PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Preface to Immune effector mechanisms in parasitic infections, a Discussion held at The Royal Society on the 19 and 20 February 1997.

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Phil. Trans. R. Soc. Lond. B 1997 **352**, 1293-1294
doi: 10.1098/rstb.1997.0112

PREFACE

During the ten years that have elapsed since the last Royal Society Discussion Meeting on immunological control of parasitic diseases, impressive advances have been made in our understanding of the basic immunology, genetics and molecular biology of host–parasite interactions. The parasite molecules active in provoking or evading immune responses have been defined, as have the host cells, and in particular T-cell subsets, involved in those responses or in manifestations of the disease. Cytokines responsible for conveying messages between different cells in order to orchestrate the immune defence system have been characterized, as have the subtleties of their interaction with the parasites themselves. The recognition and mapping of relevant genes in both parasite and host has become commonplace. New approaches to protecting vulnerable hosts against parasitic diseases (peptide vaccines, oral live vaccines and nucleic acid vaccines) have been initiated and vaccine trials have been carried out for malaria and cutaneous leishmaniasis.

Crucial to our picture of the host overcoming infection with the parasite is an understanding of the host's effector mechanisms, the natural means by which the host can eliminate the parasite from the body. Our newly acquired ability to manipulate the experimental host's immune response with cytokine-specific monoclonal antibodies or with recombinant cytokines, or to disrupt key genes involved in the host's immune response or in the parasite's defence against the host, has enabled us to expand this understanding on several fronts. This symposium reflects these advances. It emphasizes, in particular, those resulting from the study of intracellular parasites, especially parasites that inhabit the macrophage—one of the body's prime defence cells. Among the notable achievements in this respect are the recognition of nitric oxide, produced by an inducible synthase (iNOS), as a widespread killing mechanism for intracellular parasites, and the interaction of different T-cell subsets, through the secretion of cytokines, in bringing about parasite destruction.

Interaction between host and parasite is focused on the host–parasite interface—usually the surface of the parasite itself. Identification of the molecular components of that surface, and resolution of their structure and role in parasite adaptation to changing environments during the course of the life cycle, have progressed furthest for the trypanosomes and leishmanias, as outlined by M. A. J. Ferguson in this symposium. The different surface glycoconjugates can now be assigned roles not only in antigenic variation (African trypanosomes), and interaction with host cell receptors in attachment or cell entry (*Leishmania*), but also in inhibiting the macrophage oxidative burst and modulating its iNOS activity. F. Y. Liew and colleagues recount how disruption of the host iNOS gene leads to a dramatically altered Th1-cell response to *Leishmania* infection in the experimental host.

How parasites survive in what is essentially a vacuole in the macrophage's digestive system is explored with reference to mycobacteria by D. G. Russell and colleagues. Unlike *Toxoplasma*, which contrives to prevent lysosome fusion with the parasitophorous vacuole, the leishmanias and mycobacteria seemingly suffer such fusion gladly. In the case of mycobacteria, prevention of acidification is engineered by exclusion of the proton pump ATPase from the vacuolar membrane, and lysosomal cathepsins remain inactive as a result. The cytokines IFNγ and TNFα produced by activated T cells, however, can activate the macrophage to acidify the parasitophorous vacuole and kill the bacterium. To avoid this fate the mycobacterium can suppress the T-cell response by inducing synthesis of interleukin-6 (IL-6) by its host cell, thus prolonging its own survival.

That the host's immune response can be manipulated by the parasite to its own advantage is also shown by *Toxoplasma* which relies upon a powerful T-cell response to limit the growth of the rapidly dividing tachyzoite stage and induce its progression to the more slow-growing encysted bradyzoite stage during its asexual development in mouse or man; the sexual phase of the life cycle can take place only after ingestion of tissue bradyzoites by the cat. J. C. Boothroyd and co-workers describe here their genetic and developmental analysis of tachyzoite/bradyzoite differentiation using mutant strains of the parasite. J. Alexander, A. Sher and colleagues present a complementary view of this transition with their use of gene-deficient mice to demonstrate the importance of IL-12-dependent IFNγ production in stemming tachyzoite proliferation. They also show, through use of appropriate metabolic inhibitors, that while NO would appear to have no part in controlling growth at this stage it is patently active in preventing reactivation of disease through reversion to the pathogenic tachyzoite stage.

Although the mouse is a useful experimental host for many human parasites, the question of how far conclusions based on its resistance or susceptibility to such infections can be extended to humans is a constant concern. J. M. Blackwell and colleagues explain how scanning the mouse genome for genes controlling susceptibility to leishmanial infections provided candidate gene regions for human disease susceptibility genes because of conserved syteny in the five regions involved. What is more, the shared niche in the macrophage endosomal system occupied by leshmanias and mycobacteria enabled them to predict that the same candidate gene regions might determine susceptibility to diseases caused by either parasite—a forecast that has been borne out by the multicase family data presented here. Of particular

interest is the natural resistance macrophage protein gene (*Nramp 1* in mouse, *NRAMP 1* in man)—its product localizing to a late endosomal or lysosomal compartment in the macrophage where it may have a role as an ion channel or transporter, influencing the macrophage activation pathway.

Plasmodium falciparum, the causative agent of malignant tertian malarias, bears the molecular scars of a long battle between the parasite and its human host's defences. A. V. Hill and colleagues summarize recently revealed interactions between variable components of the parasite, and particular variants of the human leucocyte antigen (HLA) system. HLA genotype affects susceptibility to severe malaria in West African children and the T lymphocytes that effect such resistance along with their target parasite epitopes have been characterized. Some parasite epitopes exhibit substantial polymorphism and certain variants appear to escape T-cell recognition. These authors suggest operation of altered peptide ligand antagonism, whereby a T-cell response to an index peptide can be ablated by variants of the corresponding T-cell epitope, thus introducing yet another immune avoidance mechanism exploited by parasites. The ability of certain major histocompatibility complex (MHC) class II genes to increase susceptibility to parasitic infections by suppressing T-cell responses has long remained a mystery but an explanation is offered here by B. Müller and A. Mitchison.

Vaccination against malaria has been one of the foremost goals of immunoparasitologists but one that has repeatedly receded into the distance in the wake of each supposed breakthrough. Yet our understanding of effector mechanisms involved in destroying early developmental stages of the parasite in the liver is now at an advanced stage: we know that CD8+ T cells, CD4+ T cells, cytokines and nitric oxide can all mediate destruction of infected hepatocytes *in vitro* and *in vivo*. D. L. Doolan and S. L. Hoffman have dissected the protection induced by immunization with irradiated sporozoite, DNA and synthetic peptide/adjuvant vaccines, and found that different T-cell-mediated immune responses may confer protective immunity to *Plasmodium yoelii* in the same strain of mice, according to the method of immunization. In addition, the mechanism of protection may vary among different strains of mice. These findings have important implications for the development on the one hand of vaccines aimed at protecting a heterogeneous human population and on the other of assays that predict protective immunity.

Parasites inhabiting the host's alimentary tract might be expected to encounter problems quite different from those living inside a host cell or free in the blood. Antigenic variation has now been explored in great detail for African trypanosomes and, more recently, malaria parasites, but T. E. Nash's demonstration that this mechanism for evading the host's immune response also occurs in the common human gut protozoan, *Giardia lamblia* came as a surprise. The relationship of parasite antigen switching to the host's immune response remains enigmatic and the surface antigens involved appear to be cysteine-rich proteins with zinc finger domains—the only known zinc finger proteins associated with the surface of a cell. In addition to its immunoparasitological interest, host–parasite interaction in giardiasis may have more fundamental lessons to teach us.

In gut helminth infections, host effector mechanisms commonly result in expulsion of the parasites from the body. R. K. Grencis explains that this expulsion usually depends upon a vigorous T-cell response and the secretion of a variety of cytokines. This response regulates a variety of subsiduary ones—eosinophilia, intestinal mastocytosis and elevated immunoglobulin E (IgE) production, the protective importance of which varies with the species of parasite. The balance between Th1- and Th2-responses can be critical in determining the progress of the infection. In contrast to the intracellular infections where Th1-responses are associated with elimination of the parasites, protection against gut helminth infections is dependent upon a strong Th2-response.

Finally, K. Marsh and R. W. Snow open up the wider picture of the relationship between immunity, vector transmission and the total morbidity of malaria. They point out that a more satisfying view of this relationship will demand a better understanding of the mechanisms by which humans in endemic areas acquire protective immunity.

This Discussion Meeting highlighted several avenues of progress in the immunobiology of parasitic infections. Convergence of effort on the part of workers in several complementary disciplines should now enable the identification of potential targets for prophylactic and immunotherapeutic intervention. It is hoped that this knowledge will soon be translated into practical action against some of the world's most debilitating diseases, effectively reducing their tragic toll of human life and suffering.

May 1997

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