Prospects for vaccination against the ticks of pets and the potential impact on pathogen transmission

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1. Introduction

Ticks are the most important vectors of emerging and re-emerging diseases of pets, many of which are potentially transmissible to humans (Glickman et al., 2006; Beugnet and Marié, 2009). Tick species such as Rhipicephalus sanguineus, Ixodes scapularis, Ixodes ricinus and Dermacentor reticulatus infest humans and pets and transmit disease-causing pathogens such as Borrelia spp. (Lyme disease and various borreliosis), TBEV (tick-borne encephalitis), Anaplasma phagocytophilum (human and canine anaplasmosis), Francisella tularensis (tularemia), Rickettsia spp. (human and animal rickettsiosis), OHFV (Omsk hemorrhagic fever), Babesia canis (canine babesiosis), and Ehrlichia canis (canine monocytic ehrlichiosis) (de la Fuente et al., 2008; Beugnet and Marié, 2009). Other arthropods such as mosquitoes, fleas and sand flies also transmit vector-borne diseases (VBD) affecting humans and pets (Day, 2011; Beugnet and Marié, 2009). Vector-borne infectious diseases of pets and humans are emerging or re-emerging as a result of ineffective control programs, demographic and societal changes and increasing acaricide/insecticide and drug resistance (Glickman et al., 2006). Vaccines have not been developed or successfully implemented for most VBD affecting humans and pets (Day, 2011). Therefore, control of arthropod vectors is important for the eradication of VBD (de la Fuente and Kocan, 2003; Speranc¸ a and Capurro, 2007; Karunamoorthi, 2011; Coller et al., 2012).

2. Vaccines for the control of arthropod vectors and vector-borne pathogens

Vaccination is an environmentally friendly alternative for the control of vector infestations and pathogen infections that allows control of several VBD by targeting their common vector (de la Fuente and Kocan, 2003, 2006; Willadsen, 2004; de la Fuente et al., 2007, 2011). The hypothesis behind vaccine action is that ectoparasites feeding on immunized hosts ingest antibodies specific for the target antigen that could reduce their levels and biological activity and/or interact with conserved epitopes in other proteins resulting in reduced feeding, developmental and reproductive performance, with a possible reduction in vector capacity (de la Fuente et al., 2006a, 2006b, 2011; Merino et al., 2011a, 2011b; Moreno-Cid et al., 2011, 2013; Bensaci et al., 2012). Therefore, the greatest vaccine effect is in the reduction of larval infestations in subsequent generations, which results in the reduction of ectoparasite populations and thus the exposure of susceptible hosts to vector infestations and VBD (de la Fuente et al., 2007). The limiting step in the development of tick vaccines is the identification of protective antigens (de la Fuente and Kocan, 2003). However, recent results have shown that it is possible to use vector protective antigens for the control of arthropod vector infestations and pathogeninfection (de la Fuente and Kocan, 2003, 2006; Willadsen, 2004; de la Fuente et al., 2006a, 2006b, 2007, 2011; Merino et al., 2011a, 2011b; Moreno-Cid et al., 2011, 2013; Bensaci et al., 2012; de la Fuente and Merino, 2013).

3. Vaccines for the control of arthropod vectors of pets

The growing interaction between pets and people underlines the importance of developing new interventions for themonitoring and control ofVBD (Glickman et al., 2006). However, very little progress has been made for the control of ectoparasite infestations and VBD of pets using vaccination with vector protective antigens. Recent developments in both ticks and tick-borne pathogen genomics and the study of tick-pathogen and tick-host interactions have advanced our understanding of the genetic factors and molecular pathways involved at the host-vector-pathogen interface (de la Fuente and Estrada-Peña, 2012; de la Fuente, 2012). These technologies are generating extensive information and suggested candidate protective antigens for the control of tick infestations affecting pets and humans (e.g. for R. sanguineus, Trimnell et al., 2005; Anatriello et al., 2010; Villar et al., 2010; Vancová et al., 2010; Rodríguez-Mallon et al., 2012). However, only three publications have reported results on vaccination trials in pets using vector protective antigens for the control of ectoparasite infestations. As discussed bellow, these trials were conducted on the most relevant host-tick model in dogs for the control of R. sanguineus infestations using three different antigen preparations,tick gut protein extract, Subolesin/akirin (SUB/AKR) and Bm86 (Szabó and Bechara, 1997; Canales et al., 2009; Perez-Perez et al., 2010).

3.1 Tick gut protein extract: The pioneering work of Allen and Humphreys (1979) demonstrated the feasibility of controlling tick infestations using vector protein extracts. Szabó and Bechara (1997) used this principle to demonstrate control of R. sanguineus infestations in dogs vaccinated with tick gut protein extracts. The most significant effect obtained in ticks fed on immunized dogs was the reduction in the number of ticks that laid eggs, thus showing a significant effect of the vaccine on reducing oviposition. Reduction in tick oviposition is one of the most important effects obtained with tick vaccines thatimpact on reducing tick populations in the field (de la Fuente and Kocan, 2003, 2006; Willadsen, 2004; de la Fuente et al., 2007).

3.2 Subolesin/akirin: SUB, initially named 4D8, was discovered as a tick protective antigen in a mouse model of I. scapularis infestations. SUB is the ortholog protein of insect AKR that have a broad function as transcription factors explaining the profound effect of gene knockdown by RNA interference (RNAi) on tick and insect physiology, as well as on development and gene expression in ticks (de la Fuente et al., 2006b, 2011). SUB/AKR are functionally important for arthropod immunity to pathogens and, at least in ticks for other molecular pathways, including those required for tissue development and function and for pathogen infection and multiplication (de la Fuente et al., 2011). SUB gene knockdown by RNAi resulted in sterile female and male ticks and was proposed as a method for tick autocidal control (de la Fuente et al., 2006c; Merino et al., 2011a). In different experiments, vaccination with SUB/AKR provided control for hard (Ixodes spp., Rhipicephalus spp., Amblyomma americanum, Dermacentor variabilis) and soft (Ornithodoros spp.) ticks, mosquitoes (Aedes albopictus), sand flies (Phlebotomus perniciosus), poultry red mites (Dermanyssus gallinae) and sea lice (Caligus rogercresseyi) infestations and tick infections with A. phagocytophilum, A. marginale, Babesia bigemina and Borrelia burgdorferi (de la Fuente et al., 2013; Merino et al., 2013).

These results suggested that vaccination with SUB reduces protein levels in feeding ticks by an unknown mechanism but probably mediated by antibody-antigen interactions in the cell cytoplasm (de la Fuente et al., 2011), which affects SUB translocation to the nucleus and/or function as a transcriptional regulator of its own expression and of genes involved in several biological processes playing an important role in tick feeding and reproduction and in pathogen infection (de la Fuente et al., 2011; Merino et al., 2013). These results suggest that SUB/AKR could be used to develop a universal vaccine against multiple arthropod vectors (de la Fuente et al., 2011). However, the results of the vaccine trial with recombinant A. albopictus AKR failed to demonstrate a significant effect of mosquito SUB ortholog protein against R. sanguineus infestations in dogs (Canales et al., 2009). The observed trend towards reduction of oviposition and nymphal and larval infestations (Canales et al., 2009) suggested that vaccination with R. sanguineus SUB might improve vaccine efficacy. In fact, in a preliminary unpublished trial, dogs living in the countryside (Alcolea de Calatrava, Spain) were vaccinated with SUB (two doses on weeks 1 and 5 and revaccinated a year after of the firstimmunization) by request oftheir owners.Animals were heavily infested with R. sanguineus. After vaccination many ticks did not complete feeding and animals remained protected (no need for acaricide treatment) for the next 24 months, suggesting that further experiments are required to evaluate the protective capacity of SUB vaccine against tick infestations in dogs.

3.3 Bm86: The protective antigen, Bm86, was obtained from the gut of semi-engorged Rhipicephalus (Boophilus) microplus adult female ticks (Rand et al., 1989). This antigen has been the only antigenthus far to beused inmarketed vaccines for the control of ectoparasite infestations (de la Fuente et al., 2007). Use of the recombinant Bm86 gut antigen in commercial vaccine formulations protected against cattle ticks, R. microplus, R. annulatus and R. decoloratus infestations and conferred partial protection against phylogenetically related Hyalomma and Rhipicephalus spp., but failed to protect against the more phylogenetically distant Amblyomma spp. (de la Fuente and Kocan, 2003, 2006). Perez-Perez et al. (2010) used Bm86 to vaccinate dogs experimentally infected with R. sanguineus larvae, nymphs and adults. The results showed a significant reduction in tick infestations for all instars and in female tick weight and oviposition, suggesting that vaccination with Bm86 could be used for the control of R. sanguineus infestations in dogs. Recently, a preliminary experiment in R. sanguineus demonstrated a synergistic effect of SUB and Bm86 knockdown (de la Fuente et al., 2006d), suggesting the possibility of combining these antigens to improve control of dog tick infestations.

4. Tick paralysis

Tick paralysis is not an infectious disease, but is worth briefly considering in this review because it is caused by ticks and it affects dogs and cats, livestock and in some cases, humans (Hall-Mendelin et al., 2011). This toxicosis is caused by neurotoxins produced by tick salivary glands and results in a rapidly ascending flaccid paralysis (HallMendelin et al., 2011). To protect against Ixodes holocyclus tick-induced paralysis, research has been directed towards developing a vaccine using a recombinant inactive form of the toxin (Masina and Broady, 1999; Bratu and Lutwick, 2002).

However, other tick species such as R. sanguineus may also cause paralysis in dogs and thus require development of prevention measures (Otranto et al., 2012).

5. Conclusions

Experiments with tick vaccines demonstrated that it is possible to controltick infestations using ectoparasite antigens. Commercial vaccines containing Bm86 demonstrated the possibilities oftick vaccines as part ofintegrated control programs to reduce cattle tick populations while reducing acaricide applications to prevent selection of resistant ticks and contamination with chemical residues. Recent results suggestthat structurally and functionally conserved arthropod antigens could be used to confer protection against multiple vector species and pathogen infection. The few vaccination experiments reported in dogs also suggest that vaccines with arthropod-derived antigens may be effective for the control of vector infestations in pets. Recently, new candidate tick protective antigens have been discovered that offer new possibilities for developing vaccines for the control of tick infestations and pathogen infection in animals (Merino et al., 2013; Hajdusek ˇ et al., 2013). Taken together, these results suggest that effective vaccines for the control of vector infections and VBD of pets could be developed with vector-derived antigen(s) alone or in combination with pathogen-derived antigens using the information obtained from the molecular characterization of the host-vector-pathogen interface.