Parasite immune evasion and exploitation: reflections and projections

R. T. DAMIAN

Department of Cellular Biology, University of Georgia, Athens, GA 30602, USA

SUMMARY

Recent developments in parasite immune evasion and exploitation are reviewed with special reference to the papers presented in this volume. Parasites, broadly defined, of animals with good immune responses have evolved many strategies that adapt them to survive and reproduce. These strategies may be passive, or may involve active intervention with host immune regulation, and can be categorized as immune evasion, immune exploitation and molecular piracy. The concept of immune evasion began with Paul Ehrlich's demonstration of antigenic variation in African trypanosomes and was reinforced by later ideas on molecular mimicry. Molecular mimicry is updated in the light of recent discoveries about degeneracy and plasticity of TCR/MHC-peptide recognition. Possible connections between two of its postulated consequences, evasion and autoimmunity, are discussed. Another putative consequence of molecular mimicry, host antigenic polymorphism, is also updated. The concept of exploitation of host immune responses by parasites has been reinforced by new data on its first known examples, especially the immune dependence of schistosome egg excretion. Newer examples include use of host cytokines as parasite growth factors, virokines, viroreceptors and helminth pseudocytokines. Finally, questions of host gene capture by viruses and possible horizontal gene transfer between host and parasite mediated by retroviruses are examined. The latter is compared with molecular conservation as a source of molecular mimicry and other aspects of host–parasite coevolution.

Key words: Parasite–host coevolution, immune evasion, immune exploitation, molecular piracy, molecular mimicry, autoimmunity.

INTRODUCTION

I was both pleased and honoured to have been asked by the editors of this volume to contribute an endpiece to this excellent and stimulating series of papers on the exploitation of immune and other defence mechanisms by parasites. The 'reflections' part of their charge was relatively benign and easy to do. 'Projections' always carry a certain risk, although the risk is minimal for one nearing the end of one's career!

The papers in the present volume cover nearly the gamut of parasites, as broadly defined, from relatively simple viruses to complex helminths. They also cover a wide range of possible mechanisms of host–parasite adaptation, with the adaptation to the host immune response the focus. As these articles abundantly demonstrate, parasites have a variety of strategies that may adapt them to evade and even exploit the immune response of their hosts. Some of these strategies are rather passive, while others may involve active manipulation, as it were, of the host's defensive responses. These strategies include immune evasion (Ogilvie & Wilson, 1976; Bloom, 1979; Dessaint & Capron, 1993), immune exploitation (Hayunga, 1979; Damian, 1987*a*), molecular piracy (Ahuja & Murphy, 1993), and strategies that defy categorization. We employ pigeonholes, to be sure, but only for convenience. As many of the papers herein presented show, biological realities often resist our pigeonholing attempts. They all have in common, however, lessons to teach us about the abilities of parasites to manipulate the immune response, and as one paper points out, they could well teach us lessons about the immune response itself (Barry and McFadden, this volume).

The concept of immune evasion by parasites has been around for a very long time. In fact, although it seems generally to have been forgotten, it was Paul Ehrlich (honoured as the 'Father of Immunology' at the First International Congress of Immunology in 1971), who discovered the first and still one of the best examples of immune evasion by a parasite. This is of course the phenomenon of antigenic variation in the African trypanosomes. In his Nobel Lecture, delivered in Stockholm in December of 1908 (subsequently published in 1909 and 1910), Ehrlich summarized experiments done by himself and his colleagues, Franke, Röhl and Gulbransen on the 'disappearance of receptors' clearly demonstrating the ability of these organisms to shift their antigenicity *in vivo*. It is perhaps unfortunate that Ross & Thomson (1910) are so often given the credit for the discovery of antigenic variation in trypanosomes, even though the term 'antigen' was never mentioned in their paper. Their contribution, however, was important enough: their now-classic oscillating parasitaemia curve in a case of sleeping sickness, which of course is best explained by variant antigen-driven immune responses.

Hommel (this volume) re-examines the question of antigenic variation in malaria parasites, and concludes that modulation of ligand expression on *Plasmodium* goes beyond simple immune escape to

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become rather 'an elegant process of host–parasite adaptation', or immune exploitation if you will. This process is co-dependent as well upon parasite-driven modulation of host cellular receptors for the parasite's changing ligands.

The idea of molecular mimicry (Damian, 1964), also known as adaptation tolerance (Sprent, 1962), immunoselection for eclipsed antigens (Damian, 1962), or selection for fitness antigens (Dineen, 1963) has historical significance in that it added to the then special case of antigenic variation in African trypanosomes 'to create a new conceptual environment… [that] encouraged… new questions… [and] approaches to uncover other candidate evasive mechanisms' (Damian, 1987*b*).

It may be that molecular mimicry has enjoyed somewhat greater success as a paradigm for autoimmunity than for parasite immune evasion. One of the clearest early enunciations of this aspect of molecular mimicry was that of Rowley & Jenkin (1962), with a more modern restatement by Oldstone (1987). Some of the more classic examples (Oldstone, 1989) of potential inciting agents for autoimmune diseases through a molecular mimicry mechanism include group A streptococci (rheumatic fever, glomerulonephritis, etc.), mycobacteria (rheumatoid arthritis), and *Klebsiella pneumoniae* (Reiter's Syndrome, ankylosing spondylitis). In multiple sclerosis (MS), T cell clones specific for an encephalitogenic epitope of myelin basic protein were found to strongly recognize certain viral peptides (Fujinami & Oldstone, 1985; Wucherpfennig & Strominger, 1995), and molecular mimicry by *Campylobacter jejuni* has been suggested to be a factor in the development of Guillain–Barré Syndrome (Yuki *et al*. 1993). Among traditional parasites, a recent report demonstrates that the presence of *Trypanosoma cruzi* amastigotes in the heart is both necessary and sufficient to induce cardiomyopathy in a murine model for human Chagas' disease (Tarleton, Zhang & Downs, 1997). The authors thus argue against molecular mimicry-based autoimmunity as playing a significant role in this disease model. On the other hand, the characteristic occurrence of neuropathies in Chagas' disease (Köberle, 1968), along with the existence of several reports that not only show molecular mimicry between *T. cruzi* and components of the nervous system, but also show some functional relevance of autoreactive antibodies or T cell lines (Hontebeyrie-Joskowicz *et al*. 1987; Ferrari *et al*. 1995; Elies *et al*. 1996) are sure to keep the controversy surrounding the significance of autoimmunity in Chagas' disease alive for some time to come.

Basic to the autoimmune concept of molecular mimicry is the premise that mimicked parasite epitopes would be sufficiently different from host epitopes to result in immune stimulation, which the host's self or 'model' epitopes would normally fail to do. It is now recognized that the essential difference could reside at the level of antigen processing and presentation route in the case of extracellular parasites (Davies, 1997). But the idea of subtler differences between model and mimic at the peptide level has recently been strengthened by the discovery that T cell receptor (TCR) recognition of MHC-bound peptides is surprisingly quite degenerate. Cogent examples for autoimmunity include the study of Wucherpfennig & Strominger (1995), who analysed myelin basic protein (MBP) peptide structural motifs for both major histocompatibility complex (MHC) class II binding and TCR recognition. They found that a T cell clone (TCC) from an MS patient that was specific for MBP recognized eight distinct but structurally related viral and bacterial peptides. Later, using the powerful combinatorial peptide library approach, Hemmer *et al*. (1997) showed that an even higher level of degeneracy was allowed in epitope recognition by autoreactive T cells. Some of their artificial ligands were even more potent agonists for the human TCC they used than its nominal self epitope, MBP(86–96). In another report (Ausubel *et al*. 1996), it was shown that the TCR–MHC complex was highly plastic due to the existence of two functional pockets in the TCR. The knowledge that peripheral autoreactive T cells exist in health (Fredrikson *et al*. 1994; Wekerle *et al*. 1996), and the degeneracy and plasticity of TCR recognition disclosed by the elegant studies mentioned above, raise important new questions about how autoimmunity is normally avoided. They also suggest new ways in which immune evasion through molecular mimicry could take place. Such structural approaches to molecular mimicry could lead to new insights into the relationship between two of its postulated consequences, autoimmunity and immune evasion (Damian, 1964). For example, Barnaba & Sinigaglia (1997) have suggested, based upon the findings and quantitative arguments of Hemmer *et al*. (1997), that microbially cross-activated peripheral T cells could be anergized by a pool of cross-reactive self peptides, acting as altered peptide ligands (ALPs). In this case, autoimmunity would be switched off while at the same time immune clearance of pathogens would be inhibited. Thus two formerly disparate aspects of molecular mimicry are united in this concept, which suggests that subtle control mechanisms must exist to allow a compromise between these two consequences of immune recognition. How some of these ALP-based control mechanisms, ALPs in this case of the circumsporozoite protein of *Plasmodium*, could lead to immune evasion is the subject of the report by Plebanski, Lee & Hill in this volume.

Baum, Davies & Peakman (1996) have recently presented a provocative proposition that molecular mimicry may actually involve 'three-way mimicry' between autoantigen, foreign infectious peptide, and self MHC peptide. This idea has important impli-

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cations for the question of the role of infectious diseases in maintaining host antigenic, including MHC, polymorphisms. The paper by Plebanski *et al*. (this volume) is important because it stresses the possible significance of parasite and host polymorphisms in host–parasite adaptation. Long ago it was suggested that biochemical (Haldane, 1949) and antigenic (Damian, 1962, 1964) polymorphisms of pathogens could favour the development of host biochemical and antigenic polymorphisms. These ideas have stimulated much discussion (Snell, 1968; Wills, 1991; Apanius *et al*. 1997). They remain controversial and occasionally resurface in more modern formulations (Murphy, 1993, 1994). The report of Hill *et al*. (1991) on the association of certain HLA antigens with protection against malaria in west Africa still provides some of the best evidence for the role of infectious diseases driving human MHC polymorphisms. Antia and Lipsitch (this volume) present a mathematical model for an acute infection in a host with a good immune system, and expand their model to include complicating considerations such as host polymorphisms.

The original conceptions of molecular mimicry were of a passive evasive tactic to escape from, or reduce, immune detection of parasites through the possession of shared host–parasite epitopes ('eclipsed antigens' [Damian, 1964] or 'eclipsed epitopes' [Damian, 1989]). This original concept was subsequently expanded to include escape through a more aggressive form of mimicry (Damian, 1979, 1984). This was necessitated by the finding of parasite-mimicked epitopes of host immunoregulatory molecules or their receptors; in the early days, molecules such as α_2-macroglobulin (Damian, Greene & Hubbard, 1973), murine MHC (Sher, Hall & Vadas, 1978; Gitter & Damian, 1982; Simpson *et al*. 1983), and immunoglobulin and complement receptors (Kemp *et al*. 1977; Torpier, Capron & Ouaissi, 1979; Tarleton & Kemp, 1981). Grencis & Entwistle (this volume) present the interesting finding of an IFN-γ-like molecule being produced by the intestinal nematode, *Trichuris muris*. Whether this is an example of homology (conservation) or convergence (mimicry), as discussed below, remains to be determined, as does the molecule's functional relevance. These authors speculate that an inappropriate Th1 immune response may be stimulated if the *T. muris* molecule proves to be a functional mimic. Pritchard, Hewitt & Moqbel (this volume) refer to such parasite products as 'pseudocytokines', and they discuss other pseudocytokines that could influence the balance between Th1 and Th2 T cell subsets, particularly within the framework of helminth-induced allergy.

Still later, the concept of molecular mimicry was further broadened to include receptor mimicry to gain immunologically privileged intracellular sites (Damian, 1988, 1989). Numerous examples of receptor mimicry were reviewed by Hall (1994).

As was pointed out a decade ago (Damian, 1987*a*), the concept of the exploitation of host immune responses by parasites had been 'in the air' for a while. This concept may have gotten a fillip by the evidence gathered together for it, by its naming, and a formal definition given it in that paper. As was stated, 'to qualify as an example of immune exploitation, the parasite's adaptation must be specifically directed to take over some facet of host immune responsiveness in such a way that the parasite's life needs are met, its reproduction is facilitated, or its propagation to new hosts is made possible. In other words, it must be an obligatory interaction between parasite and host, mediated through both the parasite's antigenicity and the host's immune recognition system.' Discoveries made since 1987 have made it clear that the above definition should be broadened to include non-antigen-specific mechanisms of exploitation that involve important players in the host immune system. In particular, examples of cytokines serving as parasite growth factors (Mazingue *et al*. 1989; Amiri *et al*. 1992; McKerrow, this volume) should be included.

The exploitation of the host immune response as a means for the propagation of parasites to new hosts is the subject of the article by Doenhoff (this volume) in which he examines relationships between schistosome egg-induced granulomas and the rate of egg excretion in mice. This expands upon his earlier elegant demonstrations of the immune dependence of egg excretion in experimental schistosomiasis (Doenhoff *et al*. 1978, 1986; Doenhoff, Hassounah & Lucas, 1985). As mentioned by Doenhoff (this volume), a recent study done in Kenya in which concurrent HIV and schistosome infections were studied (Karanja *et al*. 1997), strongly suggests that the excretion of *Schistosoma mansoni* eggs in humans is also dependent upon an intact immune response. Doenhoff (this volume) also reviews evidence that coinfection with HIV and *Mycobacterium tuberculosis* compromises transmission of tubercle bacilli, presumably through a similar mechanism of granuloma inhibition in immunocompromised patients.

Two of the most suggestive, possible earlier examples of immune exploitation were immune granuloma-mediated egg excretion in schistosomiasis and nutritional use of specific antibodies by taeniid tapeworm cystercerci (Damian, 1987*a*). The former is brought up to date by Doenhoff (this volume). The evidence is becoming compelling that the immune schistosome egg granuloma does subserve this function. The latter possibility has received some subsequent experimental support (Hayunga, Sumner & Letonja, 1989) although specificity still remains an issue. It seems a problem deserving of further investigation.

Possible cases of immune exploitation in other

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host–parasite systems are revealed in the articles by Launois, Louis & Milon, by Mosser & Brittingham and by Maillard, Luthi, Acha-Orbea & Diggelmann (this volume). Maillard *et al*. review microbial superantigens (SAg) and discuss their possible roles in transmission. The clearest example of immune-dependent viral transmission is provided by the mouse mammary tumour virus, whereas bacteria may be favoured by superantigen production through immune deviation, although this is conjectural at this time. These authors also refer to the work of Lafon *et al*. (1994) who showed that in the murine rabies model, SAg-reactive cells are responsible for limb paralysis. One may wonder if this phenomenon could play a role in rabies transmission from mice to carnivores in nature. Wild rodents are found infected with the rabies virus (Winkler, 1991) and could possibly infect foxes through the oral route, as well as by biting (Blancou, Aubert & Artois, 1991).

The papers by Launois *et al*. and by Mosser & Brittingham present two very different strategies used by *Leishmania* parasites to exploit and evade the immune response to their advantage. Launois *et al*. discuss how CD4 T cell subset polarization through early parasite manipulation of host cytokines leads to dermal parasite expansion in a Th2 environment, which should favour infection of vector sandflies. In a Th1 environment, the parasites are driven to deeper tissues, where they can quietly persist until possible reactivation by incompletely known mechanisms. The relationship of these options to the epidemiology of leishmaniasis should be a fascinating subject for future investigation. In relation to the persistence of pathogens in macrophages, the article by Hilbi, Zychlinsky & Sansonetti (this volume) argues that macrophage apoptosis in shigellosis is proinflammatory and that it ultimately leads to clearance of the infection. They review macrophage apoptosis in other infections including those by protozoan parasites: the evidence suggests that the phenomenon could play an important role in immune evasion and parasite persistence.

The contribution by Mosser & Brittingham (this volume) focuses on how *Leishmania* promastigotes gain entry into mononuclear phagocytes by subverting and exploiting the hosts' complement opsonizing system. Related to this is the article by Füst (this volume) which discusses the mechanisms and implications of the enhancement of HIV infections by antibodies or antibody/complement mediated infection of target cells. One of the values of a collection such as is found in the present volume is the juxtaposition of topics usually separated by artificial boundaries. Surely the time has come to study more thoroughly concurrent infections in both human populations and experimental animals.

The paper by Stewart & Heppner (this volume) stands somewhat apart from the others in that it examines the role of the immune response in the progression of a cancer so far unlinked to a known infectious agent, namely, cancer of the breast. An impressive amount of evidence is brought together to support the hypothesis that the progression of this type of cancer is actually facilitated by the immune response. Interestingly, the breast itself is identified as an immunological organ, and this emphasis should benefit infectious disease specialists and parasitologists, who often must consider the trans-mammary passage of pathogens.

In his opening chapter in this volume, Locksley refers to the possibility of convergent evolution of host and parasite genomes through long association as a factor in the development of parasite evasive mechanisms and chronicity, a concept discussed at length by Klein & O'Huigin (1994). An alternative explanation is provided by molecular conservation, which has been discussed within the context of molecular mimicry on several occasions (Damian, 1988, 1989, 1991). The problem, like many other problems in evolutionary biology, including molecular evolution (Doolittle, 1994), is to distinguish between convergence (mimicry) and conservation (homology) as responsible for shared host–parasite epitopes, or other molecules. Recent advances in evolutionary developmental biology have emphasized and affirmed the stem position of the Platyhelminthes in the evolution of other metazoan animals, including both other parasitic helminths and the vertebrate hosts that include ourselves (Field *et al*. 1988; Raff, 1996). Most of the basic biochemistry and organization of metazoan life was already well-established in the primitive flatworms and passed on to their wormy, parasitic descendants. In a sense, we are parasitized by our 'ancestors'! A case in point is the mediation of apoptosis by conserved cysteine protease genes including that for IL-1β-converting enzyme and the *Caenorhabditis elegans* cell death gene *ced-3* (mentioned by Hilbi *et al*. this volume). Therefore, like Locksley (this volume), we should be less than surprised about reports of cytokine-like or cytokine-receptor-like molecules in helminths.

However, I am more a follower of Howell (1985) than of Locksley (this volume) on the possible importance of gene capture in the development of evasive or exploitative mechanisms by parasites. Howell suggested that horizontal transfer of DNA between hosts and parasites could result in immune evasion and other adaptations for successful parasitism, but also in certain cases giving advantages to hosts. He implicated retroviruses as likely agents of this genetic exchange. The recent discovery of the first invertebrate retrovirus, the gypsy element of *Drosophila* (Kim *et al*. 1994; Song *et al*. 1994, 1997), should make us slow to dismiss horizontal transfer of genes between hosts and parasites as being of potential importance in their mutual adaptation.

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When considering viruses, the evidence for gene capture or 'molecular piracy' is overwhelming (Barry & McFadden, this volume). Captured molecules include both 'virokines' (Kotwal & Moss, 1988) and 'viroreceptors' (Upton *et al*. 1991), and many strategies for immune evasion and exploitation are possible, as discussed by Barry & McFadden.

In considering horizontal gene transfer, the results of a group of Japanese workers may be very significant (Tanaka *et al*. 1989; Nara *et al*. 1990; Iwamura *et al*. 1991, 1995; Irie & Iwamura, 1993). They have reported on the occurrence of host DNA sequences, including sequences shared with murine type A and C retrovirus, in schistosome genomes. These reports have engendered considerable debate (Simpson & Pena, 1991; Iwamura & Irie, 1992; Clough, Drew & Brindley, 1996), centering around whether or not the host-type sequences are actually host-derived contaminants. Nevertheless, these reports have been valuable in re-focusing attention on Howell's proposition. I can only agree with Iwamura & Irie (1992) that further 'progress in this field must be expected'.

Controversies like the one mentioned above, the question of autoimmunity in Chagas' disease, and many others spice up parasitology and infectious disease research, and make the study of parasite–host interactions ever more exciting. This spice further enhances the olio that contains many challenging scientific problems for the intensely curious and the intensely humane: problems of intrinsic and emerging importance for global public health in an uncertain, exponentially changing world (Garrett, 1994). The integration of diverse areas of research specialization and approaches as evidenced in the present volume will play a huge part in taking parasitological research to the next level, and one can only wonder at what wonders the next decadal collection focusing on parasite immune evasion and exploitation will contain.

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