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The biological and practical significance of antigenic variability in protective T cell responses against *Theileria parva*

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Abstract

The evolution of antigenically distinct pathogen strains that fail to cross-protect is well documented for pathogens controlled primarily by humoral immune responses. Unlike antibodies, which recognise native proteins, protective T cells can potentially recognise epitopes in a variety of proteins that are not necessarily displayed on the pathogen surface. Moreover, individual hosts of different MHC genotypes generally respond to different sets of epitopes. It is therefore less easy to envisage how strain restricted immunity can arise for pathogens controlled by T cell responses, particularly in antigenically complex parasites. Nevertheless, strain restricted immunity is clearly a feature of a number of parasitic infections, where immunity is known to be mediated by T cell responses. One such parasite is *Theileria parva* which induces potent CD8 T cell responses that play an important role in immunity. CD8 T cells specific for parasitized lymphoblasts exhibit strain specificity, which appears to correlate with the ability of parasite strains to cross-protect. Studies using recently identified *T. parva* antigens recognised by CD8 T cells have shown that the strain restricted nature of immunity is a consequence of the CD8 T cell response in individual animals being focused on a limited number of dominant polymorphic antigenic determinants. Responses in animals of different MHC genotypes are often directed to different parasite antigens, indicating that, at the host population level, a larger number of parasite proteins can serve as targets for the protective T cell response. Nevertheless, the finding that parasite strains show overlapping antigenic profiles, probably as a consequence of sexual recombination, suggests that induction of responses to an extended but limited set of antigens in individual animals may overcome the strain restricted nature of immunity.

Keywords: Antigenic variability; CD8 T cell; Protozoan parasite; *Theileria parva*; Genetic recombination; Vaccination

1. Introduction

The concept that immune selection can result in the evolution of antigenic variability within pathogen populations is well established. Broadly speaking, two types of antigenic variability are recognised. The first involves the capacity to undergo a regulated process of antigenic variation, mediated by differential expression of a set of genes present in the genome of the organism, which generates sequential populations of organisms that differ in their surface antigens, thus allowing persistence of infection in individual hosts. The second type of antigenic variability manifests as the presence of pathogen strains that differ antigenically as a consequence of acquired mutations, such that animals that have acquired immunity to one strain remain susceptible to other strains. Both of these mechanisms are well documented in pathogens for which antibody responses play an important role in immunity. Thus, African trypanosomes and *Plasmodium* parasites (Barry and McCulloch, 2001; Kyles et al., 2001), as well as the bacterial pathogens *Anaplasma marginale* and *Borrelia*

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burgdorferi (Liang et al., 2004; Palmer et al., 2006), display classical antigenic variation. Some of these organisms exhibit additional inter-strain antigenic variability. For example, different strains of the African trypanosome species *T. brucei* and *T. congolense* express different repertoires of variant surface glycoproteins (Barry and Carrington, 2004). Inter-strain antigenic variability, defined by differential antibody recognition, is a feature of a number of viral and bacterial infections, some of the best documented examples being RNA viruses including foot and mouth disease and influenza viruses (Thomson, 1994; Steinhauer and Skehel, 2002), which are antigenically heterogeneous and include serologically distinct strains that fail to cross-protect.

Antigenic variability is less well defined for pathogens that are controlled primarily by T cell-mediated immune responses. This is a consequence of the fundamentally different ways in which pathogens are recognised by antibody and T cells. Antibodies recognise native proteins and responses are usually directed against a few surface-exposed proteins, which tend to be recognised by all individuals, thus focusing immune selection on these proteins. By contrast, because T cells recognise processed peptides presented by major histocompatibility complex (MHC) proteins, theoretically they can mediate immunity by responding to a variety of antigens including non-structural as well as structural proteins. Moreover, polymorphism in MHC molecules results in variation in the types of peptides that are bound and presented to T cells, so that individual hosts of different MHC genotypes generally respond to different sets of epitopes, often in different proteins. This places greater constraints on the ability of pathogens controlled by T cell-mediated immune responses to evolve into antigenically distinct strains. However, in the case of CD8 T cells, there is evidence that despite their potential to recognise a large number of epitopes, responses in individual animals are often focused on a few epitopes (Yewdell, 2006). This phenomenon, known as immunodominance, is particularly well documented for viral infections including HIV (Goulder et al., 1997) and herpesviruses (Crotzer et al., 2000) in humans where there is evidence that CD8 T cell responses control the levels of persistent infection. In some HIV-infected individuals focusing of the CD8 T cell response on a single epitope results in selection of mutations in the target epitope allowing escape from immune control and an increase in viral load until a response to another epitope is generated.

Strain restricted immunity is a feature of a number of parasitic infections, for which immunity is known to be mediated by T cell responses. One such parasite is *Theileria parva* which induces potent CD8 T cell responses that have been shown to have an important role in immunity. Detailed studies of the antigenic specificity of the CD8 T cell response to this parasite have provided evidence that a profound immunodominance in the T cell response is largely responsible for the failure of parasite strains to cross-protect. Herein, we will summarise this evidence, discuss its relevance with respect to the biology of the parasite and potential vaccine development and consider its wider relevance to other apicomplexan parasitic infections.

2. Biological properties of *T. parva* relevant to pathogenicity and immune recognition

T. parva is a tick-transmitted protozoan parasite that undergoes successive development in nucleated cells and erythrocytes in the mammalian host. The principal target cells are T and B lymphocytes (Baldwin et al., 1988; Emery et al., 1988; Morrison et al., 1996). Unlike malaria parasites which have a similar development cycle, disease is attributable to the nucleated cell stage of development. Following invasion of lymphocytes by sporozoites, development of the schizont stage is associated with transformation of the host cells which are induced to proliferate (Fawcett et al., 1984; Dobbelaere et al., 2000; Dobbelaere and Rottenberg, 2003). Division of the parasite is synchronised with that of the host cell, so that parasite multiplication occurs by clonal expansion of the infected cells (Hulliger et al., 1964). This process appears to be dependent on the ability of the parasite to associate with the host cell mitotic spindle. Available evidence indicates that the parasite up-regulates a number of signalling pathways promoting cell proliferation and simultaneously down-regulates apoptotic pathways (Dobbelaere et al., 2000). In infected cattle, parasitized cells multiply rapidly and disseminate throughout the lymphoid system causing an acute lymphoproliferative disease, often leading to death within 3–4 weeks of infection (Irvin and Morrison, 1987).

A number of features of the development of *Theileria* parasites within lymphocytes are particularly relevant to considerations of immune recognition. Firstly, unlike other apicomplexan protozoa, which typically reside within endocytic vacuoles, *Theileria* parasites develop within the cytoplasm of host cells (Fawcett et al., 1982). This is achieved by dissolution of the host endosomal cell membrane shortly after invasion of the host leukocyte by the infective sporozoite stage, which occurs by receptor-mediated