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Complement activation by parasites

A review

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Summary

Activation of complement by parasites (living parasites or purified parasite antigens) is involved in several mechanisms of the host parasite relationship. In most of the experiments performed in vitro, complement activation was found to be lethal for the parasites, but sometimes it could be essential for the development of parasitemia. Both classical and alternative complement pathways may be activated by parasites; the classical pathway nearly always requires the involvement of antibodies whereas the alternative pathway is activated directly by products released by the parasites or present in their teguments. Activation of complement, especially via the alternative pathway may also be a prerequisite for cellular adherence to parasites which can then cause their death.

Key words: complement activation; *Schistosoma; Echinococcus; Taenia; Ascaris; Hymenolepis; Trichinella;* trypanosomes; *Plasmodium; Babesia; Toxoplasma.*

Introduction

The involvement of complement in the immunological mechanisms of the host response to parasitic infections has been suggested in the last few years by several workers. Both the classical and alternative complement pathways, in the presence or absence of antibodies, may be activated by parasitic tegument or purified parasitic antigens. This paper was prepared in order to summarise most of the work related to the activation of complement by parasites.

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Helminths

a) Schistosoma mansoni

In schistosomiasis, the involvement of complement in the cercaricidal action of normal serum was suggested by previous experiments (Culbertson, 1936; Standen, 1952; Gerken et al., 1973). More recently it has been shown that this activity is dependent on complement activation by the alternative pathway (Machado et al., 1975). Incubation of *Schistosoma mansoni* cercariae with fresh normal serum is followed by immobilization of their tails and the consumption of appreciable amounts of total hemolytic complement (Machado et al., 1975). This activity, which does not require the participation of antibodies, was also observed with a C4-deficient guinea pig serum (Machado et al., 1975). In contrast, guinea pig sera depleted in C3 or properdin were inactive against cercariae.

The second complement-dependent mechanism of cytotoxicity against immature forms of *S. mansoni* requires the participation of specific antibodies (Clegg and Smithers, 1972; Murrell and Clay 1972). In fact, the serum of rhesus monkeys hyperimmunised by 2–4 exposure to *S. mansoni* cercariae contains an antibody, which together with labile factors present in fresh monkey serum, was lethal to schistosomula cultivated in vitro (Clegg and Smithers, 1972). This activity was also demonstrated in serum from rabbits and rats infected with *S. mansoni* (Murrell and Clay, 1972; Capron et al., 1974). Antibodies cytotoxic for schistosomules were also found in serum from patients infected with *S. mansoni* (Capron et al., 1973; M. Capron et al., 1977). No significant correlation was shown between the activity of this lethal factor and the titre of antibodies observed by the classical serological tests (Capron et al., 1973). In contrast, a significant relation was demonstrated between the presence of the lethal factor and both the delayed hypersensitivity to *S. mansoni* antigen (Capron et al., 1973; 1974) and the severity of the disease (Capron et al., 1974; M. Capron et al., 1977). The antibody involved in this model has been shown to belong to the IgG class (Capron et al., 1973; M. Capron et al., 1977) and complement is activated probably by the classical pathway.

Several in vitro mechanisms of cellular adherence to *S. mansoni* schistosomula have been described (Dean et al., 1974; Capron et al., 1975; 1977; Philipps et al., 1975; Perez and Smithers, 1977; M. Capron et al., 1978). Two of them involve complement. The first concerns adherence of mast cells (Sher, 1976; Sher and McIntyre, 1977) and the second, adherence and killing of schistosomula by eosinophils (Ottesen et al., 1977; Ramalho-Pinto et al., 1978). In both these cases, the alternative pathway of complement was earlier activated by schistosomula (Sher, 1976; Ramalho-Pinto et al., 1978). The adherence of eosinophils to schistosomula may also be obtained, independently of complement, with IgG antibodies (Ottesen et al., 1977; M. Capron et al., 1978). C3 (the third component of complement) was demonstrated on the tegument of cercariae

(Machado et al., 1975) and schistosomula (Sher, 1976) previously incubated with normal serum. Mouse C3 was also detected in the tegument of adult female *S. mansoni* developed in mice and in some of its eggs (Kabil, 1976). In this way, complement may play some part in producing partial acquired immunity in schistosomiasis. Complement activation by *S. mansoni* antigens has also been described. In fact, a glycoprotein prepared from *S. mansoni* cercarial extracts generates anaphylatoxic activity in normal serum (Gazzinelli et al., 1969).

b) Echinococcus granulosus and E. multilocularis

Lysis of protoscoleces of *E. granulosus* and *E. multilocularis* has been demonstrated following incubation in normal sera from a number of different host species (Herd, 1976; Kassis and Tanner, 1976). This lytic effect of serum was destroyed by heat inactivation and complement was consumed during the process of lysis (Kassis and Tanner, 1976). Electron microscopic studies after the in vitro complement mediated lysis of *E. multilocularis* showed that total disintegration of protoscoleces by complement proceeds through formation of "tegumental bubbles" and disruption of the external plasma membrane (Kassis et al., 1976). The presence of C3 on the protoscoleces of *E. granulosus*, previously incubated with normal human serum, was demonstrated by immunofluorescence (Rickard et al., 1977). The alternative complement pathway is involved in the lysis of *E. granulosus* protoscoleces since C4-deficient guinea pig serum has the same lytic effect as normal serum (Rickard et al., 1977). In contrast, the lysis of protoscoleces of *E. multilocularis* by fresh human serum appears to be dependent of the classical pathway (Kassis and Tanner, 1977a). Moreover, inoculation of protoscoleces of *E. multilocularis* in rats previously depleted of complement by cobra venom factor, showed a rapid development in vivo of large cyst masses of *E. multilocularis* as compared with those of untreated infected rats (Kassis and Tanner, 1977b). These observations strongly suggest a role for complement in the immunological mechanisms operating in hydatid disease. Complement activation was also observed with the crude unfiltered hydatid fluid of *E. granulosus* and *E. multilocularis* (Kassis and Tanner, 1976; Hammerberg et al., 1977).

c) Taenia taeniaeformis and T. crassiceps

The permeability of larvae of *T. taeniaeformis* and *T. crassiceps* to macromolecules was demonstrated as being dependent on antibodies and complement activation (Murrell, 1971; Hustead and Williams, 1977). Both live and dead larvae of *T. taeniaeformis* or *T. crassiceps* incubated in normal serum rapidly depleted hemolytic complement levels in the surrounding medium (Hammerberg et al., 1976; Hustead and Williams, 1977; Hammerberg and Williams, 1978a). Recently, it has been shown that the interaction between factors present in the cystic bladder fluid of metacestodes of *T. taeniaeformis* or

released by these parasites maintained in vitro, and the complement system resulted in the generation of anaphylatoxin-like activity in vitro, the conversion of C3 and the production of increased vascular permeability in vivo (Hammerberg and Williams, 1978a). The substances appeared to initiate complement fixation non-immunologically via both the alternative and classical pathways (Hammerberg and Williams, 1978a). The results obtained with immunochemical studies are consistent with the possibility that this active substance is a polysulfated proteoglycan (Hammerberg and Williams, 1978b). The possibility has been raised that local consumption of complement around the metacestode in vivo could contribute to its successful evasion of inflammation and immune rejection during infection (Hammerberg and Williams, 1978b).

d) Ascaris suum

The ability of normal mouse peritoneal exudate cells and fluids to mediate in vitro cell adherence reactions to *A. suum* depends on the presence in exudate fluid of a heat labile component, probably complement, and a heat-stable component, probably immunoglobulin (Ziprin and Jeska, 1975). The inhibition of this cell adherence reaction by EDTA and its restoration by the addition of both calcium and magnesium ions demonstrated the involvement of the classical complement pathway (Ziprin and Jeska, 1975). Complement components were also found on the tegument of *A. suum.* In fact, infective or parasitic larvae or *A. suum* were able to bind purified human C3 labelled with ^{125}I (Leventhal and Soulsby, 1977).

e) Hymenolepis diminuta and H. microstoma

Mouse C3 was detected by immunofluorescence on the tegumental surface of adult *H. diminuta* and *H. microstoma* developed in mice (Befus, 1977). Electron microscopic studies confirmed the presence of C3 in *H. diminuta* worms developed in mice and rats (Threadgold and Befus, 1977). Further investigations on the role of complement in these infections are necessary for a better understanding of the host-parasite relationship.

f) Trichinella spiralis

Cell adherence reactions to *T. spiralis* was demonstrated as being dependent on heat labile factors present in fresh normal rat and guinea pig serum (Stankiewicz, 1975). The alternative complement pathway is involved in this interaction since C4-deficient guinea pig serum has the same effect as normal serum (Stankiewicz, 1975). In contrast, no adherence was observed with a C3 depleted serum.

Protozoa

a) Trypanosomes

In trypanosomiasis, two mechanisms of complement-dependent parasitic lysis have been described in the last few years.

The first requires the participation of antibodies and complement is generally activated via the classical pathway (Anzian et al., 1972). The immune serum from animals infected with *Trypanosoma cruzi* is able to lyse in vitro the culture forms of this parasite (Denison, 1943a; 1943b; Muniz and Borriello, 1954). The kinetics of this reaction are similar to that followed by immune lysis of sensitized sheep red blood cells (Anziano et al., 1972). Moreover in mice infected with virulent blood forms of *T. cruzi*, complement depletion with cobra venom factor caused a marked exacerbation of the disease evidenced by significantly increased levels of parasitemia and early mortality as compared with those of untreated infected mice (Budzko et al., 1975). These observations showed a possible in vivo role for complement in the control of trypanosomes. However, C4-deficient and C3-depleted rats, after infection with blood forms of *T. lewisi*, showed a parasitemia similar to that observed in normocomplementemic rats (Jarvinen and Dalmasso, 1976). Complement levels in normal rats throughout the course of *T. lewisi* infection were significantly decreased (Jarvinen and Dalmasso, 1976). This reduction is probably associated with the formation of circulating immune complexes which have already been detected in human and experimental trypanosomiasis (Fruit et al., 1977). In this model, complement does not appear to play a major role in the control of the infection. Moreover, C5-deficient mice infected with *T. musculi* showed a parasitemia similar to that found in normal mice (Dusanic, 1975). From these observations it may be concluded that there is no obligatory involvement of complement in the control of parasitemia in all the models of trypanosomal infection. Recently, a complement-dependent antibody mediated cytotoxicity against *T. rhodesiense* in serum from rats infected with this parasite has been described (Diggs et al., 1976). In this case, the activation of the alternative pathway of complement is sufficient for antibody cytotoxicity (Flemmings and Diggs, 1978).

The second complement-dependent mechanism of trypanolysis does not require the involvement of antibody and complement is activated via the alternative pathway (Nogueira et al., 1975; Kierszenbaum and Weinman, 1977). In this case, the incubation of fresh normal human, rabbit, sheep, rat, guinea pig, hamster, chicken, pigeon, toad and frog sera with *T. cruzi*, lysed all the culture (epimastigote) forms (Rubio, 1954; Nogueira et al., 1975). Normal toad, frog and chicken sera are also able to lyse in vitro *T. cruzi* blood (trypomastigote) forms (Rubio, 1954; Kierszenbaum et al., 1976). One millilitre of normal chicken serum has the capacity to destroy as many as 10–30 million organisms (Kierszenbaum et al., 1976). Moreover, *T. cruzi* trypomastigotes given intravenously to chickens previously depleted of complement by cobra venom factor,

can be detected in their blood-stream for at least 24 h post-infection, whereas in untreated animals they became undetectable after 1 min and destroyed flagellates are observed (Kierszenbaum et al., 1976). Normal mouse serum does not lyse any form of *T. cruzi* (Rubio, 1954), but the administration of normal chicken serum to mice infected with *T. cruzi* provoked a marked decrease in their parasitemia (Kierszenbaum et al., 1976). These observations suggest a possible action in vivo of chicken complement against blood forms of *T. cruzi.* Epimastigote forms of *T. cyclops* are also lysed by normal human serum via the alternative pathway of complement activation (Kierszenbaum and Weinmann, 1977). The complement activation by living parasitic cells should be studied especially in vivo since this property may be very important for a better understanding of the mechanisms involved in the control of trypanosome parasitemia.

Activation of complement by whole or purified trypanosomal antigens has been described (Musoke and Barbet, 1977; Nielsen and Sheppard, 1977). This was observed with the variant-specific surface antigen of *T. brucei* (Musoke and Barbet, 1977) and antigens from *T. lewisi* (Nielsen and Sheppard, 1977; Nielsen et al., 1977; 1978) and *T. congolense* (Nielsen and Sheppard, 1977). The prolonged hypocomplementemia observed in human and experimental African trypanosomiasis has been suggested to be due to the action of the trypanosome-derived complement-activating factor released by the parasites in the blood (Assoku et al., 1977).

b) Plasmodium

Malarial paroxysms in man due to *Plasmodium vivax* have been related to a fall in serum complement levels and in those of certain complement components (Neva et al., 1974). This drop in complement was also linked to schizont rupture and the appearance of humoral antibody (Neva et al., 1974). In this case, complement was activated via the classical pathway since levels of C4 fell in parallel with the decrease of whole complement. Moreover, C4 levels in rhesus monkeys after 1–2 weeks of infection with *P. coatneyi* were significantly decreased and these falls were temporally related to the process of schizont rupture (Atkinson et al., 1975). In addition depletion of late complement components by cobra venom factor did not alter either the degree or course of parasitemia during the pre-immune or immune stages of *P. coatneyi* infection in monkeys (Atkinson et al., 1975). These results delineate a new pattern of cyclical consumption of early components of the classical complement pathway associated temporally with schizont rupture and suggest that the late-acting complement components are not required for protective host immunity in malaria. The role of complement components in the susceptibility to *P. berghei* infection in mice was also studied (Williams et al., 1975). There was no difference in the infectivity and course of *P. berghei* infection in the co-isogenic C5 deficient and non-deficient strains (Williams et al., 1975). This suggested that C5 is not essential for penetration of erythrocytes by *P. berghei.*

c) Babesia rodhaini

The ability of *B. rodhaini* to penetrate red blood cells appears to depend on factors of the alternative complement pathway (Properdin and Factor B) as well as magnesium ions and the third (C3) and the fifth (C5) components of complement (Chapman and Ward, 1977). Other experiments have demonstrated that rats maintained on a magnesium-deficient diet were afforded some degree of protection against *B. rodhaini* (Norman et al., 1970). Furthermore, rats were less susceptible to red cell parasitization after treatment with cobra venom factor (Annable, 1972). Finally, mice deficient in both C3 and C5 components of complement failed to develop babesial infections (Annable, 1972). The evidence suggested that an intact complement system is essential for the development of babesial parasitemia. In this case, the role played by complement is prejudicial to the host.

d) Toxoplasma gondii

Experiments performed to determine the influence of the C5 component of complement in experimental *Toxoplasma* infection revealed that mice deficient in C5 had reduced mortality from acute toxoplasmosis (Araujo et al., 1975). This observation might be related to those noticed in *B. rodhaini* infection. However, further investigations on the role played by complement components in *T. gondii* infection are necessary to confirm these results.

Conclusions

From the data reviewed it appears that the activation of complement is involved in several control mechanisms of parasitic infetion. 1. Complement, in the absence of antibodies, may be activated by living parasites. In this case, complement activation is preferentially via the alternative pathway, which results in most cases in the destruction of parasites. Sometimes, this activation is favourable for the parasite; the penetration of *Babesia rodhaini* in red blood cells for example depends on a previous complement activation by this parasite. 2. Complement is activated by the parasite-antibody complex. In this action, complement activation is by the classical pathway, and the parasites in most of the cases are destroyed. 3. Adherence of cells to parasites which have previously activated complement preferentially via the alternative pathway. This interaction is sometimes followed by the killing of the parasites. It appears necessary to evaluate more exactly the role of these mechanisms in the host-parasite relationship.

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