulatory cell-derived IL-10 and TGF-β would inhibit potentially pathogenic immune responses by: (a) diverting the differentiation of naïve, Th0 lymphocytes to T regulatory lineages rather than to other, proinflammatory types (22, 23); (b) promoting the differentiation of tolerogenic antigen-presenting cells (APC) (these cells would lead to the differentiation of regulatory T and B lymphocytes) (24); (c) directly inhibiting the proliferation of and synthesis of proinflammatory cytokines by effector T cells (20, 21). Self- or allergen-reactive Th1 cells would sporadically release the IL-2 necessary to maintain the Treg response, before being controlled by regulatory cytokines. For the sake of clarity, the inflammatory reaction due to infection in **(A)**, the APC required for Treg antigen recognition in **(A,B)**, and regulatory B cells are not depicted in the Figure.

of IgA synthesis in B cells (25), diverting potentially autoreactive B cells from synthesizing the more pathogenic IgE and IgG isotypes. In accordance with this hypothesis, there is evidence that the majority of human splenic B cells are first stimulated by antigens in gut-associated lymphoid tissues (26), which are skewed toward the presence of regulatory cytokines (27).

The hypothesis proposed above would be consistent both with antigen-specific and non-specific immune regulation. In the first case, the regulatory lymphocytes would act specifically on autoantigen- and allergen-reactive T cells (in the case of Treg cells by binding to the same antigen-presenting cells that memory effector lymphocytes or naïve lymphocytes are bound to). Non-specific immune regulation would perhaps result from increased extracellular concentrations of regulatory cytokines (23). As far as the authors' knowledge goes, no evidence for antigen-specificity or non-specificity of the phenomena dealt with in the hygiene hypothesis has been provided in the literature.

A particular type of regulatory cell that could be involved in an infection-triggered immune regulatory chain of events is the IL-10-secreting Th1 cell (14, 28, 29), since, contrasting with other regulatory cells, it is not anergic (28), and would, therefore, be more easily driven to expansion. IL-10-secreting Th1 cells have been shown to expand during infections, have been associated with the control of allergy and autoimmunity (14, 28) and are believed to result from cytokine synthesis switching in effector T cells (29). They would, therefore, unlike other Tregs, be formed in proinflammatory conditions, something that would entail their presence in large numbers in animals with infectious diseases. In fact, high proportion of the cells that infiltrate muscle tissue in *T. cruzi*-infected mice synthesizes both IL-10 and interferon (IFN-)gamma (Mengel J. et al., unpublished data).

Supporting the hypothesis proposed herein, it has been observed that peripheral blood mononuclear cells from individuals who have been infected by helminths produce IL-10 in the absence of *in vitro* stimulation, whereas they produced no additional IL-10 when stimulated *in vitro* by helminth antigens (30). This finding could be explained by the IL-10 being produced by crossreactive regulatory T or B cells that would already had been stimulated by autoantigens *in vivo*. Crossreactivities between helminth antigens and autoantigens have indeed been described (31–35).

It is proposed in this Opinion that the IL-2 required for the maintenance of an immune regulatory state would derive from Th1 cells. These cells would be activated by autoantigens or allergens when the immune regulatory cells had faltered due to the very lack of IL-2. One could therefore envisage, therefore, that a functional immune regulatory state would be maintained by the recurrent but transient activation of potentially pathogenic autoreactive or allergen-reactive effector Th1 lymphocytes. These lymphocytes would then be immediately controlled, before they could cause overt disease, by the prompt activation of previously expanded immune regulatory cells by the released IL-2. An alternance of short periods of potentially pathogenic immune responses and long periods in which these responses were kept in check would therefore ensue.

Some autoimmune diseases, such as collagen diseases and multiple sclerosis, have periods of clinical activity separated by remission intervals. At least in some occasions this could reflect disturbances in the immunological environment, whose regulatory potential would augment following periods of disease activity in which IL-2 would be made available.

THE PARASITES' GOOD LUCK: SOME CROSSREACTIVITY MAY PROTECT THEM FROM THE IMMUNE SYSTEM, NO CROSSREACTIVITY MAY NOT BE AN OPTION AT ALL

An initial requisite for an infection-triggered regulatory state be maintained in the absence of infection, as proposed in this Opinion, is that the infecting organism should crossreact with self or with a foreign antigen that the host would be in almost permanent contact with. This requisite would perhaps favor the occurrence of the phenomenon in infections by complex pathogens, of which helminths, of course, are the best representatives, since the number of different epitopes present in an organism would be a function of the number of different proteins synthesized by it, which in its turn tends to increase with the organism complexity. However, there is not, *a priori*, *any* reason why the phenomenon would not occur with infections by non-helminthic pathogens.

The number of different epitopes present in complex organisms, constituted by specialized cells, such as helminths, mites, or human beings, could indeed be enormous. Even in a simpler unicellular microorganism, such as *Trypanosoma brucei*, a total of 8,960 mRNA transcripts have been predicted (36), and, therefore, there is a potential for the same number of different antigens to be expressed. Since at least one to four epitopes per polypeptide have been shown to be presented to $CD4^+$ lymphocytes by antigen-presenting cells in a single individual (37–39), the probability that at least a few among the thousands of a complex organism epitopes would be similar to a few of the thousands of epitopes of another complex organism could be very high indeed. This probability of occurrence of crossreaction is greatly increased in function of the degenerate recognition of peptides by the $CD4^+$ T-cell antigen receptor (TCR), i.e., complete identity between peptides is not a requisite for crossreactivity (39), and, last but not least, to sequence homologies among phylogenetically related proteins.

Several examples of crossreactivity of pathogens with autoantigens have been reported [e.g., (31–35, 39–45)], some of which due to phylogenetic homologies (32–34, 42, 44). A particular study has shown that, depending on the HLA allele, 80–290 MHC II-binding peptides from *Mycobacterium tuberculosis* crossreact with human autoantigens (45).

On the other hand, it is conceivable that a pathogen would face a compromised immune response even when only one of its antigens stimulated pre-expanded autoreactive immune regulatory cells, through the mechanism of linked or bystander suppression (7, 8). Thus, there could be, in fact, a selective pressure for pathogens to expose epitopes crossreacting with self to the host immune system.

Another requisite for the intensification of the immune regulatory state by infections, namely the infectious agents inducing the production of regulatory cytokines, could also favor a major role played by helminth infections, as these are often associated with the so-called "modified Th2-cell responses," in which IL-10 is produced concomitantly with IL-4 and IL-13 (3).

TESTABLE PREDICTIONS OF THE PROPOSED HYPOTHESIS

If the immune regulatory cells are maintained in an active state or as memory cells by autoantigens and customary allergens, they should be specific for these antigens. This is amenable to be experimentally tested, as animals that had had past chronic infections should respond normally to the immunization with unrelated foreign antigens but be less prone to the experimental induction of autoimmune diseases. Another question to be answered is whether the regulatory cells, in addition to react with self and allergenic antigens, would also react with crossreactive infectious agent antigens. A possible approach to answer it could involve the use of flow cytometry to enumerate Treg cells capable of binding to MHC tetramers associated with crossreactive peptides, or to enumerate crossreactive antigen-binding B10 cells.

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