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## The mouse model of schistosome immunity

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Since the 1950s and 60s which saw initiatory work on schistosome immunity in rhesus monkeys [1, 2], research in this field has profited most from the development of rodent models. This paper will deal mainly with the recent knowledge acquired from studying schistosome infection in the mouse and is concerned primarily with the relative roles of polypeptide and carbohydrate epitopes in the host-parasite relationship.

### *Characteristics of mouse immunity*

Resistance to reinfection in all experimental animals can be induced consistently in two ways: by exposure to normal cercariae and the subsequent development of an adult egg laying infection; or by exposure to radiation attenuated cercariae, where the larval schistosomula die at some point during their migratory pathway before maturity is reached [3].

The immunity induced in these two ways appears to differ in several aspects. In the mouse model resistance following exposure to normal cercariae develops about the time egg laying commences and peak immunity is reached some 4–6 weeks later [4]. Resistance is clearly correlated with the presence of eggs in the tissues or with other factors which are related to eggs such as the degree of portal hypertension [5, 6]. The intra-hepatic transfer of 4 week worms into naive mice has shown that immunity is induced by the adult stage without necessary prior exposure to cercariae or schistosomula [7]. This immunity is called 'concomitant immunity' because in this situation the schistosomula of the challenge infection are partially destroyed whilst the adult worms of the primary infection remain unharmed [8].

In contrast, immunity following exposure to irradiated cercariae, called 'vaccine immunity', develops two weeks after exposure, plateaus about week 5 and remains high indefinitely [4]. Obviously this type of immunity is not asso-

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ciated with the adult stage of the parasite nor with egg induced pathology, but is induced by the radiation-damaged schistosomula during their curtailed migratory pathway. As in concomitant immunity, the target of vaccine immunity is the schistosomulum [9].

Perhaps the crucial difference between concomitant and vaccine immunity is to be seen in their relative specificities. It has long been known that concomitant immunity can cross the species barrier [8], whereas vaccine immunity is species-specific [10]. There can be little doubt from the exquisite specificity of vaccine immunity and its lack of association with egg induced pathology that protection in this model is based on a lymphocyte associated immunity, and this has been borne out by the demonstration of thymic and B-cell dependency of this immunity [11]. Because of the non-specific nature of concomitant immunity, and its association with liver damage, it has been suggested that this form of resistance is dependent on non-immunological factors, perhaps involving vascular changes in the liver which affect the circulatory patterns of challenge schistosomula [5, 6, 12].

There are, however, two compelling lines of evidence which demonstrate that at least a major part of the resistance developed by infected mice is immunologically based. James and Cheever [13] have shown that 'P' strain mice, which have a genetic defect in macrophage function, develop poor levels of both vaccine and concomitant immunity, despite the fact that infected 'P' mice show normal levels of egg-induced pathology. This points to a central role for activated macrophages in both models. Secondly, the monoclonal antibody (mAb) NIMP/R.14 which preferentially destroys mouse neutrophils but also abrogates the anamnestic dermal inflammatory response to challenge schistosomula, suppresses both vaccine and concomitant immunity, again suggesting a common effector mechanism in both models [14].

### *Mechanisms of immunity*

What is this mechanism? Whilst the passive transfer of immunity with serum has been demonstrated in chronically infected mice there is no doubt that the universal or consistent success of this approach has been lacking [4]. Although passive transfer of immunity has not been reported previously in the vaccine model, we can now demonstrate consistently the transfer of about 50% of donor immunity, providing we use serum from mice exposed three times to irradiated cercariae [15]. Serum from mice vaccinated only once or twice always gives a slight reduction in worm recoveries compared to controls, but the differences are seldom significant. These findings suggest at least a co-operative role for antibody, whilst the comprehensive studies on 'P' strain mice [16] indicate that delayed type hypersensitivity is involved.

When considering mechanisms, we must take into account the developmental stage and location of the schistosomula killed by the immune response. In our autoradiographic tracking studies of <sup>75</sup>Se-labelled schistosomula in vac-

culated CBA mice, we find that 58% of the challenge larvae are killed in the skin [17]. Other workers, using different mouse strains, have reported that most schistosomula are killed at the lung stage [18]. In the vaccinated rat, the evidence shows that most challenge schistosomula are killed in the lungs [9, 19, 20], whilst in the vaccinated guinea pig model the immune effector mechanisms operate mainly in the lungs and liver [20, 21]. Thus the exact site of attrition depends on unknown factors, which may reflect the strain or species of host and the level of protection induced. Certainly attrition is not confined to the skin, but frequently occurs during the lung stage or even later. We know from *in vitro* studies, however, that schistosomula are susceptible to antibody and complement and to antibody-dependent cellular cytotoxic (ADCC) mechanisms only within the first 24 h of their development [22]; beyond that time schistosomula fail to bind antibody and develop intrinsic resistance to immune killing [23]. How, then, do we explain the attrition of schistosomula *in vivo* at a stage when they are not susceptible to these immune mechanisms *in vitro*?

Typical ADCC reactions involving cell adherence and degranulation onto the parasite surface, as described from *in vitro* studies, are not a characteristic feature of schistosomula observed within histological sections of the cutaneous or pulmonary tissues of resistant animals. Immunity in the host, as opposed to in the test tube, is (1) only partially effective, (2) associated with an anamnestic and orchestrated inflammatory response and (3) may not involve antibody binding to the parasite, particularly at the lung worm stage. Therefore, as an effector mechanism we envisage a synergistic cellular response to secreted antigens which impedes the normal development and migration of the parasite and which, through the release of mediators from non-adhering cells [24–26], eventually results in parasite damage and death. This view is essentially compatible with that of von Lichtenberg and his co-workers [27, 28] and Crabtree and Wilson [29]. Such inflammatory reactions could be induced by Type II (delayed type hypersensitivity) [30, 31], by Type I (IgE type hypersensitivity) [32], or by a Type III (Arthus) reaction [30, 33]. Additionally, inflammatory responses to non-related microorganisms may entrap the parasites and initiate the damaging lethal process [34].

#### *A possible molecular basis for concomitant and vaccine immunity*

Since we view concomitant and vaccine immunity as resulting from similar immune mechanisms, the difference in their characteristics must then depend on the antigens involved. Thus species specific target epitopes should be recognized by vaccinated animals and cross-reacting epitopes by infected animals. We have therefore looked for differences in the recognition of antigens by serum from vaccinated and infected mice and have concentrated on antigens which are exposed on the schistosomula surface. This set of antigens has been shown by many laboratories to be protective both *in vivo* and *in vitro* (see Table 1). Retrospectively, we would argue that the protective role of surface antigens in

Table 1. Mouse monoclonal antibodies recognizing surface antigens of *S. mansoni* schistosomula

mAb	Reference	Protective*	Isotype	Target epitope**	Cross reacts with eggs	Cross reacts with other species	Surface antigen recognized
3AF12 D-6	47	+	G1	C	+	+	200Kd 38Kd 17Kd
2GH12 H-1	48	+	G3	C	+	+	200Kd
E1	49	+	G2b	C	+	+	200Kd 38Kd
M22C1C	50	-	G3	C	+	+	38Kd
NIMP/M43	43	-	M	C	+	+	200Kd
NIMP/M45	43	-	M	C	+	+	200Kd
M22H12C	51	+	G2a	P	-	-	32Kd
NIMP/M47	43	±	G2a	P	-	-	20Kd
NIMP/M50	43	+	G1	P	-	-	20Kd

\* + signifies protection by passive transfer; ± signifies lethal activity in vitro only.

\*\* Target epitope carbohydrate (C) or polypeptide (P) as determined by binding to TFMS- or periodate-treated schistosomula.

vivo is in eliciting inflammation when released from the parasite, rather than acting as targets in situ. Although modulation of surface antigens during early maturation is complex, at least a proportion of surface antigens are released, as has been shown by the analysis of media in which schistosomula have been maintained; such antigens are known as schistosomula-released products, or S. R. P. [35–37].

When schistosomulum surface proteins and glycoproteins are labelled with  $^{125}\text{I}$  and immunoprecipitated by serum from infected and vaccinated animals, there are only minor differences in the amount and variety of molecules precipitated [38]. Thus, although these molecules may form the targets for both concomitant and vaccine immunity, these experiments do not explain the differences in the two types of resistance.

A radioimmunoassay which measures the binding of antibody to the schistosomulum surface, however, gave a different result. In this assay the binding of infection serum was 3–4 times greater than the binding of vaccine serum. This was true even when the vaccine serum had been taken from animals exposed three times to irradiated cercariae [39]. Thus there *is* a clear distinction between infection serum and vaccine serum. Treatment of the schistosomula with reagents which destroy carbohydrates, i.e. trifluoromethanesulfonic acid (TFMS) and sodium periodate, reduced the binding of infection serum to the levels attained by vaccine serum. These experiments have shown that the majority of epitopes on the schistosomulum surface are carbohydrate in nature and are recognized only by infection serum.

Further investigations on these surface carbohydrate epitopes have shown that they are also associated with the schistosome egg. The absorption of infection sera with schistosome eggs totally abolished its binding to schistosomula in the radioimmunoassay. Binding was reduced to the same extent when the serum was absorbed with eggs that have been subjected to 100°C for 30 min and then treated with protease [40].

What role do these surface carbohydrates have in immunity? To answer this question we examined a number of protective and non-protective mAbs recognizing schistosomula surface antigens, to determine whether they were recognizing carbohydrates or polypeptides. We are grateful to Drs. Harn, Phillips and Bickle for allowing us to include their mAbs in this study. In summary, we found that mAbs against *S. mansoni* schistosomula surface antigens can be divided into two kinds: those that recognize carbohydrate epitopes, i.e. they do not bind to TFMS- or periodate-treated schistosomula in the radioimmunoassay, and those that bind to TFMS-treated parasites and presumably recognize polypeptide epitopes [40]. Table 1 shows that both types can be protective, but it is notable that the carbohydrate-recognizing mAbs all cross react with the egg stage of the parasite and are not species specific. In marked contrast, the polypeptide-recognizing mAbs do not cross react with eggs and are species specific.

The surface antigens  $M_r$  200K, and  $M_r$  38K, as detected by  $^{125}\text{I}$  surface



labelling, feature prominently as targets of the carbohydrate-recognizing mAbs. These two surface antigens are those recognized by the protective mAb IPLSml raised in rats by Capron's group [41] which also recognizes a carbohydrate epitope [42]. Thus the  $M_r$  200K and  $M_r$  38K antigens express the cross reacting carbohydrate epitopes, although as yet the presence of the same epitopes on other molecules cannot be excluded.

From our binding studies we may conclude that the majority of surface epitopes on the schistosomula are carbohydrate; they are expressed on other species of schistosomes and are shared with eggs. We suggest that these are the targets of concomitant immunity and thereby explain the lack of species specificity of this form of protection and its correlation with the presence of eggs in host tissues. The much less abundant species-specific polypeptide epitopes, which are not associated with eggs (but do cross react with the adult worm), are also targets of protective antibodies and may form the basis of vaccine immunity.

#### *Modulation of immunity by blocking antibodies*

It is notable that of the six mAbs recognizing carbohydrate epitopes shown in Table 1, three are protective and three are not. We have undertaken a series of studies with our non-protective mAbs NIMP/M43 and M45 to determine whether they play a modulating role in immunity. As an initial approach we have examined their ability to block the in vitro lethal activity (i.e. killing by antibody plus complement) of protective mAbs. Both M43 and M45 were found to reduce the ability of the mAb NIMP/M50 to kill schistosomula in vitro [43]. This result was unexpected because the mAbs involved recognize distinct epitopes.

We know from competitive radio-immunobinding assays, that antibodies which recognize the target carbohydrate epitope of M45 are present in high amounts in serum from infected mice which have developed concomitant immunity but are less abundant in serum from vaccinated mice [44]. We asked the question, therefore, do these anti-carbohydrate antibodies in infection serum cause a modulation of in vitro cytotoxicity similar to the effect seen by the two IgM mAbs?

Our first experiment was to absorb out the anti-carbohydrate antibodies from infection serum. We chose to do this with cercariae, since the surface of this stage is rich in epitopes which are recognized by M45 [44]. The result showed that when infection serum is absorbed with cercariae, its ability to kill schistosomula in vitro in the presence of complement, is actually increased threefold; absorption of vaccine sera with similar numbers of cercariae causes no significant changes in its lethal activity [44].

The second experiment was to fractionate the serum into IgM and IgG fractions using protein A affinity chromatography. As previously shown [45], only the IgG fractions of the sera mediate complement-dependent killing of

schistosomula in vitro. However, when the IgM fraction is removed from infection serum, the killing activity is increased relative to the activity of unfractionated serum. In contrast, removal of the IgM fraction from vaccine sera has no effect on the cytotoxicity of the serum [44].

Thus, we have a situation where IgM antibodies in the serum of infected mice interfere with the protective capacity of the serum as judged by its activity in vitro; such blocking antibodies are not present in vaccine serum. Carbohydrate epitopes recognized by the blocking antibodies are associated with all stages of the parasite [43], but because exposure to large numbers of irradiated cercariae fails to generate these antibodies, it appears most likely that the presence of schistosome eggs is responsible for their induction.

The presence or absence of blocking antibodies is therefore another distinguishing feature between concomitant and vaccine immunity in the mouse and may be a factor in the difficulty of consistently transferring protection with infection serum.

### *Conclusions and implications for vaccine development*

We have shown that although carbohydrate epitopes shared between eggs and schistosomula are targets of protective antibodies, they also appear to be inducers of modulating responses. At this stage we have only demonstrated a modulating role against antibody-mediated damage to schistosomula in vitro and we have no evidence for an in vivo role for modulation. However, evidence for the modulation of immunity in man by IgM anti-egg antibodies is presented elsewhere in this meeting.

How could modulating antibodies affect protective responses in the host? As already stated, we believe inflammatory reactions to migrating schistosomula are the basis of protection; if such inflammatory reactions are suppressed, then we would expect protective immunity to be reduced. In this context antibody modulation of inflammation has been described as a mechanism responsible for the suppression of granuloma around eggs injected intravenously into mice [46]. Thus it may be that the IgM anti-carbohydrate antibodies in infection serum of mice and man are components of the modulating response to the parasite egg granuloma. The two aspects of schistosome immunity, protection against reinfection and immunopathology, which for many years have been viewed as separate entities, may, after all, be related. Only a permissive host, such as the mouse, or the newer guinea pig model, can be used to investigate these possibilities.

Obvious implications arise from these considerations concerning the possible use of cross reacting carbohydrate antigens as a vaccine; for example, how would the production of blocking rather than protective antibodies be avoided? Moreover, if a strong protective response was induced would this lead to increased pathology against the egg in a case where incomplete protection was achieved? To avoid these potential problems we feel that the more specific



polypeptide antigens shared by schistosomula and adults, but not the egg, provide the better route towards immunization in man.

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