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Review Article

A REVIEW ON TICK VACCINE - CURRENT STATUS AND FUTURE PROSPECTIVE

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ABSTRACT: The conventional practice of tick management is mainly focused on treating the animals and animal shed with commonly available chemical acaricides. Yet, this method only provides a limited degree of success with several inherited pitfalls, such as acaricidal residues in meat and milk, biomagnification in the food web, selection of drug-insensitive ticks, and negative environmental impact from chemical residues. Vaccines provide an enticing alternative approach, but progress has stalled against these tenacious hematophagous arthropods. After over 30 years of vaccine research against tick and tick-borne pathogens, only a handful of native or recombinant antigen targets have been identified and evaluated as single-antigen vaccines, with inconsistent efficacy. In contrast, multi-antigen vaccines targeting several molecular functions may hold better potential for effective control in the field. However, challenges remain in ensuring consistent protein purity and expression scales, proper post-translational modification, and optimal immune responses. Therefore, epitope-based peptide vaccines that can stimulate protective immune responses represent a promising approach for tick vaccine development. Additionally, mRNA vaccines have recently emerged as an alternative vaccine platform with potential benefits in potency, speed of development, cost-effectiveness, and safety. Research continues to unlock new immunological intricacies and opportunities within ticks. Novel vaccine strategies may achieve a pivotal breakthrough against these pervasive arachnids and the dangerous diseases they spread.

Keywords: Tick Vaccine, Current status, Novel concepts.

INTRODUCTION

Ticks are next to mosquitoes as a vector of human pathogens and are the most potential vector for transmission of animal pathogens. The global economic losses due to ticks and tick-borne pathogens to the cattle industry have been estimated at 22-30 billion USD per annum [1]. Whereas, in India, the cumulative loss due to tick infestation was calculated as USD 595.07 million while due to TBDs USD 787.63 million [2]. Amongst the 107 tick species reported from India, *Hyalomma anatolicum* and *Rhipicephalus microplus* are extensively prevalent and considered as most important ixodid ticks infesting dairy animals [3].

The tick species *H. anatolicum* is the principal vector of *Theileria annulata*, *T. lestoquardi*, and *T. equi* [4, 5, 6]. It transmits *Theileria annulata* to over 250 million cattle in tropical and subtropical regions, causing tropical theileriosis which results in morbidity and mortality rates of over 40% and 90% respectively [7]. It also transmits Crimean-Congo hemorrhagic fever virus (CCHFV), which causes a zoonotic viral disease in humans with a case fatality rate of 10-40% [8]. CCHFV was first recognized in the Crimean Peninsula in 1944 and has infected over 3,000 people since 2000. It has now spread to over 30 countries across Africa, Asia, Europe, and the Middle East [9]. The virus is maintained in nature by ixodid ticks principally by the genus *Hyalomma*. [10]. Once the virus is acquired by the ticks, each of them remains infected with CCHFV throughout its lifetime, and the virus can be detected in the eggs and unfed larval stage (evidence of transovarial transmission of the CCHF virus) [11].

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Globally, *Rhipicephalus microplus* is considered the most economically important tick affecting cattle production. It is prevalent in tropical and subtropical regions of the world including South and Central America, Mexico, southern United States, South Asia, and Australia [12]. This tick species transmits bovine babesiosis and anaplasmosis, which cause significant morbidity and mortality in cattle. Economic losses are estimated at over $3 billion annually worldwide due to reduced meat and milk production, mortality, and expenses for tick control measures [13]. In India, *R. microplus* is the most widespread cattle tick, infesting over 80% of cattle populations [14]. It is responsible for transmitting bovine babesiosis and anaplasmosis to over 200 million cattle in the country. A 2006 estimate suggested the annual economic loss due to *R. microplus* infestation of cattle was $498.7 million in India [15]. The costs arise from reductions in milk yield, livestock weight gain, leather quality, mortality, and expenditures on tick control. The prevalence of chemical acaricide resistance in *R. microplus* populations has exacerbated economic losses [3]. Climate change is also projected to expand the suitable habitat range for *R. microplus* in India, allowing it to spread to more cattle in the country.

Tick control strategies rely heavily on repeated application of synthetic chemical acaricides on and off the host. Global acaricide sales amount to over $750 million annually [16]. However, continuous and indiscriminate use of these chemicals has led to widespread selection and establishment of acaricide resistance among ticks, with resistance reported in at least 20 countries [17-19]. In addition, acaricides have raised environmental and health concerns. These issues underscore the need for sustainable non-chemical alternatives, including the use of tick-resistant cattle breeds, biological control agents (biopesticides, Entomopathogenic nematodes), botanical acaricides, and anti-tick vaccines [20-22]. Of the different measures, immunization of animals against tick infestation is considered a very promising component of the integrated tick management system as the chances of development of resistance are remote [14].

History of tick vaccine

The concept of the tick vaccine was started in the year 1939 when Trager showed that repeated infestations of animals induce an acquired immune response against *Dermacentor variabilis* in guinea pigs and rabbits [23]. A similar type of response was observed when guinea pigs and rabbits were immunized against larvae of *D. variabilis* by injecting different tissue extracts of female ticks [24]. This immunity was measured by entomological parameters, *viz.*, rejection of challenged ticks, interference with feeding, feeding time, engorgement weight, and reproductive index. Allen [25] and Wikel and Allen [26] reported that a single *D. andersoni* infestation on guinea pigs conferred immunity in the form of a 20 % reduction of larval engorgement.

Several attempts have been made to immunize hosts with tick extracts. Kohler *et al.* [27] observed a reduction in the number of ticks maturing on a rabbit pre-immunized with salivary gland extract of *H. a. excavatum*, though the procedure proved to be fatal for three other rabbits used in the experiment. More satisfactorily, Schneider *et al.* [28] reported that immunization of tortoises by unfed nymph homogenate of *Amblyomma testudinis* prevented blood feeding by ticks. Allen and Humphreys [29] used two different antigens for the immunization of guinea pigs against *D. andersoni*, *i.e.*, antigen-I comprising extracts of mid-gut and reproductive organs and antigen II has all the internal organs. There was a significant reduction in the number of eggs laid by the ticks fed on the hosts immunized with antigen I than those from the control group, and no hatching was observed from the laid eggs. In the antigen II immunized group of guinea pigs, the effects were more since it restricted the tick engorgement and consequently restricted the egg production. It was reported that the antigens prepared from the fed (5 days) female ticks were effective while the antigens prepared from unfed ticks were nearly ineffective, suggesting that vital antigens were presented during the development process of ticks.

Earlier, the involvement of salivary proteins of *H. anatolicum* in hypersensitivity reaction as an indicator of resistance against homologous challenge in rabbits has been reported by Gill *et al.* [30]. Subsequently, a significant adverse effect on ticks fed on animals repeatedly infested with *H. anatolicum* was reconfirmed by Momin *et al.* [31] and Singh *et al.* [32]. Active immunization of rabbits with extracts of larvae resulted in significant protection against challenge infestation has been reported by Ghosh and Khan [33]. Further, a significant reduction of nymphs (91.3%) and adults (79.7%) fed on calves immunized with 39 kDa larval antigen [34] while 84.2%, 61.4%, and 58.7% rejection of larvae, nymphs, and adults, respectively, in ticks fed on animals immunized with 39 kDa nymphal antigen was reported [35]. Subsequently, Das *et al.* [36] used a mixture of 106.8 and 68 kDa antigens isolated from midgut extract of

H. anatolicum, and 74.4 % and 52.2 % decrease of challenged nymphs and adults, respectively, was reported. A significant DT % of 69 % and 52 % against larvae and adults of *H. anatolicum* and 60 % against *R. microplus* adults was reported by Singh and Ghosh [37] after immunization of animals with 34 and 29 kDa glycoprotein. Successively, the transmission-blocking potentiality of 37 kDa larval antigen of *H. anatolicum* was studied and recorded reduced levels of *T. annulata* infection in ticks fed on immunized calves compared to a control group of calves [38].

DIFFERENT TYPES OF VACCINES AND STUDIES FOR THE DEVELOPMENT OF TICK VACCINES

There are a few types of vaccines available - live-attenuated vaccines, inactivated vaccines, recombinant vaccines, mRNA vaccines, conjugate vaccines, subunit vaccines, viral vector vaccines, polysaccharide vaccines, and toxoid vaccines [39].

Recombinant vaccine

Practically, most of the individual native antigens and their recombinant constructs show inconsistent efficacy (Shown in Table 1). For instance, around 20 antigens have been characterized and reported to generate a protective immune response against ticks [40]. However, since 1994, the average level of protection induced by 17 native tick antigens inoculated in pure or recombinant form was in the range of 30-72%. Though variations in the efficacy of immunization protocol and the methods followed for the measurement of efficacy exist, none of them is likely proficient enough to be used as a single antigen vaccine.

Peptide vaccine

Inactivated or attenuated pathogens can activate strong and long-lasting immunity due to their capacity to induce both cellular and adaptive immune responses. Recombinant proteins utilizing different parts of the whole parasites are considered one of the attractive alternatives in the modern era for developing cross-protective vaccines [55]. However, it is not perfectly safe and economical, due to the problems associated with protein purities, difficulties in large-scale protein expression, problems with the inception of desired post-translational modification of the recombinant proteins, and poor or undesirable immune responses. Therefore, it is important to select the epitope-based peptide vaccine to trigger desired immune responses to develop a suitable vaccine [56]. These epitopes have having minimal immunogenic portion of the protein and thus allow for the proper direction of immune responses [57].

Peptide-based vaccine and its application

In general, the immune system of the host is not exposed to a single unique antigen but exposed to multiple diverse antigens of any pathogen or parasite. To date, this natural phenomenon has not been adopted in the development of peptide vaccines against ticks. The concept of multiple antigenic peptides (MAP) was first introduced by Tam [58], by demonstrating that MAP was highly effective in comparison to un-conjugated epitopes in inducing humoral immune responses [58]. In MAPs, the dendritic carriers presenting multiple copies of peptides ascertain the protection of peptides from premature degradation as well as enhance their recognition by the immune system [59]. To increase immunogenicity, various strategies have been exercised. For example, conjugation to carrier proteins, lipidation [60, 61], or fusion with particulate systems like liposomes [62, 63] or immunostimulating complexes. Another principally booming approach is multimerization which can be executed by simple polymerization [64] such as MAPs as explored by Tam [58]. The MAPs comprise a small immunologically non-reactive core of branched lysine dendrites where numerous peptide epitopes are linked. Recently, two MAP-based vaccines were constructed targeting neuropeptides that innervate salivary glands and the hindgut of *Ixodes ricinus* (SIFamide or myoinhibitory). The study was proved to be capable of eliciting protective immunity in mice and sheep against infestation of larvae or nymphs and *A. phagocytophilum*-infected nymphs, respectively [65].

Three synthetic peptides (SBm4912, SBm7462, and SBm19733) derived from *R. microplus* gut protein were used to vaccinate cattle, which were challenged with the larvae of *R. microplus*. A reduction of more than 81.05 % in the number of engorged female ticks was found [66] Another synthetic peptide, derived from the ATAQ protein, found in both gut and malpighian tubules of *R. microplus* was demonstrated to be efficacious against *R. microplus* (35%) and *R. sanguineus* (47%) [67].

Scoles *et al.* [68] developed three synthetic peptides from the previously predicted protein of RmAQP2. These peptides were conjugated to keyhole limpet hemocyanin (KLH) as a carrier molecule. Overall, there was a 25% reduction in the number of ticks feeding to repletion on the vaccinated cattle. Immune

sera from vaccinated cattle recognized native tick proteins on a western blot and reacted to three individual synthetic peptides in ELISA. The vaccinated calf with the highest total IgG response was not effective at controlling ticks. The ratio of IgG isotypes 1 and 2 differed greatly among the three vaccinated cattle; the calf with the highest IgG1/IgG2 ratio had the fewest ticks.

Table 1. Recombinant tick vaccine and its efficacy.

Tick species	Antigens	Protein identity	Vaccine efficacy %	References
Rhipicephalus appendiculatus	RAS-3, RAS-4	Serine protease inhibitor	39 and 48	[41]
R. microplus *R. annulatus*	RaFER2/RmFER2	Ferritin	64 and 72	[42]
H. anatolicum	HaFER2	Ferritin	51.7 and 51.2 against larvae and adults of *H. anatolicum* challenge infestations, respectively	[43] [43]
H. anatolicum	rHaTPM	Tropomyosin	63.7 and 66.4 against *H. anatolicum* larvae and adults infestations, respectively	
H. anatolicum	rHaCRT	Calreticulin	41.3 and 37.6 of against *H. anatolicum* and *R. microplus*, respectively	[44]
H. anatolicum	rHa-CathL	Cathepsin L	30.2 and 22.2, respectively against *H. anatolicum* and *R. microplus*	[44]
R. appendiculatus, R. sanguineus s.l.	64TRP	Cement protein	62 and 47	[45]
R. microplus	GP80/VIT87	Vitellin/Vitellogenin	68	[46]
R. appendiculatus	Voraxin- a	Tick mating factor	50 reduction egg wt.	[47]
R. microplus	BmLTI/BmTI/BmTI-A	Trypsin inhibitors	18, 32, 72	[48, 49]
H. dromedarii	GLP	Glycoproteins	63 reductions in egg hatch rates	[50]
R. microplus	Ef1a	Elongation factor	31	[51]
R. annulatus, R. microplus	Subolesin (4D8)	Regulator factor	0-83	[52, 53]
R. microplus, R. annulatus	UBE	Ubiquitin	15 and 55	[51]
R. microplus	GST-HI	Glutathione S transferase	57	[54]
R. microplus and R. annulatus	Chimeric vaccine BM95-MSP1a and SUB-MSP1a		60 against *R. microplus* and *R. annulatus* infestations in cattle.	[51]

Later, in 2023, Nandi *et al.* [69] developed and evaluated two in silico-designed anti-tick MEP (VT1 and VT2) to target both cellular and humoral immunity for the very first time. Following a challenge trial, the VT1 immunized group showed significantly lower ($p<0.001$) anti-inflammatory cytokine (IL-4) expression than the control group. Similar IL-4 reduction events were seen in the VT2 immunized group as well, however in both instances, control animals' IL-4 levels rose following challenge. The immunization trial, which demonstrated that VT2 had a stronger and longer-lasting protective antibody response than VT1, further validated these findings. The expression of Th-1 and Th-2 cytokines was also altered, with the former being up-regulated and the latter being down-regulated. Finally, entomological data also supported the hypothesis showing 93.3% and 96.9% efficacy produced by VT1 and VT2, respectively, against larval challenge. Whereas, the overall efficacy against adult challenge was 89.9% for VT1 and 86.4 % for VT2, respectively.

A new era in vaccinology - mRNA vaccines

mRNA vaccines represent a promising alternative to conventional vaccine approaches because of their

high potency, capacity for rapid development, and potential for low-cost manufacture and safe administration. However, their application has until recently been restricted by the instability and inefficient *in vivo* delivery of mRNA. Recent technological advances have now largely overcome these issues, and multiple mRNA vaccine platforms against infectious diseases and several types of cancer have demonstrated encouraging results in both animal models and humans. A new mRNA vaccine, however, may introduce a novel way to prevent the transmission of Lyme disease and other tick-borne illnesses: rather than target the pathogen, researchers hope to train the immune system to respond to the presence of tick saliva. Recently, one multi-antigen-based m-RNA vaccine formulation against *Ixodes scapularis* has been developed. Immunization of Guinea pigs with 19ISP-based mRNA vaccine followed by a challenge with *I. Scapularis* revealed formation of erythema following tick bite was observed in the animals, which were administered with 19ISP. The feeding period of challenged ticks was reduced, resulting in a reduction in engorgement weights [70].

Limitations and challenges

i) The existing anti-tick vaccines have limitations such as incomplete protection, limited efficacy against some tick species, and the need for multiple booster doses [71].

ii) Vaccine development faces challenges like antigenic variation in tick populations, limited cross-protection, and the high cost of recombinant antigen production [72].

iii) Most research has focused on *R. microplus* - vaccines effective against other major tick species are urgently needed.

Future prospects

i) Efforts are ongoing to identify new protective tick antigens through omics and bioinformatics approaches [73].

ii) New antigen delivery systems and adjuvants are being explored to enhance vaccine efficacy and duration [74].

iii) Multivalent vaccines incorporating multiple tick antigens show promise for improving cross-protection [75].

iv) Transmission-blocking vaccines targeting tick gut antigens can potentially prevent pathogen transmission [76].

v) Anti-tick vaccines could be integrated with biological control and host resistance for effective tick management [40].

In summary, anti-tick vaccines hold promise but significant research is needed to develop affordable and effective vaccines against multiple tick species and the pathogens they transmit.

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