Immunity and schistosomiasis

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Professor Boyde specialized in biochemistry a few years after qualifying. He was Professor of Biochemistry and Dean of Sciences at Makerere University from 1969–73, then moved to Hong Kong University, where he is now Head of the Department of Biochemistry.

The 'Hong Kong College of Medicine for Chinese', (in the Chinese language version, '. . . of Western Medicine. . . ') founded 99 years ago, became a principal pillar of the University of Hong Kong when that body began its work in 1911. One of the founding fathers of the College was Sir Patrick Manson, after whom is named the most widely dispersed of the human schistosomes.

He is quoted as saying, of schistosomiasis, that if he himself were infected he would decline treatment on the grounds that the disease was preferable! The chemotherapy then available had side effects that were at best unpleasant and often enough fatal: even so, his view of the disease must be classed as rather optimistic. A light, chronic infection may indeed cause the host little trouble, but of the 200 million-plus affected people world-wide a fair proportion will die of the hepatic, vascular, or nervous system sequelae, while most of the rest suffer varying degrees of debilitating illness.

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Present-day drugs for killing the adult worms are well tolerated and very effective (oxamniquine for *S mansoni* and metrifonate for *S haematobium*, praziquantel for all species). Nevertheless, transmission is continuing even in areas where mass treatment has been conducted under first-class supervision. Studying the immune reaction to schistosomes is still a matter of great practical importance, as well as a fascinating thing in its own right.

Natural history

Schistosome eggs, shed into water, hatch to give free-swimming larvae, which then develop further within appropriate snail species before being released again into the water in a concerted manner, depending in part on photoperiodicity and light intensity. Now called cercariae, these larvae can penetrate the intact skin, then lose the tail and begin a process of migration and development, ending as adult worms which inhabit the veins of the intestine (*S mansoni* and *S japonicum*) or bladder (*S haematobium*).

In a mixed infection, the male worm remains permanently in a groove of the female's body. Eggs are plainly meant to reach the lumen of the intestine or bladder and hence the outside world, but a proportion escape to lodge in the liver or elsewhere, causing much of the clinically serious disease.

The tegument of the worm must be of great importance to its evasion of immune killing; nothing like enough is yet known of its molecular make-up.[1] There is an 'acellular syncytium' which covers the surface of the animal. The outer lipid-bilayer membrane of this bears polysaccharide chains, some linked to lipid membrane components and some to proteins. Analysis of liberated 'circulating antigen' (see below) suggests that some chains resemble the glycosaminoglycans, though it is hazardous to draw any such conclusions ahead of the hard structural data, and in turn much more difficult to obtain such structural information for polysaccharides than for proteins and nucleic acids.

Species vary in their susceptibility to infection. One of the problems of control is that a variety of small mammals can support human schistosomes and may possibly allow fully effective transmission in the wild (but see ref. 2). Mice are used in laboratory studies and to maintain strains of the parasites. In the rat, however, the human parasites die after about 3 weeks, so that although primary infection and the primary host response are able to proceed apparently normally, some unknown mechanism peculiar to the species then comes in to kill the adults.

It might be very helpful to know how the rat manages it!

Immune relationships

Egg antigens are mentioned below in a different context. From the point of view of effective immunity to infection we need to study the response to larval or adult worms.

The most striking observation is that adult worms are to a large extent themselves immune from immune attack, and the parasite antigens become undetectable during maturation.[1] Other parasites have functionally similar characteristics, but the schistosome appears to achieve its privileged status in a distinctive manner.

The adult worm 'acquires' host antigens. If this were confined to soluble species from the blood, and glycolipids, one might be unimpressed by

PRAZIQUANTEL'S PRIZE

The French Prix Galien for development of an outstanding drug has gone this year to Bayer and to E Merck, Darmstadt, for the joint development of praziquantel.

Marketed (as Biltricide) in 1980 after 10 years of research in close co-operation with WHO, praziquantel represents a breakthrough in the treatment of schistosomiasis and of neurocysticercosis. For bilharzia it provides a single, well-tolerated, short regimen for all three forms of the disease in place of differing, sometimes toxic, drugs for each form; in cysticercosis it is simply the first useful drug therapy for the disease.

Bayer is the first pharmaceutical company to have won the Prix Galien twice: they received it in 1980 for development of nifedipine (Adalat).

Press release

the possible functional significance of the observation. The antigens acquired include, however, those of the major histocompatibility complex (MHC, Classes I and II), which at once suggests an explanation for the privileged immune status of the animal (it is being recognized by the host as 'self') and argues that a very sophisticated mechanism must exist for acquiring the antigens and processing them so that they appear in an appropriate condition on the tegument surface.

The parasite gut seems an unlikely candidate for this role. Rather we must look to uptake at the tegument surface, presumably by endocytosis in the same kind of way as individual cells are known to handle any material binding to them, and then processing within a series of vesicles before the antigens are returned to the surface. Can we see in this a function for that syncytial layer?

Though the adults are protected, the larvae (schistosomula) are more readily killed by antibody-dependent mechanisms, and irrespective of whether the antibodies are raised against larvae or adults. Indeed adult worms induce antibodies that are active against larvae![1] A population biologist might be interested. Is the established adult parasite working to suppress competition from newcomers?

The actual means of killing is particularly interesting especially since platelets are involved—a cell type not previously known to have an immune capability of this kind.[3a] It is probably IgE antibodies bound to the immune-cell surface, rather than any other antibodies, that are important in killing by macrophages, platelets and eosinophils—the latter requiring also an activating signal from sensitized mast cells.

Protection against infection

A normal situation in endemic areas is that adult worms live in the host for many years, and some unfortunates acquire extremely heavy parasite burdens. This may make the prospects for immune control seem rather bleak, but there is clear evidence from both the laboratory and the field that existing or recently cured infection is indeed partially protective.[4a]

In view of the privileged immune status of the adult, there was a natural bias in experimental work to using vaccines derived from larval worms, but this now seems un-necessary and even unhelpful. An ingenious approach, but one which seems unlikely to be usable on a wide scale, is to irradiate cercariae so that they live for only a few days in the host. Infection by such cercariae gives definite partial protection in mice and cattle.

Not surprisingly, attention has been more closely focused on protein antigens and there is a voluminous, confusing literature on various such materials, of unknown nature and function, isolated by half-understood biochemical separation techniques. Good antibody responses are achieved, and monoclonal antibodies have been derived to some of them. The importance of all this may be less in control than in diagnosis, as discussed below, though actual protective immunization, based probably on the IgE response, has been observed.[3b]

Very recent news[3b] is the cloning of

a DNA fragment coding for one such antigen and its use in preparing a protein antigen that was effective experimentally in mice, baboons, and also in rats, where the antibody response came into play earlier than the natural rejection mentioned above. To be exact, the engineered protein is of 25 kD and corresponds to a natural 28 kD protein but lacks the N-terminal portion of the chain. It seems quite possible that an abnormal protein of this kind might be a better antigen and produce a more effective immune response than the native one. Since these are also obvious advantages to an engineered protein as a source material for producing a vaccine, this work will be followed with avid interest.

Serological diagnosis

Diagnosis of schistosomiasis may seem rather easy but, especially in epidemiological work, there are other matters to consider than merely case recognition. Skin tests exist and the circum-oval precipitin test (COPT) is a simple, cheap, and elegant means for detecting circulating antibodies against egg antigens. Several research groups have developed more sensitive and specific tests for circulating antibodies against either eggs or worms. In some cases there were problems with cross-reactivity to different parasite genera. Many of these tests are no doubt useful in detecting egg-negative cases and in very recent or asymptomatic infections, but it is not clear that any one is better than the rest. Obvious major weaknesses are that tests for antibodies remain positive for some time after chemotherapeutic cure and that there is no necessary correlation with severity of infection or of illness. These matters are nowadays just as important as detection, so that many groups have struggled to establish assessment criteria based on either clinical examination, counting eggs under the microscope, blood in the urine (*S haematobium*), or tests directed essentially at liver status. My own intended research is in the latter area and focuses on the mitochondrial isoenzyme of aspartate transaminase.

Various attempts have been made to relate levels of antibody against either egg or worm to severity of infection, but the results are unconvincing. More plausible candidates would be methods to measure levels of antigens liberated from the worms, and the earliest work in this area is nearly 30 years old.[1] Schistosome-derived polysaccharide material can be detected in the blood and urine of infected people. It has been unexpectedly difficult to exploit this further because the isolated material is itself only very weakly antigenic. But the Capron group, among others, now has a monoclonal antibody that can be used to quantify the circulating levels of a protein antigen.[3c] Thus far the method is confined to *S mansoni*. It might be equally valuable to measure levels of egg antigens.

To break away once more from an over-concentration on immunology, a quite different candidate for measurements of severity of infection would be the ecdysteroids—hormones liberated by the parasites and which can be quantitated in blood.[3d]

Conclusions

Although the adult worm has evolved

a sophisticated system for evading immune attack, a 'cloak of invisibility', there is now good hope of achieving a vaccine that will be at least partially protective, especially against the infecting larval stage. Actually to eliminate any disease by such means, however, requires exceptionally efficient vaccines.[4b] Even a combination of drugs and vaccines is unlikely to eliminate schistosomiasis. This will come about, if at all, by a change of lifestyle of the people and vastly greater economic prosperity—as in Japan.

Immunodiagnostic and other tests have a part to play for many years to come in epidemiological studies and control operations.

■

References

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