Vaccination Against Immunopathological Disease in Schistosomiasis Japonica

Schistosomes present a formidable challenge to the immunoparasitologist interested in vaccination against the establishment or persistence of infection. Immune evasion mechanisms appear to be highly developed in schistosomes. These include blindfolding (masking) of parasite surface antigens by absorbed host molecules, inherent resistance of the surface to immune attack, rapid turnover of surface molecules and the liberation of antibody-degrading enzymes.[1-3] The relative value or importance of these mechanisms varies according to the parasite life-cycle stage.

A variety of parasite preparations have been tested for development as prototype vaccines and the consequent establishment of an immunoprophylactic programme in schistosomiasis japonica.[4] The best of these preparations do not confer complete protection. The question has been raised of the possible contribution of antigenic variability within the parasite population.[5] Depending on the quantum of the infecting dose of cercariae, the number of slip-through parasites may be sufficient to cause severe disease. The current quest for a vaccine against infection is now dominated by attempts to identify host-protective antiparasite immune responses, identification and isolation of target antigens, examination of recombinant DNA methods for polypeptide production, use of new adjuvants, and exploitation of newly identified mechanisms of immunoregulation in order to increase host resistance. However, these attempts are progressing at a slow pace. If a more desirable vaccine against establishment is difficult to attain and slow in coming, vaccination against the disease should be explored.[6]

Chronic schistosomiasis mansoni and japonica are immunopathological diseases in which many clinical manifestations result from the forrmation of granuloma and fibrosis due to T-cell-dependent immune responses to antigens emanating from eggs entrapped in the liver.[7,8] Increased portal pressure, hepatosplenomegaly, collateral circulation and ascites can be readily ascribed to obstructive granuloma formation and subsequent fibrosis with impedence of blood flow through the liver.

A major development in schistosomiasis research was the recognition that granuloma formation in chronically infected hosts could be modulated, i.e. the intensity of granulomatous hypersensitivity was decreased.[1,9,10] In mouse models, infected mice with both the *mansoni* and *japonicum* types of schitosomiasis, the new granuloma formed relatively late in infection were of much reduced size compared with those formed relatively early during the infection. Such modulation of immunopathological disease is referred to as endogenous desensitisation. From the very first observation of this phenomenon, it was appreciated that granuloma modulation opened up possible approaches to vaccination against severe disease. Immunisation to promote modulated granuloma response could lead to a reduced likelihood of severe hepatosplenic disease in cases infected with *S. japonicum* or *S. mansoni.* This modulation could result from several mechanisms probably operating singly or in combination:

1. Reduced efficiency of embryonation of eggs in tissues, i.e. anti-embryonation immunity.[6,11,12] Evidence has been obtained in our laboratory that in the lungs of chronically egg-sensitised mice (32 weekly intraperitoneal injections) with modulated granuloma response fresh uterine eggs mature in lower numbers than in unsensitised mice.[12] Also sera from some chronically infected humans modulate granuloma formation in egg-sensitised mice and reduce the rate at which eggs mature in the liver and intestines of infected mice.[13] Eggs vary in their sensitising and eliciting capacity for granulomatous hypersensitivity[14] in mice as well as their suitability for use in the circumoval precipitin test (COPT).[15] Thus uterine eggs cause bleb rather than segmented precipitates with sera from chronically infected individuals and blebs predominate over the more usual segmented precipitates using eggs obtained from rabbits infected for longer than the optimal 55-65 days.[11] It may be

assumed that bleb reactions represent a limited number of antigen-antibody interactions in COPT in which lyophilised eggs are incubated for 1-3 days with serum.[16-18]

2. Accelerated destruction of eggs[19-21] subsequent to their maturation to the maximum antigen-producing stage involving development of the miracidium.[22-24] Reduced efficiency of embryonation, or anti-embryonation immunity, and accelerated egg-destruction or anti-miracidial immunity, should be differentiated from inhibition of oviposition (reduced egg output per worm pair) or diversion of eggs away from the liver.[25,26]

3. Suppressor T-cell (T_s)-mediated inhibition of anti-egg responses presumably mediated by inhibitory effects on those T cells (e.g. T_D cells) or their products responsible for immunopathological responses. This possibility has received more attention recently because of the intense activity of cellular immunologists on T-cell dependent immunoregulation. The phenotype(s) of the effector T_s cells and the influence of other T-cell types remain confusing. Functions for $Ly2^+/I\text{-}J^+$ and $Ly1^+2^-/Ia^+$ cells have been proposed in the complex regulation of granuloma formation in modulated mice.[27-30]

4. Antibody-mediated inhibition of anti-egg response either by diversion of antigens away from T_D cells (e.g. opsonising antibodies) or inhibition of antigen recognition by T_D cells (e.g. anti-idiotype antibodies): The effects of immune serum (and presumably antibodies, but of unknown specificity) on granuloma formation have been described for both *S. mansoni*-mouse[8] and *S. japonicum*-mouse models.[13,31]

Of the postulated mechanisms of granuloma modulation, reduced embryonation of eggs in tissues, i.e. anti-embryonation immunity has more attractive features in terms of disease prevention. If egg maturation can be halted, then the release of immunopathological egg products can be curtailed and both the expression of and sensitisation for immunopathology should be reduced. Destruction of immature eggs through immunological mechanisms should also result in the continuous reboosting of immune responses to immature egg antigens. The ideal target for immunological intervention of embryonation would be an antigen which is stage-specific, i.e. specific for the immature egg. If antigens specific for the immature egg do not exist, or are unsuitable targets for aggressive immune attack, then an antigen shared between immature and mature eggs should be sought. Presumably, antigens can emerge through micropores of immature eggs and conversely, at least IgG antibodies should be able to gain access. Possible modes of action of antibodies to be considered include complement-dependent embryo destruction, enzyme neutralisation, and physical effects of antigen-antibody complexes such as micropore obstruction with consequent accumulation of toxic metabolites within the egg. Effects mediated from outside the egg, and perhaps more relevant to accelerated destruction of eggs, would include antibody-dependent granulocyte and macrophage-mediated killing or inhibitory activities.[19-21]

An alternative strategy of altering disease susceptibility in cases of schistosomiasis by promoting suppressor T cell-mediated immunoregulation may not be only difficult to achieve but also be associated with some danger. The mechanisms outlined earlier for the pathogenesis of chronic schistosomiasis mansoni and japonica in no way exclude the possibility that secreted egg products have serious consequences when certain T-cell-dependent immune responses are severely impaired.[32,33] Thus defective anti-egg antibody responses or defective granulomatous encapsulation of eggs and sequestering of egg products may well lead to hepatotoxic effects,[34] or diffused collagen deposition[35] in heavy infections and at least in cases of schistosomiasis mansoni.

Inhibition of the establishment or persistence of infection is clearly a more desirable consequence of vaccination than inhibition of disease (but consider tetanus and diphtheria immunoprophylaxis). However, if the former is difficult to achieve through "conventional" vaccination (and this seems certain to be the case with regard to schistosomiasis), then vaccination against severe disease may have a place in disease control. This is especially so if the strategy also leads to reduced transmission of infection in locations where non-human reservoirs of adult worms are not of epidemiological significance. Anti-embryonation responses directed towards immature eggs in the intestinal wall should lead to a reduction in the transmission of infection. Accelerated destruction of eggs should also reduce the export of eggs to the environment via the faeces.

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