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Strategies for induction of protective immunity against schistosomes

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Attempts to artificially induce protective immunity against schistosomes have employed a variety of differing immunologic strategies. These approaches can be distinguished on the basis of the nature of the parasite antigens chosen as targets for immune attack as well as by the type of immunologic effector mechanism (humoral or cell-mediated) induced:

1. Immunization with schistosomulm surface antigens

Newly transformed schistosomula have been shown to be susceptible in vitro to a variety of different antibody-dependent killing mechanisms and in vivo are partially eliminated by transferred immune sera or monoclonal antibodies recognizing surface antigens of either 16, 28, 30, 32, 38, 45, 53, 155 or 200 kd (cf. working paper by Harn in this document). In several instances, vaccination with these surface antigens (purified by affinity chromatography) has been shown to partially protect mice of rhesus monkeys against challenge infection (Smith and Clegg, 1985; Tarrab Hazdai et al., 1985). While already proven as a successful approach for immunization, vaccination with schistosomulum surface antigens poses several problems which will have to be resolved before use in the filed can be considered. Firstly, the levels of immunity induced by membrane antigens in fully-susceptible hosts have in general been low. While further boosting with antigen may increase the level of protection induced, the fact that transfer of large amounts of the corresponding monoclonal antibody usually confers an equivalently low degree of resistance suggests that the maximum level of immunity induced by vaccination with larval membrane antigens may be limited. The latter situation may result from either the extremely transient expression of the target antigens on early schistosomula (Harn et al., 1984; Bickle et al., 1986) or from the expression of the immune effector mechanism in one anatomical site through which the challenge infection rapidly migrates.

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A second problem concerns the chemical nature of the membrane target antigens themselves. The majority of these appear to be glycoproteins in which the epitopes accessible to antibody binding are likely to be carbohydate determinants. Recombinant DNA synthesis of these epitopes therefore cannto be performed using conventional high yield prokaryotic cloning systems. One solution to this problem is the use of anti-idiotypic vaccines. Anti-idiotypes have been shown to be capable of mimicking microbial carbohydrate epitopes and of eliciting anti-carbohydrate antibody responses (Stein and Soderstom, 1984; Sacks et al., 1985). Indeed, as discussed in this report (cf. paper by M. Capron) immunization with anti-idiotypes produced against a monoclonal antibody recognizing a carbohydrate surface determinant has been shown to successfully protect rats against *S. mansoni* infection (Grzych et al., 1985). Whether or not this approach could be used practically in immunizing human populations remains to be determined.

In considering vaccination with membrane molecules, it should be pointed out that the ideal target antigen or combination of antigens may not have been identified as yet. Most of the antigens which have been studied to date are expressed transiently on early schistosomula whereas recent data suggest that in immune rodents the majority of the challenge parasites eliminated belong to a later developmental stage (Dean et al., 1984; Ford et al., 1985). thus, identification of possible target surface antigens on older schistosomula would seem a high priority (cf. report by Stand).

2. Immunization with parasite excretory-secretory (ES) antigens

Evidence from histopathologic studies has indicated a close association between tissue inflammatory responses and immune elimination of challenge infections (e.g., Mastin et al., 1983; von Lichtenberg et al., 1985). It woiuld seem logical that the critical antigens triggering these responses against living schistosomula are soluble parasite molecules released into tissue spaces as a result of secretion, excretion or membrane turnover. These ES antigens could also play an important role in determining physiologic processes of the parasite such as migration, stimulation of female development, inactivation of lethal immune responses (Capron and Dessaint, 1982) and inhibition of coagulation (Tsang et al., 1977). Furthermore, as inidcated by recent work in the rat model (Auriault et al., 1985) ES products of schistosomula can serve as an enriched source of protective membrane antigens circumventing the need for both tegument isolation and detergent fractionation. Finally, as discussed below, ES antigens, as soluble released parasite products, would appear to be ideal molecules for both inducing and eliciting T-lymphocyte dependent cell-mediated immunity against schistosomes. Further characterization of this important sub-set of parasite antigens wuld therefore appear to be highly relevant to vaccine development.

3. Induction of cell-mediated immunity (CMI)

As discussed extensively in another report (by James) in this document, considerable evidence exists supporting a role for antigen specific cell-mediated immunity in murine models of acquired resistance to schistosome infection. This effector mechanism is likely to be antibody independent and mediated by the larvicidal reaction of lymphokine activated macrophages with early or late schistosomulum targets. In market contrast with antibody-dependent killing reactions, the larvicidal effect of activated macrophages does not require recognition of surface antigens and indeed, electron microscopic observations suggest that the principal damage induced by these cells is subtegumental (McLaren and James, 1985). Thus, the induction of CMI offers a strategy for vaccination which may circumvent the numerous evasive properties of the schistosome surface. Moreover, since the epitopes which trigger T lymphocyte dependent cell-mediated responses are in most cases protein rather than carbohydrate (Henson, 1985), recombinant DNA or chemical synthesis of the relevant immunogens should be straightforward. As discussed by James (see accompanying report), CMI against schistosomes is selectively induced by administering antigen by the intradermal route (James, 1985). Adjuvants such as BCG appear to augment the protection induced although one laboratory has reportee successful immunization following intradermal injection of frozen-thawed schistosomula in the absence of adjuvant (Hsu et al., 1986).

4. Selective induction of IgE antibody responses

IgE antibodies have been shown to be particularly effective in triggering macrophage and eosinophil-mediated killing of schistosomula in the rat in vitro model. That the induction of IgE responses may be important in vaccination is suggested by the observation that crude released products from schistosomula or a 22–26 kd complex isolated from this material elicit strong IgE antibody responses in rats along with unusually high levels of protective immunity (Auriault et al., 1985; Capron and Capron, 1986). Similarly, in the mouse model, injection of small quantities of larval antigen in alum, a procedure which selectively stimulates IgE responses, has been shown to successfully vaccinate against challenge infection (Horowith et al., 1982).

Conclusion

It should be apparent from the above summary that several well formulated strategies now exist for vaccination against schistosome infection. More importantly, these strategies have already proven their effectiveness in several successful experimental vaccine models employing crude schistosome extracts, purified antigens or anti-idiotypes. Indeed, from this perspective the current status of schistosome vaccine development may surpass that of malaria vaccine

research where despite rapid advances in the identification and synthesis of potential target antigens, few successful immunization models exist.

An important general problem in vaccine development concerns the optimization of methods of antigen presentation. This is particularly relevant to vaccination against schistosomes where evidence for inhibitory immune responses has been obtained (Capron and Capron, 1986). Although as indicated above strategies for selective induction of cell-mediated and IgE responses have already been successfully applied in experimental schistosome vaccines, further optimization of antigen presentation techniques should be a high priority. Indeed, this aspect of "vaccine engineering" may pose greater challenges than the now almost routine problems of antigen identification and synthesis.

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