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Editorial

Controlling ticks and tick-borne diseases…looking forward

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ABSTRACT

Tick-borne diseases (TBDs) represent a growing burden for human and animal health worldwide. Several approaches including the use of chemicals with repellency and parasiticidal activity, habitat management, genetic selection of hosts with higher resistance to ticks, and vaccines have been implemented for reducing the risk of TBDs. However, the application of latest gene editing technologies in combination with vaccines likely combining tick and pathogen derived antigens and other control measures should result in the development of effective, safe, and environmentally sound integrated control programs for the prevention and control of TBDs. This paper is not a review of current approaches for the control of ticks and TBDs, but an opinion about future directions in this area.

1. Current situation

Ticks (Acari: Ixodida) are vectors of pathogens causing diseases in humans, wild and farm animals worldwide (de la Fuente et al., 2008). The prevalence of tick-borne diseases (TBDs) has increased recently due to several biotic and abiotic factors (Jones et al., 2008; Gortazar et al., 2014; Estrada-Peña et al., 2014, 2017; Martina et al., 2017; Estrada-Peña and de la Fuente, 2017).

Several approaches including the use of chemicals with repellency and parasiticidal activity, habitat management and other personal and environment-based preventive and control measures, genetic selection of hosts with higher resistance to ticks, and vaccines have been implemented for reducing the risk of TBDs (de la Fuente and Contreras, 2015; Eisen and Dolan, 2016; Schorderet-Weber et al., 2017; Franzin et al., 2017; de la Fuente et al., 2017a; Sprong et al., 2018). However, difficulties such as tick resistance to acaracides, chemicals short-lasting effect and safety issues support that vaccines are the most effective and environmentally sound approach for the prevention and control of TBDs (de la Fuente et al., 2017a).

Currently, different experimental approaches are used for the identification of tick-derived and pathogen-derived protective antigens (de la Fuente et al., 2016a). These experimental approaches include (a) direct screening of protective antigens, (b) a rational approach for antigen selection based on tick and pathogen biology, (c) reverse genetics, (d) vaccinomics, and (e) targeting protein–protein interactions and conserved metabolic pathways (Almazán et al., 2003; de la Fuente and Kocan, 2003; de la Fuente et al., 2007, 2016a; Dai et al., 2009; de la Fuente and Merino, 2013; Merino et al., 2013; Gomes-Solecki, 2014; Šmit and Postma, 2015a, 2015b; de la Fuente and Contreras, 2015; Contreras et al., 2017a, 2017b). However, only the *Rhipicephalus microplus* BM86 or BM95 recombinant antigens became commercially available in vaccines for the control of cattle tick infestations with an effect on reducing the prevalence of certain tick-borne pathogens (TBPs) (de la Fuente et al., 2007; Rodríguez-Mallon, 2016; Valle and Guerrero, 2018). A vaccine based on these antigens is still available in various Latin American countries for the control of cattle tick infestations (Rodríguez-Mallon, 2016). Vaccines for the control of tick-borne encephalitis, Louping ill, Spanish goat encephalitis, Lyme disease, and Crimean-Congo hemorrhagic fever have been developed with different efficacy and safety (Richer et al., 2014; Gomes-Solecki, 2014; Šmit and Postma, 2015a, 2015b). However, despite these advances new vaccines are required for the reduction of tick infestations and effective and safe prevention and control of TBDs.

2. Future directions

A multidisciplinary approach is necessary for the control of TBDs and other infectious diseases (Fig. 1). Some basic information is still incomplete with regards to TBDs. For example, it is important to better understand the evolution and function of tick-host-pathogen interactions through the application of latest omics technologies and Koch's postulates to characterize tick vector competence and the pathogenicity of microorganisms found in ticks (de la Fuente et al., 2017b; Sonenshine and Macaluso, 2017). However, many of these experiments would require access to BSL3/BSL4 facilities that are not available in many institutions. Other areas that require attention due to their possible impact on the control of TBDs include characterization of tick vector and pathogen geographical distribution and life cycle (Estrada-Peña and de la Fuente, 2016), genetic factors that make hosts susceptible or resistant to tick infestations and TBDs (Anderson et al., 2017; Tabor et al., 2017; Robbertse et al., 2017), pathogen control of tick/host cell epigenetics for transcriptional reprogramming (Sinclair et al., 2014; Cabezas-Cruz et al., 2016a; Dumler et al., 2016), the application of metagenomics,

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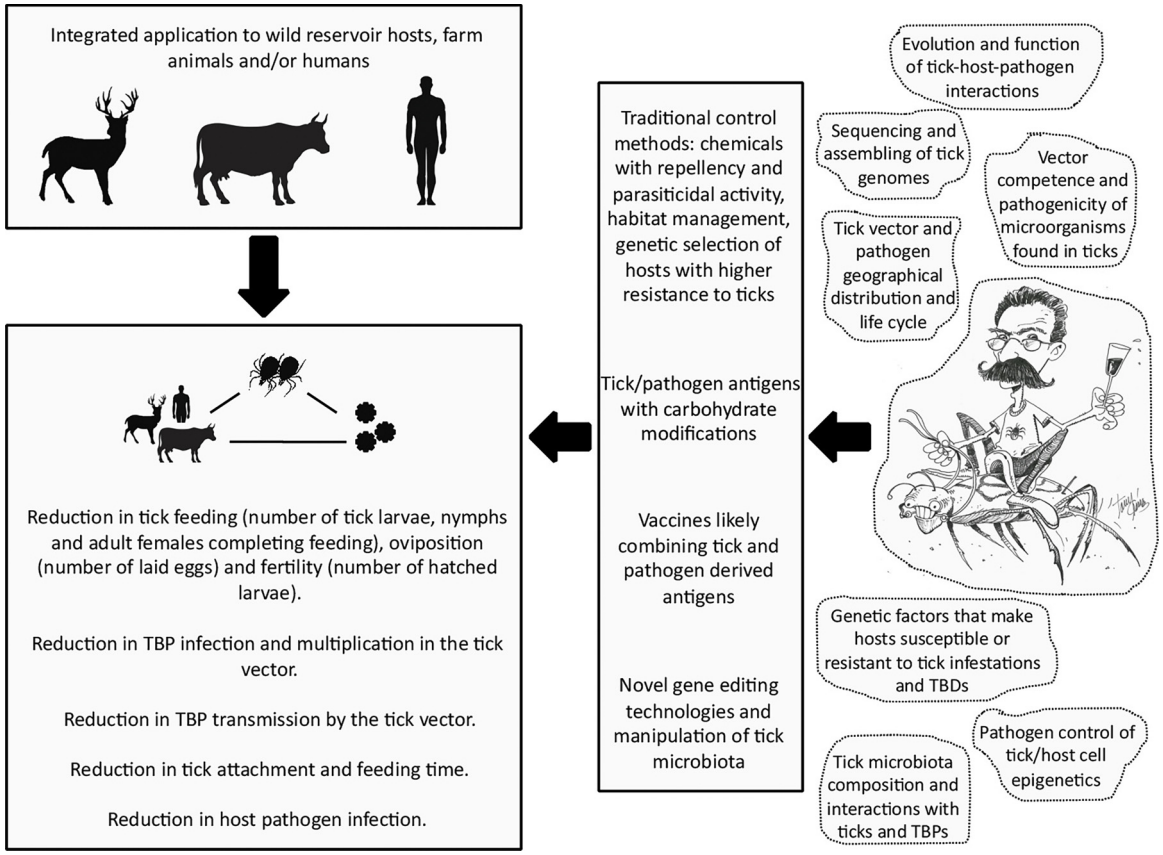

Fig. 1. Proposed future directions for the integrated control of tick infestations and TBDs. Addressing basic biological questions of tick biology and tick-host-pathogen interactions would advance the possibility of developing new control strategies for TBDs. The traditional tick control methods in combination with new effective vaccines likely combining tick and pathogen derived antigens, and gene-editing technologies would lead research for the development of new integrated interventions. These interventions could be applied to wild reservoir hosts, farm animals and/or humans to target different stages of tick and pathogen life cycles for efficient, safe and environmentally sound control of tick infestations and TBDs. Credits for the drawing: Antonio Gómez Ruiz, KGJ Colección, Ciudad Real, Spain.

metaproteomics and metabolomics for the characterization of tick microbiota composition and interactions with ticks and transmitted pathogens (Narasimhan and Fikrig, 2015; Abraham et al., 2017; Bonnet et al., 2017), and the sequencing and assembling of tick genomes using new DNA sequencing technologies (Lavín and Anguita, 2018) to aid in a better integration of omics datasets using a system biology approach (Villar et al., 2015; de la Fuente et al., 2016b). The recent publication of the first tick genome corresponding to the Lyme disease vector, *Ixodes scapularis* has provided evidence that these results will facilitate the characterization of tick-pathogen and tick-host interactions, and the identification of protective antigens (Ayllón et al., 2015; Villar et al., 2015; Gulia-Nuss et al., 2016; de la Fuente et al., 2016b, 2016c, 2016d; Kim et al., 2016; Abraham et al., 2017; Shaw et al., 2017; Oliva Chávez et al., 2017; Cabezas-Cruz et al., 2017a; Contreras et al., 2017a, 2017b; Hoxmeier et al., 2017; Villar et al., 2017).

Recently, we proposed a method for the evaluation of the risk of TBDs and vaccine efficacy (de la Fuente et al., 2017a). This approach in combination with latest omics technologies and focusing on biological processes involved in tick-host, tick-pathogen and host-pathogen interactions would allow the identification and combination of tick-derived and pathogen-derived protective antigens affecting tick infestations, tick pathogen infection and transmission, tick attachment and feeding, and/or host pathogen infection (de la Fuente et al., 2017a). Vaccines based on these antigens and producing a long-lasting immunity could then be used to prevent or reduce tick infestations and pathogen infection and transmission in wild reservoir hosts, domestic animals, and humans (de la Fuente et al., 2017a). These vaccines should be designed considering the tick vector species, TBPs, and reservoir and affected hosts, and could be used alone or in combination with other control measures for the control of TBDs (de la Fuente et al., 2017a). Additionally, research should focus not only on the discovery of protective antigens but also on antigen combinations and design for control of multiple tick/pathogen species, the characterization of vaccine protective mechanisms, optimization of vaccine formulations (i.e. antigen dose, adjuvant composition, vaccination scheme, injection route), establishing correlates of vaccine efficacy, and modeling vaccine efficacy to optimize conditions to control tick infestations and TBDs (de la Fuente and Contreras, 2015).

In 2006, we highlighted the importance of protein glycosylation in development of novel tick vaccine strategies (de la Fuente et al., 2006a). Recent results have shown that most bacteria and parasites causing major infectious diseases, including TBDs such as Lyme disease produce the Galactose-alpha-1,3-galactose (α-Gal) epitope exposed on their surface (Cabezas-Cruz and de la Fuente, 2017). These results together with the fact that during evolution humans lost the ability to synthesize α-Gal resulting in the production of high antibody titers against this carbohydrate, suggested the possibility of using probiotics or other α-Gal-containing vaccines to induce a protective immunity to α-Gal to neutralize the pathogens with α-Gal on their surface for the prevention and control of infectious diseases (Almeida et al., 1991; Yilmaz et al., 2014; Cabezas-Cruz et al., 2016b; Moura et al., 2017; Cabezas-Cruz and de la Fuente, 2017). If effective, these vaccines would constitute an effective intervention for the control of multiple infectious diseases with high prevalence worldwide (Cabezas-Cruz et al., 2017b).

However, the inactivation in primates of the gene responsible for the α-Gal synthesis might have occurred in response to the selection pressure exerted by pathogens that produce α-Gal. Therefore, the capacity of the human immune system to respond to pathogens producing α-Gal evolved with the tradeoff of the α-Gal syndrome (AGS) (Cabezas-Cruz et al., 2015). The AGS associated with the anti-α-Gal IgE immune response is a tick bite-induced allergy to red meat and tick bite that is