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EVASION OF HOST IMMUNE RESPONSE IN PARASITES: A REVIEW

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ABSTRACT

The subject of this review paper is to explain in the light of literature review, that despite a defense system of host, how parasites manage to escape and develop to complete their life-cycle. When organism becomes endoparsitic, i.e. change their life style from free living to living in another species, this has many consequences for both the apprentice parasite as well as for the potential host. The parasite has to develop strategies to avoid the actions of its host's internal defense system and for its energy supply it has to gain access to host resources.

Mechanisms Involved

A wide range of mechanisms have developed to allow parasite evade the immune responses of the host. The term parasite is to be used in a broad sense to include helminths, protozoans, bacteria and viruses (Anderson and May, 1982). The strategies used may be categorized as parasite location, avoidance of recognition or immunosuppression. These are isolated, a single parasite may use many different mechanisms.

The simplest method of evasion is to find a location where the host immune system is unable to affect the parasite. Intracellular parasites like *Leishmania, Trypanosoma cruzi* and the feeding stages of *Plasmodium* avoid the effect of antibodies. Effector cells have to be able to recognize any new parasite derived antigens at the surface while it is briefly exposed (Hyde, 1990). The intracellular environment is not a completely effective mechanisms for evasion in *Babesia* and *Plasmodium* as they are predominantly found in dissociated cells which may be destroyed by the host. This is not the sole mechanism for evasion in these species, *Plasmodium-infected* cells, for example are sequestered in organ capillary systems which are well shielded from immune effector mechanisms.

When found within cysts, *Trichinella spiralis* and *Echinococcus granulosus,* are protected by the cystic membrane. Other immunologically privileged sites invaded include the eye (*Onchocerca volvulus*), urinary tract (*Trichomonas vaginalis*) and the bile ducts (*Fasciola hepatica*).

Among parasites that invade macrophages, different methods are employed to avoid death by reactive oxygen species and degradative enzymes. Leishmania are taken up into the phagosomal vacuole but after fusion with lysosomes, they are able to resist digestion and multiply in the resulting phagolysosome (Joiner, 1998). They appear to do this by becoming coated with complement C_3b, which in the case of most other organisms much increase the rate at which they are phagocytosed but actually protects Leishmania. Activation of the complement defense system facilitates efficient and safe entry into the cells the parasite wishes to take over. Whereas Leishmania exploits complement to gain access to macrophages and to protect itself. *T. cruzi* needs to disarm this mechanism as epimastigotes (the main insect stage) are highly susceptible to lysis in human serum by the alternative complement pathway (ACP). The infective form and the vertebrate blood forms are highly resistant to ACP mediated lysis (Fentin Hall and Joiner, 1991). These both produce protein factors that interfere with pathway activation and produce molecules which resemble decay-accelerating factor produced by the host to regulate action of complement.

Antigenic Variation

Antigenic variation was first recognized in about 1910 when it was noted that successive waves of trypanosome parasitaemia observed in early stages of the infection represented antigenically distinct populations (Boothroyd, 1985). It has subsequently been noted in several species, malaria and Babesia parasites employing similar strategies to food effect (Leid *et al.*, 1987). In trypanosomes it was originally suggested that there might be a single basic antigenic type for a given strain giving hope for a transmission-blocking vaccine. There is infact a whole range of variant-specific surface groups (VSG) which protects the underlying membrane. Electron micrographs show that each variant has a thick electron dense coat which envelops the parasite and contains the antigen (Hyde, 1990). As the level of antibody increases

a small fraction of the population switches to producing a coat of a new VSG with an antigenic character circulating antibodies are no longer able recognize.

The molecular analysis of malarial antigens for different life cycle stages has led to the discovery that several potent antigens are repeated several times. Antigens are dominant natural immunogens with much of the antibody response induced being directed against repeat epitopes (Kemp *et al.,* 1987).

This method of immune evasion has been described in the smoke screen model. Protective immunity in malaria develops only after exposure for a number of years which may lead to dramatic immunological consequences. Even in the non-immune animals there may be high levels of antibody to many repetitive antigens. These antigens are acting as a smoke screen to help camouflage the parasite from the host immune system.

Multiple cross reactions are found among the antigens of the repetitive regions. High affinity antibody responses probably depend upon selection of B cells with somatic mutations accumulated in their surface immunoglobulin. These proliferate preferentially to produce antibody secreting cells.

This led to the hypothesis that in anti-malarial immune response, an abnormally high proportion of B cells that accumulate somatic mutations in surface immunoglobulins are preserved during clonal expansion. The development of high affinity antibody responses which may be important, for immunity may be delayed because of limits to B cell proliferation imposed by the size of B cell pool.

The $(NANP)_n$ sequence is the single immuno-dominant epitope of the *Plasmodium falciparum* circumsporozite protein. It was selected for use in candidate vaccines but seemingly unsuccessful (Schofield, 1990). It has though been included in the SPf 66 synthetic vaccine developed by Patarroyo and colleagues in Colombia (Valero *et al.*, 1993).

Strategy of Avoidance

Instead of continual antigenic variation some pathogens reduce antigenicity so they are not recognized as foreign. This may be a masking process where the parasite covers itself with host antigens. The a2-macroglobulin on the surface of adult schistosomes is a host molecule with potent anti-proteins activity. If attached to a molecule with the appropriate conformation it may also act as a proteinase inhibitor, preventing break-down of parasite tissues (Leid *et al.*, 1987).

Molecular Mimicry

Host MHC antigen molecules are found on the surface as a defense against natural killer cells (Maizels *et al.*, 1993). They additionally take up delay-accelerating factor, conferring from complement-medicated attack, contraption, a serum protease inhibitor, and low density lipoproteins. The fusion or incorporation of host cellular membranes into the continuously regenerated membrane leads to recognition as host related.

Another form of molecular mimicry is the synthesis of surface proteins similar to host proteins by the parasite which are unrecognizable as foreign. Tapeworms adapt a combination of these strategies synthesizing antigens that resemble blood group of MXH antigens of the host (Hyde, 1990).

Depression of the host immune response is a common event in a number of parasite infections, the mechanisms involved varying between species and is crucial for the survival of many species (Hyde, 1990). Immunosuppression may be of specific responses to particular antibodies or non-specific responses to all invaders. It may be brought about in many ways and affect humoral and cell-mediated responses by parasite proteases and protease inhibitors, respectively.

Parasite proteases may inactivate the cytotoxic mediators including cytokines which are expressed by host leukocytes and host complement if there is high specificity for individual and critical complement components or by a broad substrate specificity (Leid *et al.*, 1987). Enzymes are also found which inactivate the chemical mediators of immediate hypersensitivity reactions.

Enzymatic Role

Enzymes are produced that are capable of inactivating reactive oxygen intermediates (ROI) resulting from host inflammatory defense systems (Maizels *et al.*, 1993). The surface of secreted antioxidant enzymes which counteract the oxidative burst include superoxide dismutase, catalase, glutathione peroxidase (GPX) and glutathione S-transferases (GST). GST is localized in the external tegument of schistosomes and may be successfully used to immunize rats against challenge infections. These antigens are also components of candidate schistosome human vaccines (Mitchell, 1989).

Organisms capable of metabolizing O_2 and H_2O_2 can survive within host macrophages while species without ROI detoxifying enzymes such as T.cruzi cannot.

A direct correlation between the virulence of parasites and the presence and level of these enzymes has been postulated (Leid *et al.*, 1987).

It is proposed that the mechanism of dampening host inflammation around parasites involves the inhibition of host cellular defense mediated by parasite protease inhibitors. The inhibitors described, are not restricted to a single taxonomic group and have been found associated with nematodes, trematodes and cestodes. Inhibitors may be obtained from crude worm homogenates, they can be secreted and so may be an integral part of the tegument of cuticle.

The enzymes controlling, and therefore the whole complement system may be inhibited by the parasite. Inhibition of the murine complement (C) system is critical to successful antibody-mediated host resistance. Any impairment of host C-system will enhance the chances of parasite survival by either the classical or alternative pathways of activation.

Suppressive molecules may be derived from parasite metabolism of arachidonate (Leid *et al.*, 1987). The arachidonate acid cascade and its products which include prostaglandin, thromboxanes and leukotrienes have been explored in terms of parasite physiology and biochemistry. Metabolites have potent biological activities and can either inhibit host immunological effector mechanisms or increase host inflammation.

Work on nematodes of veterinary importance such as *Ostertagia* and *Nematodirus* led to the discovery that hypobiotic parasites result in the diminished production of antigens to stimulate the immune system. Significant periods of dormancy have been observed in Toxoplasma, *T.cruzi* and the hepatic stages of malaria. The effects can be indirectly demonstrated by drops in antibody titres.

In some case parasites do not simply evade the host's immune responses but exploit them for their own purpose (Damian, 1987). The egg-induced immunopathology of *Schistosoma mansoni* is due to the subversion of the host immune responses to mediate egg excretion and, therefore, parasite transmission and survival (Doenhoff, 1985).

In addition to encounter the immune response of the definitive host a parasite may also encounter the defenses of a vector, intermediate host or reservoir host. Similar mechanisms exist for avoidance of immune recognition and immunosuppression in insect and molluscan vectors (Christensen, 1986).

REFERENCES

Anderson, R.M. and R.M. May, 1982. Coevolution of host and parasite. Parasitol., 85: 411-426.

Boothroyd, J.C., 1985. Antigenic variation in African Typansomes. Annual Review Microbiol., 39: 475-502.

Christensen, B.M., 1986. Immune mechanisms & mosquito-filarial worm relationships. In Immune mechanisms in invertebrate vectors. Symp. Zool. Soc. Lond., No. 56 (ed A.M. Lackie). Oxford University Press.

Damian, R.T., 1987. The exploitation of host immune responses by parasites. J. Parasitol., 73: 3-13.

Doenhoff, M.J., 1985. Does the immunopathology by schistosome eggs potentiate survival. Immun. Today., 6: 203-204.

Fenton Hall, B. and K.A. Joiner, 1991. Strategies of obligate intracellular parasites for evading host defense. Immunoparasitol. Today, 7: A22-A27.

Hyde, J.E., 1990. Molecular Parasitology. Open University Press.

Joiner, M.A., 1988. Complement evasion by bacteria nd parasites. Annual Review Microbiol., 42: 201-230.

Kemp, D.J., R.L. Coppel and R.F. Anders, 1987. Repetitive proteins and genes of malaria. Annual Review Microbiol., 41: 181-208.

Leid, W. C.M. Suguet and L. Tanigoshi, 1987. Parasite defense mechanisms for the evasion of host attack. A review. Vet. Parasitol., 25: 147-162.

Maizels, R.M., D.A.P. Bundy, M.E. Slkirk, D.F. Smithy and R.M. Anderson, 1993. Immunological modulation and evasion by helminth parasites in human populations. Nature, 365: 797-805.

Mitchell, G.F., 1989. Glutathione S-transferases potential components of antischistosome vaccines. Parasitol. Today, 5: 34-37.

Schofield, L., 1990. The circumsporozoite protein of Plasmodium: a mechanism of immune evasion by the malaria parasite. Bull. W.H.O., 68: 66-83.

Valero, M.V., L.R. Armador and C. Galindo, 1993. Vaccination with Spf66, a chemically synthesized vaccine against Plasmodium falciparum malaria in Colombia, Lancet, 341: 705-710.