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The Pro-allergic Influences of Helminth Parasites

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Parasitic infection is highly allergenic, and the present paper illustrates how parasites might disrupt the regulation of IgE synthesis, resulting in heightened Th-2 responses. The study of parasites, and dysregulation of the IgE ntwork, could in turn provide information relating to the aetiology of allergic diseases such as asthma and atopic dermatitis.

Helminth parasites are highly antigenic and particularly adept at exerting a pro-allergic adjuvant effect, where Th-2 lymphocytes and their cytokines (particularly, IL3, 4* and 5) promote mastocytosis, IgE synthesis and eosinophilia (Pritchard 1993a).

An increase in our understanding of the mechanisms employed by parasites to support this potentially host-protective (Pritchard et al. 1995) or parasite-protective immune response - Th-1 responses seem to be successful in controlling invasive larval stages of some parasites (Pritchard & Wilson 1997) - would serve the dual purpose of providing: (i) a sound basis for the development of anti-parasitic immuno-therapeutic strategies; (ii) an insight into the mechanisms responsible for the development of and upsurge in allergic disease in parasite-free countries.

This article presents a brief summary of the current understanding of the factors in the immunological environment which influence T-cell development, and indicates points along this developmental pathway at which parasites and their products could influence this environment to promote allergic responses.

WHY ARE HELMINTH INFECTIONS SO ALLERGENIC?

Helminth parasites are particularly adept at stimulating IgE synthesis, and a number of parasite allergens have recently been cloned and characterised (McReynolds et al. 1993). Do certain parasite antigens have molecular properties

which support their allergenicity? This is a question which has puzzled immunologists for decades, and a number of theories have been put forward. One popular theory at present is based on the fact that many allergens have enzymatic activity (e.g. *Der p* I from *Dermatophagoides pteronyssinus*), and that enzymatic activity somehow deviates antigen processing in a way that supports the generation of Th-2 lymphocytes. It is, therefore, of interest that highly allergenic parasites such as the schistosomes and hookworms are rich sources of secreted proteinases (Smith et al. 1994, Brown et al. 1995). How do these enzymes promote IgE synthesis? One clue to a possible mechanism comes from an observation made in a population in Papua New Guinea infected with the hookworm *Necator americanus*. This population was noted to have exceedingly high levels (on average, 40 times that of normal) of soluble CD23 (the low affinity receptor for IgE) and IgE in its plasma, up to 17,000 IU/ml (Pritchard et al. 1993).

This observation led to the hypothesis that parasite proteases might accelerate the natural proteolytic cleavage of CD23 from the leucocyte surface, leading to an up regulation of immediate-type hypersensitivity through the generation of soluble CD23 (a pro-allergic cytokine) and the removal of a negative feedback signal for IgE synthesis (Pritchard 1993a). IgE containing immune complexes bind to CD23, to send a feedback inhibition signal to the B cell, which reduces IgE synthesis (reviewed by Delespesse et al. 1992). Consequently, allergens which selectively cleave CD23 would theoretically be pro-allergic. It is therefore of interest that *Der p* I, a proteolytically-active allergen of the house mite *D. pteronyssinus*, selectively cleaves CD23 from the human B cell surface (Hewitt et al. 1995). This is the first and most convincing experimental evidence that dust mites dysregulate the IgE network by directly interfering with the control of IgE synthesis, and these observations have since been confirmed by other workers.

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*There is recent evidence, in mice, that class switching to IgE can be initiated by retroviral infection, using IL-4 independent pathways (Morawetz et al. 1996). Helminths apparently do *not* use this pathway.
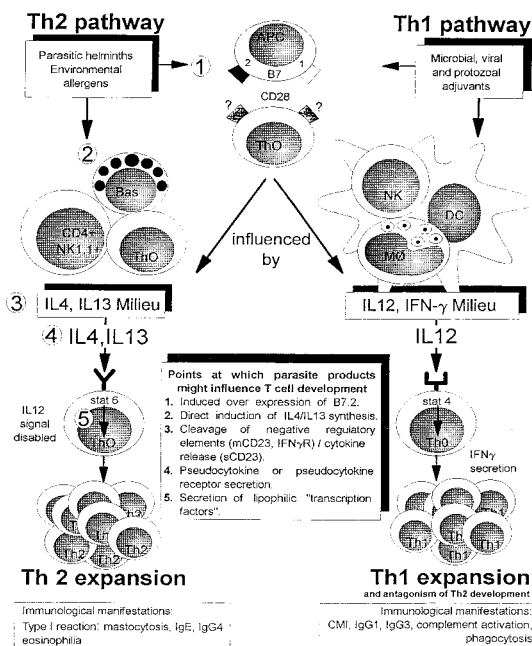
This explanation may not hold for all allergens (for example, many fatty acid binding proteins (FABP)are now proven allergens** - McReynolds, et al. 1993); however, it provides an experimental basis for testing the pro-allergic activity of at least a major group of common environmental toxins. A resumé of recent developments in our understanding of the development of helper T cell at this point would help to indicate *other points* in the development processes where parasites and their products could exert influence on Th-2 bias.

RECENT DEVELOPMENTS IN OUR UNDERSTANDING OF T CELL MATURATION

The early cytokine milieu seems to be of critical importance to the differential development of T cells. Both Th1 and Th2 cells can develop from the same T cell precursor, with IL12 from macrophages and activated dendritic cells the predominant Th1 promoting cytokine, and IL4 and IL13, possibly from basophils (Ochensberger et al. 1996), T cells themselves or CD4^{+} NK1.1^{+}, equivalents in man***, promoting Th2 development. The downstream effects of these cytokines on further T cell development would appear to be mediated through a number of transcription factors belonging to the *stat* family. Of these, *stat* 4 would appear to be activated by IL12 (with IFNγ playing a supportive role), and *stat* 6 would appear to be activated by IL4 (Kaplan et al. 1996 a,b). The other points in T cell development in which parasite products would be active are illustrated (Fig.) and described below.

The CD23 effect described would be largely mediated through B cells committed to IgE synthesis and it has already been suggested that helminths parasites may promote their own survival by stimulating polyclonal IgE synthesis, although formal proof for this hypothesis is still to be found. As well as cleaving CD23 to promote IgE synthesis, it is also possible that parasitic helminths secrete molecules which act as pseudocytokines, to maintain the Th-2 bias. Molecules with the activities of IL4, IL10 and sCD23 would fulfil these criteria.

Alternatively, if Th-2 responses, in a specific sense, begin to damage the parasite, as has been in-

**Given the ability of FABP's to sequester vitamins, and the fact that some vitamins (e.g. D3) promote Th-2 development (Rook et al. 1994), it is possible that some allergens promote the allergic response through selective vitamin uptake.

***There is also data to suggest that NK1.1^{+} T cells are *not* involved in the triggering of Th2 responses (Brown et al. 1996).

T cell development can be influenced by a number of factors in the immunological environment, and the points in T cell development where parasitic helminths and their ES products could conceivably exert an influence are shown here. For example, it is possible that helminth excretory/secretory products, particularly secreted proteinases and proteinase inhibitors (doubling as anticoagulants?), could influence the proteinase-rich antigen processing milieu to an extent that a pathway favouring Th-2 development is favoured. The mechanism by which CD28 controls IgE synthesis is sketchy. Some data supports a positive role for CD28 (King et al. 1996) through an interaction with the B7 marker (Corry et al. 1994), but it may not always stimulate through B7 (Life et al. 1995). Other data suggests that co-stimulation of T cells via CD28 inhibits IgE production (Van der Pouwkraan et al. 1996). Interestingly, the latter effect was reversed by pertussis toxin.

Proteinases could also effect IL4 secretion directly, in a non-antigenic fashion, in a manner similar to that already described for other enzymatically active allergens. It is also already known that another proteolytically active environmental allergen (*Der p* I) has the ability to dysregulate the IgE network; formal proof demonstrating a similar effect by helminth proteases is lacking, although the suggestion that they might potentiate IgE synthesis by cleaving molecules such as CD23 was first muted in the early 90's (Pritchard 1993a).

The pro Th-2 developmental pathway would then be propagated by the possible release of cytokines (IL4, sCD23) or secretion of pseudocytokines or pseudocytokine receptors (e.g. IFN-γ R) and even lipophilic homoserine lactones similar to those already shown to be active in chemical communication between bacteria (Williams 1994).

Another parasite secretion with the potential to modulate T cell development is acetylcholinesterase. Cholinergic influences on T cell development/activation have been recorded, yet it remains to be established whether extraneous sources of AChE, which would compete with T cell membrane AChE, exert any polarising effect on T cell development (Pritchard 1993b).

Abbreviations: APC: antigen presenting cell; BAS: basophil; DC: dendritic cell; ES: excretory/secretory product; MO: macrophage; NK: natural killer; Th0: undifferentiated T cell; STAT: signal transducer and activator of transcription; For further details of the downstream effects of IL4 on T cell development, (Anderson & Coyle 1994, Abbas et al. 1996).

ferred from a number of field studies described above, then it would be in the interest of the parasite to induce a Th-1 bias. This could be done through the secretion of Th-1 promoting pseudocytokines such as IFN-γ and IL-12. This may indeed be the case in *Trichuris muris* infection, although the final proof regarding the activity of this pseudocytokine is lacking. Work by Birgit Helm and her colleagues (Dudler et al. 1995, Machado et al. 1996) would also suggest that enzymatically active allergens induce IL4 synthesis by cells of the basophil lineage in the absence of sensitisation with IgE. This kind of direct activity would generate the early IL4 milieu necessary for Th-2 development. It is also intriguing that a number of pathogenic and non-pathogenic bacteria signal to each other through the secretion of lipophilic compounds which interact with cytosolic proteins to become transcription factors (Williams 1994). Could parasitic helminths do the same? A full list of parasite molecules with the putative ability to control T cell development is shown in the Table below.

TABLE

Examples of known and putative parasite secretions with the potential to support the development and growth of Th-2 lymphocytes

Excretory secretory product	Putative pro-Th-2 effect
Proteinases e.g. cysteinyl proteinases,glycosidases, lipases (cf. phospholipase A2)	(i) cleavage of negative regulatory elements (CD23, IFN-γ R/IL12R); (ii) release of cytokines (sCD23) and "anti-cytokines" (sIFN-γ R/IL12R); (iii) direct induction of IL4 and IL13 synthesis
Proteinases/ inhibitors e.g. serpins	Interference with cytosolic pathways of antigen processing/ presentation
Acetylcholinesterase	Interference with muscarinic (+ve) and nicotinic (-ve) influences on T cell function, and T-cell mAChE
Pseudocytokines/receptors/ligands	Supportive of IL4 milieu, sequestration of negative regulatory cytokines. Presentation of CD40 ligand-like molecules
Superantigens	Induction of CD40 ligand expression and class switching to IgE (Jabara & Geha 1996)
Mitogens	Expansion of IL4-receptive B (as found in "*Ascaris*" body fluid) and T cell sub-populations (Lee 1995)
Protein kinases	Deviation of developmental pathways to Th-2 via intracellular signalling processes
Lipophilic "transcription factors"	Conversion of cytosolic regulating proteins into transcription factors

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