EDITORIAL

AUTOIMMUNITY AND PARASITES

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Autoimmunity is defined as the failure of an organism to recognize its own constituent as "self", which results in an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an autoimmune disease. Despite our growing knowledge of the immunologic abnormalities that may result in autoimmunity, we do not know the etiology of any human autoimmune disease. This lack of understanding is mainly because autoimmune diseases in humans are usually heterogeneous and multifactorial, the self antigens that are the inducers and targets of the autoimmune reactions are often unknown, and the diseases may present clinically long after the autoimmune reactions have been initiated (1-3).

The susceptibility of developing autoimmune diseases is associated with multiple risk factors, such as the inheritance of susceptible genes and environmental triggers. Family studies and more recently scanning techniques, as well as breeding studies in animals, have established that autoimmune diseases usually have a complex association with multiple gene loci, the most important of these belonging to MHC genes (1, 4).

In areas where multiple infectious diseases such as parasitism are endemic, autoimmune diseases are quite rarely seen. Parasitic infections are a major theme in "hygiene hypothesis", as allergies and autoimmune diseases are less prevalent in countries with higher burdens of helminths and other parasitic organisms (5-7). Helminths – the grouping of multicellular worm parasites including nematodes, cestodes and trematodes – attenuate the host immune response in order to protect themselves. Parasites are often long-lived and inhibit immunocompetent hosts for prolonged periods; consequently it is not surprising that they should possess modulatory molecules that ameliorate host responses to enhance their survival. Parasites elicit a TH_1 type of immune

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response which has the ability to down-regulate the mediators of TH_2 responses (8-10).

Up-regulation of either T helper $(TH)_1$ or TH_2 cells is pathogenic, and these subsets down-regulate each other. The expression of chemokines/cytokines by trafficking inflammatory T cells is also crucial to autoimmunity. The absence of those down-regulating parasites leads to insufficient stimulation of the TH_1 arm of the immune system and to an overactive TH_2 which in turn leads to asthma, hay fever, multiple sclerosis, etc (11-14).

As already noted, allergies are inflammatory diseases dependent on TH_2-type responses and initiated by increased IgE to allergen mast cell degranulation and eosinophilia. The release of mediators leads to the production of pro-inflammatory cytokines (15-17).

T cells can be categorized according to the cytokines they produce. Type 1 helper T(Th1) cells produce mainly IFN-γ, TNF-β and IL-2, whereas type 2 helper T (Th2) cells produce mainly IL-4, IL–5 and IL-13. Since sclerosis and type 1 diabetes are mainly mediated by Th1 cells and allergic diseases by Th2 cells, alteration of the cytokine balance is an appealing threrapeutic possibility (11-12). There is evidence that the shift in balance between Th1-type cytokines and Th2-type cytokines that occurs during pregnancy alleviates the symptoms of rheumatoid arthritis. Such changes in the cytokine profile may be responsible for the beneficial effects of allergen desensitization and of glatiramer acetate, a polypeptide to treat multiple sclerosis (18-22).

Although autoimmune lesions are infiltrated by activated CD4+ T helper (TH)1 cells, evidence is accumulating to indicate that TH2 cytokines are also implicated. Various cellular anti-self responses are mediated by chronic overexpression of tumor necrosis factor TNF-α , together with interferon (IFN)-α/β as key factors in autoimmune processes. IFN-α/β is an early effector of innate immune responses which triggers non-specific receptors, such as the Toll-like receptors, therefore, an anti-inflammatory regulatory network, which is characterized by the production of elevated concentrations of IL-10, TGF-β and synthesis of NO from APC and regulatory T cells and also NKT cell participation, ensures that inflammatory T cells (TH1, TH2) are kept under control(23-25). Several parasite antigens alone were able to induce classic macrophage activation and consequent increase in NO levels: glycophosphatidylinositol-anchored mucin-like glycoproteins (GPI) are potent inducers of NO by IFN-γ primed macrophages. Another *Trypanosoma cruzi* antigen involved in classic macrophage activation is the parasite-released molecule Tc52, which synergizes with IFN-γ to stimulate NO production. Tc52 signals via TLR2 and confers resistance against lethal infection in BALB/c mice. In addition to classical cell types of the innate immunity, cumulative findings indicate that cardiomyocytes are actively integrated in the inflammatory response during *Trypanosoma cruzi* infection, releasing NO, cytokines and chemokines, which in turn, might attract leukocytes to the inflammatory site and control intracellular parasite replication. It was shown that heart tissue collected from *Trypanosoma cruzi*-infected rats expressed IL-6, IL-1β, TNF-α, and iNOS. Hearts from mice infected with *Trypanosoma cruzi* also expressed iNOS mRNA and pro-inflammatory cytokines. Moreover, parasite-infected cardiomyocytes express mRNA for TNF-α, IL-1α and iNOS, as well as CXCL3/MIP-2β and CCL5/RANTES among other chemokines. In humans, *Trypanosoma cruzi* infection induces both humoral and cellular autoimmunity to several host antigens. In this respect, elimination of parasite in acute phase could potentially abrogate the induction of autoimmunity. In fact, anti-Chagas as well as anti-*Trypanosoma cruzi* antibody titers decreased in parallel with anti-parasite treatment and positively correlated with clinical symptoms (25-27). Thus, cytokines and chemokines play several roles in regulating and amplifying inflammation in autoimmune states. Chemokines are the key modulators of inflammation, acting through G-protein-coupled receptors and encouraging migration of cells to the site of inflammation (28).

Helminth infections through induction of regulatory mechanisms, such as IL-10 production, are able to modulate the inflammatory immune response involved in the pathology of autoimmune and allergic disease (28-29). *Schistosoma mansoni* antigens can induce the secretion of regulatory cytokines from DC, MΦ, and NKT cells as well as B1 B cells, resulting in the expansion of Th2 and Treg populations that might be responsible

for maintaining self-tolerance. DC and MΦ are fundamental to directing immune responses along either a tolerating or activating pathway, therefore it is not surprising that helminths have evolved strategies targeting receptors on these cells. Toll like receptors (TLRs) and C-type lectin receptors (CLRs), broadly expressed on DCs and MΦs, are the main parasite targets for evading immuno-surveillance (30).

Researchers have evaluated the influence of *S. mansoni* infection on the immune response and development of a number of infections and autoimmune diseases. Infection with *S. mansoni* affects the immune response to vaccine antigen. Individuals vaccinated with tetanus toxoid antigen who were infected with *S. mansoni* produced the type 2 cytokine, IL-4, rather than IFN-γ in response to restimulation *in vitro*, while uninfected vaccinated individuals *in vitro*, produced type 1 cytokine, IFN-γ (31). Zaccone et al. found that injection of *S. mansoni* eggs into 5 week-old NOD mice totally inhibited the development of the disease, and later it was demonstrated that soluble extract of *S. mansoni* worm or egg completely prevented the onset of autoimmune type 1 diabetes in NOD (non-obese diabetes) mice (32). Since insulin-dependent diabetes mellitus is mediated by a Th1 response against beta cell antigens, it is probable that the parasite antigens induce IL-10 production and prevent the disease by switching the immune response toward the Th2 type. Indeed, T cells from diabetes-protected mice make IL-10 after re-stimulation *in vitro* with *S. mansoni* antigen (33). *S. mansoni* infection also decreased tissue damage and clinical manifestation of other Th1-mediated auto-immune diseases such as multiple sclerosis and Crohn's disease. In a mice model to study experimental autoimmune encephalite (EAE), a multiple sclerosis-like disease, it was demonstrated that infection with *S. mansoni* delays the onset of the disease and prevents inflammation in the central nervous system (34-35). Attenuation of the clinical course of EAE was followed by a reduction in the synthesis of pro-inflammatory mediators, such as IFN-γ, TNF-α and NO, by spleen and central nervous cells *in vitro*, while the levels of IL-4 and IL-5 in plasma were, as predicted, higher in the parasite-infected group (34).

Smith et al first showed that schistosome eggs secrete a molecule that blocks activity of certain chemokines both *in vitro* and *in vivo*. The purified recombinant *S. mansoni* chemokine binding protein (smCKBP) suppressed inflammation in several disease models. smCKBP is unrelated to host proteins and is the first described chemokine binding protein encoded by a pathogenic human parasite and may have potential as an anti-inflammatory agent (36).

Furthermore, mice exposed to *Trichinella spiralis, Hymenolepis diminuta* or *Heligmosomoides polygyrus* make less IL-12 and IFN-γ, but more IL-4 and immunoregulatory IL-10 (7, 37-38).

Also colonization of IL-10 in mice with *H. polygyrus* augments mesenteric lymph node T cell regulatory function and expression of FoxP3 mRNA which codes for a transcription factor expressed by T cells that inhibits autoimmune inflammation (38).

Scott found that during *Leishmania major* infection, IL-12 in combination with chemotherapy, abrogates a Th2 response. These results have implications for treatment of infectious diseases, autoimmunity, and allergy. Currently, we are studying how such switching occurs. Finally, we found that TNFRp55-/- mice are unable to heal leishmanial lesions in spite of eliminating the parasites. This result suggests that the tumor necrosis factor receptor (TNFR) p55 plays a critical, and previously unrecognized, role in down-regulating pathogen-induced inflammatory responses (39).

Regarding the interaction between worms and allergy, a few variables need to be taken into account: phase (acute or chronic) of helminth infection may increase manifestations of allergy, whereas chronic infection with parasites decrease atopy. The modulation of the immune response by helminth is dependent on having an adequate load (14).

In conclusion, the human immune system has been shaped by its relationship with parasitic worms and this may be a necessary requirement for maintaining our immunological health.

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