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Cross-Reaction as a Common Phenomenon among Tissue Parasites in Farm Animals

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Abstract: Infection of animals with parasites continues to cause worldwide great economic losses. Accurate serological diagnosis of parasitic infections is a good initial approach to improve its control. However, the low specificity of current serological techniques constitutes a problem due to cross-reactions among animals with different infections. Cross-reactivity is a widely spread trait among phylogenetically related and unrelated parasites. It emerges from the wide existence of common antigens, which suggest that antigenic continuity is the rule rather than the exception. Adoption of monoclonal antibodies as well as pure fractions in the serological discrimination between different infections is recommended to reduce the effect of this phenomenon. Examples for cross-reactivity between some tissue parasites infesting farm animals were documented such as *Taenia* and *Echinococcus*; *Taenia saginata, Taenia solium* and *Echinococcus granulosus, Trichinella spiralis* and *Toxoplasma gondii*. Cross-reaction is not only restricted to species belong to the same phylum, but also extended to helminthes of different phyla such as the high degree of cross-reactivity between sera of animals infected with *T. solium, Hymenolepis nana* and *E. granulosus.* Also, a cross-reaction between three important zoonotic helminthes *Fasciola gigantica, T. spiralis* and *E. granulosus* was recorded. Despite their drawbacks in accurate immunodiagnosis, extensive similarities in the antigenic composition among parasites often permit the use of a diagnostic antigen from one species potentially to protect from another. Evidence for protective immune cross-reactivity between *Schistosoma mansoni* and *Fasciola hepatica* is well documented. The low molecular weight cross-reactive component of 14 KDa isolated from *S. mansoni* (Sm14) could form the basis of a single effective cross-protective vaccine against both parasites based on its proved prophylactic potentials. Consequently, optimism of developing multi-purpose vaccine candidates against parasitic infections, in the near future, is a reality rather than imagination.

Key words: Cross-Reaction · Tissue Parasites · Cross-Protection

INTRODUCTION

Parasites present a mosaic of immunogenic epitopes to their hosts and evoke complex cellular and humoral responses. Some of these epitopes are exclusive to each species while others are common [1]. The complexity of parasites and host-parasite relationship is daunting.

Antigenic complexity certainly renders difficult the task of identifying and characterizing (at the epitope or whole antigen level) what for the host are beneficial, irrelevant or counterproductive immune responses. Structural complexity as multicellularity coupled with adaptability and the capacity for repair all lead to the reasonable prediction that multiple immune effector mechanisms will be necessary for expression of host resistance. As a consequence, multiple immune evasion strategies will have been developed by parasite populations. Complexity also contributes to the difficulties in diagnosis and in particular, quantitating parasite loads [2, 3]. Identification of antigens and more importantly their epitopes, that are the targets of host-protective immune responses will be achieved through a combination of (i) Production of functional anti-parasite monoclonal antibodies active *in vivo* or *in vitro* (ii) Production of functional anti-parasite T-cell clones active *in vivo* or *in vitro* (iii) Identification of immune responses in genetically resistant phenotype (iv) Identification and characterization of relatively invariant epitopes in variant

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antigens that vary as a result of evolutionary pressure from immune responses that are potentially host protective (v) Determination of the availability to the immune system and precise location of antigens and epitopes on various developmental stages of parasites through the use of specific antibodies [2]. Of relevance to the antigen complexity is the intriguing phenomenon of serological cross-reactivity among parasites of different species, genera and even phyla that its analysis presents a difficult challenge. This phenomenon emerged from antigen conservancy or existence of common components among parasites. It is responsible for false diagnostic results particularly when the infections were caused by closely related parasites. However, by the use of monoclonal antibodies it is now possible to identify epitopes of individual molecules whose shared structural similarities are recognized by sera of infected hosts [4]. More importantly is the adoption of pure fractions than crude extracts in serological diagnosis of parasitic infections [5, 6]. Analysis of cross-reactivity among parasites is of significance for understanding the evolutionary conservation of antigens. It is also important in the development of sensitive and specific serodiagnostic assays and for eliciting cross-protective immunity in hosts against multiple parasitic infections using cross-reactive components [7]. The most famous example of heterologous resistance was that observed between *S. mansoni* and *F. hepatica* [8]. A low molecular weight common component of 14-kDa isolated from *S. mansoni* stimulates a protective response against both *S. mansoni* and *F. hepatica* infections. Such a dual-purpose vaccine, aimed primarily for veterinary use against an economically important disease such as fasciolosis, may represent an attractive route for the development of a vaccine against human schisotsomiasis [9]. Recently, a proteomic-based approach identified 28 immunoreactive proteins that are common to both adult *Fasciola hepatica* and *Schistosoma mansoni*. Some of the identified proteins could be used to develop vaccines against fascioliasis and schistosomiasis [10]. Moreover, the heterologous protective capacity exhibited by Tso18 (a vaccine candidate isolated from *T. saginata* oncosphere) and its extensive presence in different cestodes point to its potential as a broad spectrum vaccine among cestodes.

Collectively, the current article highlighted cross-reaction examples between tissue parasites in farm animals with emphasis on cross-protective components which raised the possibility of developing multipurpose vaccine for veterinary use. This is of fundamental significance in terms of real progress towards effective immunoprophylaxis against parasitic infections.

Cross-Reaction and the Problem of Accurate Diagnosis: Immunodetection refers to any detection method that exploits the interaction of an antibody and antigen. Immunodiagnostic cross-reactivity of sera from animals with different parasitic infections is a common result of antibody based serological assays. This observation is attributed to the widely spread antigenic structural homology between parasites even those taxonomically different [11]. It is responsible for false diagnostic results particularly when the infections caused by closely related parasites [4]. Analysis of cross-reactivity among parasites is of significance for understanding the evolutionary conservation of antigens. It is also important in the development of sensitive and specific serodiagnostic assays and for eliciting cross-protective immunity in hosts against multiple parasitic infections using cross-reactive components.

Cross-Reaction among Tissue Parasites: Cross-reactivity among helminthiases was found with the use of antigens belonging to phylogenetically related parasite species, *E. granulosus, T. solium* (Tso) and *T. crassiceps* cysticercus vesicular fluid (Tcra-VF) by sharing same antigenic components. Lower cross reactivities were obtained by immunoblot assay (IB), when only peptides were considered as antigens, and the use of *T. crassiceps* purified glycoproteins demonstrated high sensitivity and specificity in the diagnosis of human cysticercosis [12]. It has also been demonstrated that *T. solium* and *T. crassiceps* share antigenic components, including those of low molecular mass peptides; 18 and 14 KDa [13, 14]. Monoclonal antibodies (Mab) against *T. crassiceps* and *T. solium* cysticerci were produced and showed cross-reactivity with a 14-KDa protein from *T. solium* and with 18- and 14 KDa proteins from *T. crassiceps* [15]. These MAbs and antibodies from cerebrospinal fluid (CSF) as well as serum samples from subjects with neurocysticercosis (NC) reacted with 18- and 14 KDa *T. crassiceps* proteins purified by immunoaffinity chromatography using Sepharose column coupled with MAbs (anti-excretory/secretory or anti-vesicular fluid antigens [16]. Recently the gene family encoding for the taeniid 8-kDa antigens was found to be comprised of many members with high diversity, which will provide molecular evidence for cross-reaction or

specific reaction among metacestode infections and may contribute to the development of promising immunological methods for diagnosis of metacestodosis [17]. Cross-reaction was also observed between *T. saginata, T. ovis* and *E. granulosus* using peptides with significant homology between the three parasites in the diagnosis of *T. saginata* infection in cattle [18]. Also, cross-reaction was proved between hydatid cyst fluid of *E. granulosus* and *Cysticercus tenuicollis* fluid using SDS-PAGE and DNA analysis [19]. Cross-reaction between ES antigens of *T. spiralis* and *T. pseudospiralis* was proved by two-dimensional western blot. An immunoelectron microscopical study showed that stichocyte granules and cuticle surface (known to contain ES antigen) had cross-reactive antigens between the two species[20]. Sato and Kamiya [21] proved that intermediate filaments in helminth tissues are responsible for cross-reaction between *T. britovi*, *S. mansoni* and *E. multilocularis*. Also, strong cross reactivity between *T. spiralis* muscle larval antigens and *T. gondii* tachyzoites including 4 common immunoreactive proteins; 130.95, 113.60, 55.38 and 28.42-kDa was detected by Hassanain *et al* [22].

Although, the final host of the coccidial parasite Neospora caninum is dog, its economic impact is felt mostly in the intermediate cattle host, whereas it is a major cause of abortion [23,24]. Molecular mimicry has been demonstrated to occur in several parasites including homology or complete identity at the protein level, similarity at the level of amino acid sequence and structural similarity [25]. Zhang *et al.* [26] reported that, *N. caninum* ribosomal phosphoproteins (NcP0) showed 94.5% amino acid identity to *T. gondii* P0 (TgP0) and suggested that P0 is a cross reactive antigen between *N. caninum* and *T. gondii.*

Cross-Reaction: A Basis of Multi-purpose Parasitic Vaccines: Apart from improving animal health and productivity, veterinary vaccines have a significant impact on public health through reductions in the use of veterinary pharmaceuticals and chemicals and their residues in the human food chain. Vaccines may be used to prevent clinical signs of disease after infection or help control, eliminate, or even eradicate an infection at the population level. Both vaccine effectiveness and mechanism of action may vary depending on the required outcome [27]. Treatment or vaccination of domestic animals as the obligatory intermediate hosts of parasites that share a two-host life cycle offers the possibility of controlling transmission [28, 29]. A widely existed phenomenon of cross-reaction must be manipulated in a manner that maximizes its significance. Utilization of cross-reactive components in cross-protection against multiple parasitic infections is the fundamental approach to achieve this goal. It has been shown that one aspect of biological variation between *Trichinella isolates* is an expression of variation in immunogenicity [30, 31]. One explanation for this variation is that isolates vary in their possession of antigens critical to the development of the powerful immune and inflammatory responses through which resistance is expressed. If this is indeed the case, and if it is also true of other widely distributed important nematodes, then strategies for the development of immune-prophylactic reagents will need to take such antigenic variability into account [32]. The extensive similarities in the natural history, pathology, and antigenic composition among cestodes [33, 34] often permit the use of a protective or diagnostic antigen from one species potentially to be applied to another [35, 36]. Rosas *et al*. [37] tested the use of the Tso18 antigen of *T. saginata* as a DNA vaccine in a murine model of cysticercosis by using *T. crassiceps*, another cestode that naturally infects rodents and exhibits extensive antigenic cross-reactivity and cross-immunity with *T. solium* and develops easily and rapidly in the peritoneal cavity of mice. Thus it has been successfully employed to test promising antigens and vaccine approaches [33, 36, 38,39] against *T. solium* cysticercosis [40,41]. The protective capacity of the Tso 18 (reduction of parasite burden by 57.3-81.4%) and its extensive distribution in different stages, species and genera of cestodes points to the potential of Tso 18 antigen for the possible design of a vaccine against cestodes [37]. It has been shown that total T. crassiceps antigens can cross-protect pigs against T. solium cysticerosis [42].

In the case of hemoprotozoal parasites, even within the same life cycle stage hemoprotozoal parasite infections are not self-limiting and parasites can proliferate continuously in the blood stages if not checked by the immune response or drug treatment [27]. *Babesia bovis* causes an acute and often fatal infection in adult cattle, which if resolved, leads to a state of persistent infection in otherwise clinically healthy cattle. Persistently infected cattle are generally resistant to reinfection with related parasite strains, and this resistance in the face of infection is termed concomitant immunity. The antigenic diversity of *B. divergens* is particularly important consideration in the development of

a culture-derived *B. divergens* exoantigen-containing vaccine which is expected to induce cross-protection against isolates from different geographical areas [43, 44]. Wright *et al*. [45] proved that cattle exposed to *B. bigemina* and challenged with *B. bovis* were only mildly affected, while those not challenged were severely affected. Immunoblotting studies performed in both homologous and heterologous systems showed that there were polypeptides of similar molecular weight in both species. Heterologous protection (50 and 75%) against *B. bigemina* was observed in splenectomized calves due to immunization with enriched antigen fraction of *B. bigemina* or with infection with *B. bigemina,* respectively [46].

Subunit vaccine research in *Theileria* has been focused to date on surface antigens of the sporozoite stage. The studied antigens are called SPAG-1 and P67 from *T. annulata* and *T. parva*, respectively. Both antigens were originally defined by neutralizing monoclonal antibodies which importantly recognized non variant epitopes within each species [47]. This evidence of a common protective epitope is particularly important in the case of *T. parva* which is quite heterogenous in terms of cross-immunity profiles. It is thought to be due to polymorphism in the schizont antigens targeted by cytotoxic T cells. Hall *et al*. [48] confirmed that both SPAG-1 and P67 antigens confer protection against homologous species challenge. More importantly, they mutually confer a degree of cross-species protection raising the prospect of a common vaccine in the future. The cross-reactive antigens of *N. caninum* and *T. gondii* are important in the exploration to determine the common mechanisms of parasite–host interaction. Whereas, a gene encoding *N. caninum* apical membrane antigen 1 (NcAMA1) was identified by immunoscreening of a *N. caninum* tachyzoite cDNA expression library with antisera from mice immunized with recombinant *T. gondii* apical membrane antigen 1 (TgAMA1). NcAMA1 showed 73.6% amino acid identity to TgAMA1. Mouse polyclonal antibodies rose against the recombinant NcAMA1 (rNcAMA1) recognized a 69-KDa native parasite protein by western blotting. Two-dimensional electrophoresis and Western blotting indicated that an approximately 57-kDa cleavage product was released into the excretory/secretory products of *N. caninum*. Preincubation of free tachyzoites with anti-rNcAMA1 IgG antibodies inhibited the invasion into host cells by *N. caninum* and *T. gondii*. These results indicated that AMA1 is a cross-reactive antigen between *N. caninum* and *T. gondii* and a potential common vaccine candidate to control two parasites [49]. An attenuated strain of *T. gondii* (mic1-3KO strain) conferring strong protection against chronic and congenital toxoplasmosis was used to protect mice against lethal *N. caninum* infection. Mice immunized with mic1-3KO tachyzoites by the oral and intraperitoneal routes developed a strong cellular Th1 response and displayed significant protection against lethal heterologous *N. caninum* infection, with survival rates of 70% and 80%, respectively, whereas only 30% of the nonimmunized mice survived [50]. The chicken MAb 6D-12-G10 demonstrated cross-reactivity with the tachyzoites of *N. caninum* and *T. gondii* [51]. This MAb (6D-12-G1-) reacted with the apical end of sporozoite of *C. parvum* and *C. maris* and merozoites of *C. parvum* as revealed by indirect immunofluorescent assay. Western blotting analysis revealed that MAb 6D-12-G10 reacted with the 48-kDa band of *C. parvum* and *C. muris* oocyst antigens. These results indicated that the target antigens recognized by this chicken MAb might have a shared epitope, which is present on the apical complex of apicomplexan parasites[52]. This epitope could be valuable as vaccine candidate against these apicomplexan.

CONCLUSION

Based on previously reviewed data, it could be concluded that cross-reaction is a widely spread phenomenon among parasites either they are taxonomically similar or different. It is attributed to the existence of common or cross-reactive antigens. One explanation of this phenomenon is that all parasites emerged from common components at the beginning of creation. With the evolution and under stress of host immune responses, some of these parasites acquired exclusive molecules to defend themselves against these responses. Therefore, the existence of common structures is the rule. Cross-reaction has a negative impact on accurate diagnosis. However, the utilization of monoclonal antibodies and pure fractions of parasitic extracts could participate in minimizing this drawback. Moreover, adoption of more sensitive techniques rather than conventional ones in the diagnosis or detection of parasite antigens or its DNA, also share in eliminating cross-reactivities in diagnostic assays. On the other hand, the fundamental significance of cross-reaction is the use of a protective or diagnostic antigen from one species potentially to be applied to another. This approach solves the problem of antigen scarcity. Furthermore, utilization of cross-reactive components in protecting animals against multiple infections, effectively participate in parasites control.

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