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Developments in anti-tick vaccines

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Abstract
The tick infestations lead to severe irritation of the animals, discomfort, pyrexia, paralysis, worry, toxicosis, anaemia and transmit the different haemoprotozoan diseases resulting in huge economic losses to the livestock industry worldwide due to their global distribution. Hence, most of the ticks in a dairy cattle or buffaloes and sheep-goat are controlled mainly by the chemotherapeutic agents called acaricides to increase the production and productivity of these animals. Chemical control, albeit predominant, has been hampered by poor utilization of active agents, indiscriminative utilization and sub-therapeutic dosages, thus leading to development of resistance and requiring the use of greater concentrations of active compounds and extra regular application, year by year. Moreover, due to the development of multidrug resistance in ticks in livestock, there is a need for development of the vaccines against the ticks. In the global market, different vaccines against bacteria and viruses are available but vaccines against the ticks are very few. Vaccines may help control ticks by non-chemical ways, thereby, reducing acaricide resistance. The release of commercial recombinant vaccine against the cattle tick *Boophilus microplus*, plays a significant role as a novel control measure of cattle ticks, due to the feasibility of vaccination. A number of factors create some hindrances to the progress towards usable, commercially available vaccines, thereby, limiting their use. However, Gavac and TickGard are available commercially worldwide. Vaccine candidates which act against tick vectors and pathogens transmitted by ticks, are discussed in the present communication.

Keywords: vaccine, gavac, tickgard, tick, livestock

Introduction

The ticks are responsible for huge economic losses to farmers throughout the world due to direct losses from parasitism of the ticks upon the host animal and from diseases vectored by the ticks. Brazil's and Australia's economies suffer annual losses of USD $2 billion and AUD $170 million, respectively, due to *R. microplus* parasitism of cattle [1, 2]. The United States eradicated cattle ticks in the 20th century and annual savings to their agricultural economy was estimated to be USD $3 billion in today's currency [3].

Two main approaches have been considered for tick vaccine development: the use of 'exposed' antigens and the use of 'concealed' antigens [4]. 'Exposed' antigens are those exposed naturally to the host immune system during tick infestation. These antigens are used to immunize the hosts by continuous boosting of tick exposure. 'Concealed' antigens are not exposed to the host immune system and, therefore, repeated immunizations are required to maintain elevated antibody titres.

Bm86, a protective antigen molecule is an 89KDa glycoprotein isolated from the gut tissue of the ticks and acts against *B. microplus*. The Bm86 is involved in intracellular response, acts as typical membrane bound receptor in conjugation with another membrane spanning protein and transduces signals from outside to inside of the cell. Based on this antigen**,** a recombinant vaccine against *B. microplus* has been commercialized as TickGard in Australia [5] and Gavac in Cuba [6]. The concealed Bm86 antigen has been expressed both in *Escherichia coli* and *Pichia pastoris*.

Three additional antigens have been identified *viz*. Bm91, BmA7 and Bm95 from *B. microplus.* Bm91 is 86 KDa molecule present in the salivary glands and gut of ticks. BmA7 is a 63 KDa**,** glycoprotein isolated from semi-engorged adult female ticks. It is located on the surface of the digestive cells of gut tissues, surface of both ovaries and salivary glands. Bm86, Bm91 and BmA7 are membrane bound glycoproteins. Geographic differences also exist

between different strains thus indicating variation in susceptibility to Bm86 based vaccine. The Argentine *B. microplus* has a 21 amino acid difference when compared to Australian Yeerongpilly Bm86 molecule. That is why the Argentine isolate has been renamed as Bm95 [7]. TickGard Plus vaccine comprises of *E. coli* expressed Bm86 and Bm91. Lysis of tick gut cells occurs as a result of the binding of anti-Bm86 antibodies along with other immune effector components like complements with subsequent leakage of material from the gut into the haemocoel. The resulting consequences of this host induced tick pathology are mortality of engorging adults with a more substantial effect upon tick reproductive performances. A Bm86 ortholog of *Hyalomma anatolicum anatolicum*, Haa86, was cloned and expressed by Azhahianambi *et al.* [8]. The vaccination of cattle with the recombinant Haa86 antigen can protect against homologous tick challenge as well as reduced tick transmission of *Theileria annulata*, thus protecting the animals against lethal exposure Jeyabal *et al.* [9].

'Dual action' tick vaccines

These vaccines employ such antigens which have properties of both exposed and hidden antigens like 64TRP.

64TRP

A 15 kDa protein from *R. appendiculatus*, 64TRP, was identified as a putative cement protein involved in attachment and feeding of ticks. The immune response to this 'exposed' salivary antigen cross-reacts with 'concealed' tick gut antigens, therefore, providing a dual action as a vaccine combines the advantages of both exposed and concealed antigens [10, 11]. Recombinant forms of *R. appendiculatus* 64TRP produce potent humoral and delayed type hypersensitivity reactions [10].

Tick vaccines directed against multiple tick species

Early experiments with *B. microplus* Bm86-based vaccines demonstrated cross-protection against *B. annulatus* and *B. decoloratus* infestations and conferred partial protection against *Hyalomma* spp. and *Rhipicephalus* spp. [12, 13, 14]. However, immunization with Bm86 failed to protect against *Amblyomma* spp. [14] and against some geographical strains of *B. microplus* [7, 15]. So, there is a need for discovery of more conserved tick-protective antigens that could be used to control infestations by multiple tick species in wide geographical areas.

Subolesin

Subolesin (4D8), a highly conserved protein involved in modulation of tick feeding and reproduction was discovered in *Ixodes scapularis.* Preliminary experiments using the recombinant *I. scapularis* subolesin (SUB) have shown a protective effect against *Dermacentor variabilis* and *A. Americanum* [16]. Phylogenetic analysis interpreted that SUB is an orthologue of Akirin.

Targeting both the tick vector and tick-borne pathogens

Although the efforts to develop vaccines against tick-borne pathogens constitute a separate research focus, targeting both the tick vector and pathogen will probably be a feasible and productive strategy. The recombinant Bm86 homologue antigen of *H. a. anatolicum*, rHaa86 and Tams 1 antigen of *T. annulata* were produced in *P. pastoris* and *E. coli*, respectively in the Division of Parasitology, Indian Veterinary Research Institute. A cocktail vaccine containing Tams 1 and rHaa86 antigens protected Indian cattle against *H. a. anatolicum* and *T. annulata* [17].

Transmission–blocking vaccines

These are those vaccines which block transmission and establishment of tick borne pathogens in the host like Salp15 and TROSPA.

Salp15

Salp15**,** a secreted salivary protein with host immune suppressive properties inhibits CD4+ T-cell activation [18], complement activity [19] and dendritic cell function [20]. The OspC, an outer surface protein is produced by *B. burgdorferi.* When ticks take a blood meal, the spirochetes start its synthesis in the midguts of infected ticks. Salp15 physically binds to OspC on *B. burgdorferi* spirochetes surface during exit from the salivary glands, facilitating the survival of spirochetes, pathogen transmission and host infection [21, 22]. The Salp15-OspC interaction potentially obscures OspC from the host immune response protecting the spirochete [21].

TROSPA

It is a tick receptor for *B. burgdorferi* OspA that has been identified in the tick mid gut [23, 24]. Tick-borne pathogens can acclimatize from the vector to the mammalian host through different gene expression. For example, outer surface proteins OspA and OspB are produced when Lyme disease spirochetes enter and reside in ticks [25] but they are down regulated during transmission to the host. Other genes which assist transmission from ticks and colonization of the host such as OspC and bba52 are upregulated. TROSPA expression is upregulated during *B. burgdorferi* infection and downregulated during tick engorgement. The physiological function of receptor is unidentified but binding of OspA to TROSPA is essential for *B. burgdorferi* to colonize the tick gut, thus supporting bacterial infection in the vector [23]. *B. burgdorferi* infection enhances expression of specific tick genes such as TROSPA and salp15 that can be targeted to prevent the transmission of *Borrelia* spirochetes and other tick-borne microbes [26]. Blocking TROSPA with TROSPA antisera or via RNA interference (RNAi) decreases *B. burgdorferi* adherence to the gut of *I. scapularis*, and results in reduction of bacterial colonization of the vector and, potentially, pathogen transmission to the host [23]. When bacterial OspA is used as a Lyme disease vaccine then it can block pathogen transmission as anti-OspA antibodies destroy the spirochetes in the tick gut before transmission to the host occurs [27].

Anti-Idiotype antibody vaccines and DNA vaccines have also been tried against ticks and have given some positive responses.

Other anti-tick vaccine candidates

Salp25D

Salp25D is expressed by *I. scapularis* salivary glands and midguts [28] and has homology to per oxi redoxin antioxidants [29].

tHRF

The tick histamine release factor (tHRF) from *I. scapularis* was characterized by Dai *et al.* [30]. tHRF is secreted in tick saliva, upregulated in *B. burgdorferi* infected ticks and it appears to have a role in tick engorgement and efficient *B. burgdorferi* transmission [30].

Schuijt *et al.* [31] identified the *I. scapularis* salivary protein TSLPI (Tick Salivary Lectin Pathway Inhibitor) that protects *B. burgdorferi* from direct killing by the host complement system.

Ferritins

Ferritins, the iron-storage proteins play an important role in the homeostasis of iron during tick feeding. Kopacek *et al*. [32] characterized a common heavy chain type ferritin 2[32], without functional orthologs in vertebrates as a gut-specific protein secreted into the tick hemolymph, where it acts as an iron transporter [33]. The number of workers emphasized its impending use as a future dual action tick and tick-borne diseases protective antigen candidate.

Serpins

Serpins are serine protease inhibitors of a large family of structurally related proteins found in a wide variety of organisms along with hematophagous arthropods. They are known to regulate many important functions such as blood coagulation, food digestion, inflammatory and immune responses [34] and, therefore, are attractive target antigens for tick vaccine development. Cocktail vaccine consisting recombinant *R. appendiculatus* serpins RAS-3, RAS-4 and a 36kDa immune-dominant protein RIM36, decreases tick infestations.

Voraxin

Voraxin is combination of two polypeptides triggering engorgement and ovarian development in *Amblyomma hebraeum.* This Voraxin has provided positive results in anti-tick vaccine trials [35].

New approaches for the identification of protective antigens

The recent technologies developed for gene discovery *viz*. expression library immunization and evaluation of expressed sequence tags show promise for systematic, rapid and global antigen screening and provide a widespread approach to selection of candidate vaccine antigens [36]. EST (Expressed sequence Tags), ELI (Expression Library Immunisation) and RNA Interference (RNAi) are the new approaches for the identification of protective antigens.

Immediate and Future research goals

- Recognition of new and novel antigens with the aim of protection against tick infestations using rapid screening methods such as ELI.
- Characterization of the genetic variability in tick strains that has evolved in extensively unconnected geographic regions and environmental conditions.
- Assessment of vaccine formulations against diverse tick species and in several animal hosts.
- Enhancement of anti-tick vaccines with new antigen formulations and delivery systems.
- The host immune response generated by vaccine antigens should be characterized.
- Knowledge of biological function and regulation of expression of antigens in vaccine preparations and the effect of vaccine induced antibodies on tick physiology and reproduction should be applied meticulously.
- Identification of antigens which block tick transmission pathogens followed by evaluation and characterisation of the effect of vaccination on the transmission of tick-borne pathogens [17, 35, 37].

Conclusion

There is an urgent need for development of highly efficient vaccines against ticks for their control and to reduce or substitute the use of acaricides, especially in the regions where extensive acaricide resistance in ticks has developed. Modern, new and proficient molecular technologies will greatly help towards the development of improved vaccines against ticks in near future by effective antigen discovery.

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