Biologia (2022) 77:1533–1554
https://doi.org/10.1007/s11756-021-00966-9

REVIEW

Prevention of tick-borne diseases: challenge to recent medicine

Dominika Hromníková[1] · Daniel Furka[2,3] · Samuel Furka[2,3] · Julio Ariel Dueñas Santana[4] · Táňa Ravingerová[3] · Vanda Klöcklerová[1] · Dušan Žitňan[1]

Received: 16 June 2021 / Accepted: 10 November 2021 / Published online: 9 March 2022

Abstract

Ticks represent important vectors and reservoirs of pathogens, causing a number of diseases in humans and animals, and significant damage to livestock every year. Modern research into protection against ticks and tick-borne diseases focuses mainly on the feeding stage, i.e. the period when ticks take their blood meal from their hosts during which pathogens are transmitted. Physiological functions in ticks, such as food intake, saliva production, reproduction, development, and others are under control of neuropeptides and peptide hormones which may be involved in pathogen transmission that cause Lyme borreliosis or tick-borne encephalitis. According to current knowledge, ticks are not reservoirs or vectors for the spread of COVID-19 disease. The search for new vaccination methods to protect against ticks and their transmissible pathogens is a challenge for current science in view of global changes, including the increasing migration of the human population.

Highlights

- Tick-borne diseases have an increasing incidence due to climate change and increased human migration
- To date, there is no evidence of transmission of coronavirus COVID-19 by tick as a vector
- To date, there are only a few modern, effective, and actively- used vaccines against ticks or tick-borne diseases
- Neuropeptides and their receptors expressed in ticks may be potentially used for vaccine design

Keywords Tick-borne disease · Vector · Vaccine · Neuropeptides · COVID-19

Abbreviations

TBEV	Tick-borne encephalitis virus
LB	Lyme borreliosis
TBE	Tick-borne encephalitis
TBPs	Tick-borne pathogens
OspA	Outer surface protein
TROSPA	Tick receptor for outer surface protein A
TSLPI	Tick mannose binding lectin inhibitor
tHRF	Tick histamine release factor
Salp15	Salivary gland protein of 15 kDa
CCHF	Crimean-Congo haemorrhagic fever
SUB	Subolesin
TBF	Tick-borne fever
ompA	Outer membrane protein A
AipA	Infection protein A
dsRNA	Double stranded RNA
MIP	Myoinhibitory peptide
SIFa	SIFamide
TK	Tachykinin
AT	Allatotropin
AST-A	Allatostatin A
ILP	Insulin-like peptide
PDF	Pigment dispersing factor
Elev	Elevenin

✉ Dominika Hromníková
hromnikova.d@gmail.com

[1] Department of Molecular Physiology, Slovak Academy of Sciences, Institute of Zoology, Dúbravská cesta 9, 84506 Bratislava, Slovakia

[2] Faculty of Natural Sciences, Department of Physical and Theoretical Chemistry, Comenius University, Mlynská dolina, Ilkovičova 6, 84104 Bratislava, SK, Slovakia

[3] Department of Cardiovascular Physiology and Pathophysiology, Slovak Academy of Sciences, Institute of Heart Research, Dúbravská cesta 9, SK 84005 Bratislava, Slovakia

[4] Chemical Engineering Department, University of Matanzas, Km 3 Carretera a Varadero, 44740 Matanzas, CU, Cuba

Introduction

In recent years, modern medicine and biology have focused their attention on tick-borne diseases, the incidence of which is increasing due to factors such as climate change, but also increased human and animal migration. We classify ticks among obligate ectoparasitic hematophagous arthropods capable of transmitting various viruses, bacteria, or parasites (Hoogstraal 1981). They usually use the blood of reptiles, birds and mammals as a source of food. Ticks belong to the Arthopoda phylum, subphylum Chelicerata comprising the Arachnida class with several subclasses; while the subclass Acari includes ticks (Anderson and Magnarelli 2008). Most Ixodidae prefer mammals and birds; however, for example *Ixodes ricinus* (Linnaeus, 1758) and *Amblyomma* sp. also feed on reptiles (Dantas-Torres et al. 2008; Rizzoli et al. 2014). Due to climate change, some tick species, e.g. *I. ricinus* are moving to higher geographical locations, up to altitudes above 1000 m (Medlock et al. 2013). *Ixodes* spp. and *Dermacentor* spp. are questing, i.e. passively waiting on the vegetation until their host approaches. On the other hand, *Amblyomma* spp. and *Hyalomma* spp. are actively looking for their host.

Ticks are ectoparasites with high reproductive potential and a wide host range. They transmit the widest range of pathogens, including viruses, bacteria and protozoa, collectively called tick-borne pathogens (TBP) to humans and animals, often endangering human life, but also the lives of livestock (Parola and Raoult 2001; Anderson and Magnarelli 2008; de la Fuente et al. 2008a, b; Dantas-Torres et al. 2012; Brites-Neto et al. 2015). Transmission of the pathogen to the host is enabled through the tick salivary glands and gut (Šimo et al. 2017; Pospisilová et al. 2018). TBPs are thus taken up by ticks during their feeding on infected hosts. From the midgut, TBPs pass through the gut epithelium to the hemocoel, from where they can further penetrate into the SG epithelium, where they multiply and are transmitted to a new host through saliva (Šimo et al. 2017; de la Fuente et al. 2017a, b; Kurokawa et al. 2020).

The global number of cases of tick-borne diseases is increasing every year (Silatsa et al. 2019; Muhanguzi et al. 2020). While tick-borne diseases are a serious problem, especially for the human population in Europe and Northern America, they also pose a significant threat to livestock production in sub-Saharan Africa, Latin America, and Asia. The European Parliament has expressed concern about the spread of Lyme borreliosis (LB) as a major risk to public health (Sprong et al. 2018). Based on the spread models for LB and tick-borne encephalitis (TBE), an increase in infection risk is expected (Paules et al. 2018). Other tick-borne diseases, such as anaplasmosis, rickettsiosis, babesiosis, theileriosis and others, have also emerged and spread in new regions (Vayssier-Taussat et al. 2015; de la Fuente et al. 2017a, b; Gharbi et al. 2020). Recently, a huge threat to the economy and agriculture are ticks of the genus *Ornithodoros*, which transmit African swine fever with a mortality of almost 100% (Gaudreault et al. 2020).

Ticks induce skin damage in vertebrates and counteract haemostasis and inflammation (Chmelař et al. 2016). Without external suppression, these processes would cause tick rejection, disrupt food intake, and arrest development. For this reason, ticks have evolutionarily- developed sophisticated defence strategies. For example, tick saliva contains proteins that inhibit haemocoagulation (Prevot et al. 2016; Decrem et al. 2008), modulate angiogenesis (Chmelař et al. 2016) and affect normal defensive functions of B-cells, T-cells and dendritic cells (Anguita et al. 2002; Hannier et al. 2004; Hovius et al. 2008a, b).

These are all reasons why we need to pay attention to the issue of ticks, the diseases they transmit, treatment and also prevention in the form of vaccines. The aim of the present review is to summarize current knowledge on vaccines against ticks with emphasis on novel approaches in vaccine design based on disrupting the regulation of the tick digestive mechanisms.

Vaccination against ticks and tick-borne diseases

Tick antigen-based vaccines

Acaricides are a commonly-used and effective measure to combat ticks. As significant resistance of ticks to these substances has recently been reported (Rodríguez 2016; Rodriguez-Vivas et al. 2018), including the accumulation of acaricides in the environment and animal products (Abbas et al. 2014), the scientific community has focused on searching for new control measures against these ectoparasites. An anti-tick vaccine is based on the presumption that the host develops immunity to the tick and thus prevents it from feeding on the host blood. The first proposal was published in 1939 (Trager 1939). After many decades, the first anti-tick vaccine targeting the gut protein Bm86 of the cattle tick *Rhipicephalus* (*Boophilus*) *microplus* (Canestrini, 1888) was developed (Kemp et al. 1989; de la Fuente et al. 1999).

One option in identifying potential anti-tick vaccines is to analyse antigens using the RNA interference (RNAi) method. Although RNAi is a method used primarily to study genes that affect important physiological functions, these genes may not be immunogenic (Aljamali et al. 2002). Antigens are screened by this method for sequence identity,

directly in the transcriptome or cell proteome (Antunes et al. 2019). It is possible to use a so-called cocktail vaccine against several tick antigens at the same time—the advantage of which is usually higher efficacy (Sherrard-Smith et al. 2018). This type of broad-spectrum vaccine also makes it possible to establish protection against several tick species (Ndawula and Tabor 2020). However, in the case of the use of cocktail vaccines, there may be an undesirable reduction in antibodies to related types of antigens, which may significantly reduce the effectiveness of vaccination (Ndawula and Tabor 2020).

The study of the role of proteins found in tick saliva has become a powerful tool in vaccine design in the prevention of tick-borne diseases, because saliva creates the pathway of pathogen transmission into the host blood (Labuda et al. 2006). Tick saliva is a carrier medium for the transmission of pathogens (Nuttall and Labuda 2008). Anti-tick vaccines have been designed based on the observation that some mammals were able to develop immunity against tick-feeding after being bitten (Anguita et al. 2002). At the same time, it has been found that the highest probability of pathogen transmission by ticks is during their contact with a naïve host, i.e. a host that has never had ticks before (Leboulle et al. 2002). The reason why vaccination against ticks is crucial is due to the fact that it is easier to vaccinate against ticks than against every possible pathogen they transmit.

One of the most widely used vaccines is the Gavac™ vaccine, which was developed against the cattle tick in Cuba. The vaccine reduces tick infestation by reducing the ability to feed and by preventing females from reproducing (de la Fuente et al. 1999). It is a recombinant vaccine based on the gut protein Bm86 of *B. (R.) microplus* (Willadsen et al. 1995). The antibodies recognize the Bm86 protein present in the tick gut cells to which they bind and form irreversible lesions that damage the gut wall. A secondary consequence in tick females is reduction in oviposition leading to infertility (Rand et al. 1989; Rodríguez et al. 1994; Rodríguez et al. 1995a, b). In an animal clinical study, almost 600,000 dairy cattle were vaccinated, and the use of the vaccine reduced the number of clinical cases of babesiosis from 54 to 1.9 cases per 1,000 cattle. Accordingly, the mortality rate dropped from 6 to 0.18 cases per 1000 cattle, making the vaccine one of the strongest tools for preventing the economic loss caused by babesiosis (Valle et al. 2004). Gavac™ is based on the same peptide as the older Australian vaccine named TickGard(PLUS). In a comparative study of IgG antibody levels, it was found that the protective efficacy of these vaccines was 49.2% for Gavac™ and 46.4% for TickGard(PLUS) (Andreotti 2006). In the case of vaccination using TickGard(PLUS), the tick reproduction index was reduced by 72% under laboratory conditions and infestation of vaccinated cattle (Jonsson et al. 2000).

In this paper, we deal with tick-borne diseases as follows: viral, bacterial, protozoan, and focus mainly on zoonotic pathogens and the current state of vaccine availability against them. The work is mainly focused on pathogens that cause diseases in humans. Theileriosis and babesiosis were also added because they are very important from the economic point of view, causing significant economic damage.

Viral diseases

Crimean-Congo haemorrhagic fever

Crimean-Congo haemorrhagic fever (CCHF) is a severe viral disease transmitted by ticks with an incubation period of less than seven days and a mortality of up to 50% (Ergonul 2006). It occurs in Asia, Africa, and Europe. The name is derived from a combination of the names „Crimea “, the location where the disease was first described, and „Congo “, where the virus was isolated from a febrile patient (Chumakov 1949). The disease is caused by a ssRNA nairovirus, CCHF virus. The disease is transmitted by ticks of the genus *Hyalomma* (family Ixodidae), in particular *H. marginatum* (Koch, 1844). The main targets of the virus are mononuclear phagocytes, mucous membranes, and hepatocytes (Burt et al. 1997).

The disease begins suddenly with fever, headache, shoulder and back pain, vomiting, and diarrhea may also occur (Hoogstraal 1979a, b). The affected person has a reddened face, congested conjunctiva and pharynx, sometimes with minor bleeding. Bleeding from the gums, nose, lungs, bladder, and intestines occurs in severe forms of the disease (Hoogstraal 1979a, b). However, these symptoms affect only a small percentage of patients. Nevertheless, the prognosis is uncertain in all cases. It is possible to predict the fatal development of the disease on the fifth day of infection. The cut-off blood parameters for this assay are: platelets $< 20 \times 109$ / L, aspartate aminotransferase > 680 U/L, fibrinogen < 110 mg/dl or less (Ergonul et al. 2006). On the seventh day of infection, a haemorrhagic phase occurs. Death occurs on the tenth day. The disease can be confirmed by PCR, similar to other diseases (Mazzola and Kelly-Cirino 2019).

There is no vaccination against the disease (Table 1), and there has been no significant progress in the treatment of the disease in the last ten years. Fortunately, hope for a mRNA vaccine was described in 2020 (Tipih and Burt 2020).

Tick-borne encephalitis

TBE is a viral inflammation of the brain. It is a seasonal disease for which no effective treatment is known. The first case was described by the Austrian, H. Schneider, in 1931

Table 1 Overview of tick-borne diseases

Disease	Pathogen	Principal vectors	Vaccine
Crimean-Congo haemorrhagic fever	ssRNA nairovirus, CCHF virus	Ixodidae: *Hyalomma marginatum*	no vaccination
Tick-borne encephalitis	Tick-borne encephalitis virus	Ixodidae: *Ixodes ricinus, I. persulcatus*	FSME-IMMUN, Encepur, EnceVir
Lyme borreliosis	*Borrelia burgdorferi, B. afzelii, B. garinii*	Ixodidae: *Ixodes ricinus (B. afzelii, B. miyamotoi), I. persulcatus (B. afzeli, B. garinii), I. scapularis (B. burgdorferi), I. pacificus (B. burgdorferi)*	no vaccination
Anaplasmosis	*Anaplasma phagocytophilum*	Ixodidae: *Ixodes ricinus, I. persulcatus, I. scapularis*	no vaccination
Tick-borne rickettsiosis	*Rickettsia rickettsii, R. peacockii, R. montana, R. rhipicephali*	Ixodidae: *Dermacentor variabilis (R. rickettsii, R. montana, R. rhipicephali), D. andersoni (R. peacockii), Rhipicephalus sanguineus (R. rickettsii, R. loxicephali), Amblyomma americanum (R. rickettsii)*	no vaccination
Babesiosis	*Babesia divergens, B. microti, B. bovis*	Ixodidae: *Ixodes ricinus, I. scapularis, R. microplus*	Gavac™ (*R. microplus*)
Theileriosis	*Theileria annulata, T. parva, T. equi*	Ixodidae: *Dermacentor variabilis (T. equi), Rhipicephalus sanguineus (T. parva), Hyalomma* species *(T. annulata), R. appendiculatus (T. parva), Amblyomma americanum*	Mugaga (*T. parva*)

as "meningitis serosa epidemica" of unknown etiology (Schneider 1931).

We now know that the disease is caused by the tick-borne encephalitis virus (TBEV) of the genus *Flavivirus* with three known subtypes, which most often enter the body after the attachment of an infected tick or the consumption of raw milk from infected sheep, cows, and goats. The virus subtypes are named after the geographical origin and include the European subtype (TBEV-Eu), the Siberian subtype (TBEV-Sib), and the Far East subtype (TBEV-Fe) (Süss 2011). The vector of TBEV-Eu is *I. ricinus*, while the remaining two subtypes are transmitted mainly by *I. persulcatus* (Schulze, 1930) and *I. ovatus* (Neumann, 1899) (Süss 2011). These species of ticks play a key role in the spread and epidemiology of the disease (Gresikova and Kaluzova 1997; Labuda and Randolph 1999).

The reservoir hosts of the virus are mainly rodents. There is no human-to-human transmission. The individual subtypes differ in terms of symptoms at an early stage. TBEV-Fe causes various chronic diseases, with the frequency of meningeal and focal forms not exceeding 26% and 64%, respectively (Pogodina et al. 2004). Complete recovery from the disease occurs in 25% of all cases (Ternovoi et al. 2007). Mortality reaches up to 30% (Dumpis et al. 1999). In the case of TBEV-Sib, focal encephalitis accounts for 5% of cases, while meningeal forms up to 47% of cases. Complete recovery occurs in more than 75% of infected patients and mortality is less than 2% (Pogodina et al. 2004). TBEV-Eu, with an incubation period of 7 to 28 days, causes an atypical influenza-like disease lasting approximately 4 days. Symptoms include fever, joint pain, headache, leukocytopenia, thrombocytopenia, and elevated liver enzymes as common symptoms. This is followed by an asymptomatic phase which lasts one week, and 70% of patients do not develop further symptoms. However, meningitis, meningoencephalitis, meningoencephalomyelitis, or meningoencephaloradiculitis occur in 30% of patients. Specific antibodies are found in cerebrospinal fluid. Mortality in adults is less than 2%; however, only a small proportion of patients recover completely from the disease without chronic neurological sequellae (Mickiene et al. 2002; Lindquist and Vapalahti 2008).

There is, however, an effective, three-dose, antigenic vaccine (Table 1) (FSME-Immun) that was developed in Austria against TBEV-Eu, which was approved as early as 1976 (Kunz

et al. 1976). The reason why Austria was the first to initiate vaccine development is the fact that this country had the highest mortality from TBE of all European countries (Kunz 2003). To date, the vaccine has undergone several modifications (Zent and Bröker 2005), using human albumin (source) to stabilize it. Its efficacy in adults (Loew-Baselli et al. 2006) and children under 15 years of age is close to 100% during the first year. Antibodies in the body of both adults and children remain active after three years and provide protection up to 94%—98% (Loew-Baselli et al. 2011).

A newer alternative (approved in 1994) to FSME-Immun is the German vaccine Encepur, which is intended for protection against TBEV-Eu. It does not currently contain any stabilizers (Amicizia et al. 2013). Its efficacy is almost 100% during the first year (Schöndorf et al. 2007), but has improved long-term protection, representing up to 98% after 5 years of vaccination (Schöndorf et al. 2007). No pharmacokinetic interaction between FSME-Immun and Encepur vaccines has been demonstrated, and therefore, both vaccines are routinely administered concomitantly (Prymula et al. 2012) with recommended revaccination after 5 years (Plentz et al. 2009).

Effective vaccines against TBEV-Sib and its subfamily are produced in Russia, including TBE Moscow Vaccine® against the Sofjin strain (TBEV-Fe), as well as the strain-based EnceVir (TBEV-Fe 205). However, to date, no randomized studies have been performed on these vaccines and therefore, their licenses are valid only in Russia. Efficacy is 84%—92% one year after vaccination (Krasilnikov et al. 2004).

State-of-the-art vaccines against TBE focus on the processes that take place immediately after the tick has been attached to the host. One possibility is to focus on the formation of the cement cone, which fixes the tick in the skin of the host. The 64P cement protein identified in *Rhipicephalus appendiculatus* (Neumann, 1901) is a suitable candidate for the preparation of broad-spectrum anti-tick vaccines (Rego et al. 2019) because its homologues are highly conserved in various ticks. The recombinant 64TRP vaccine based on the 64P cement protein significantly reduced the transmission of TBEV by *I. ricinus* in the laboratory mouse model. Immunized animals developed inflammatory and immune reactions at the tick-bite site, which counteracted tick feeding. The protective effect of this vaccine was comparable to FSME-Immun (Labuda et al. 2006). In addition to restricting tick feeding, there is a cross-immune reaction with antigenic epitopes of the tick midgut. A cross-immune response leads to gut rupture and subsequent tick death (Trimnell et al. 2002).

Bacterial diseases

Lyme borreliosis

LB is caused by spirochetes of the *Borrelia burgdorferi* sensu lato (s.l.) (Burgdorfer et al. 1982) complex, predominantly in the Northern hemisphere (Rosa et al. 2005; Rizzoli et al. 2011; Steere et al. 2016). It is the most common disease transmitted by ticks. The name "Lyme disease" historically comes from the epicentre of infected children in the American city—Old Lyme (USA, CT), where the disease was first described as a separate entity, despite the fact that scientific evidence has been found since the early twentieth century (Heyman et al. 2010). The incidence of the disease is dominant in northern and temperate climates. Dominant vectors are ticks of the *Ixodes* genus. In Europe, it is *I. ricinus* (Hofhuis et al. 2017) and in Asia, *I. persulcatus* (Rumer et al. 2011), while in the USA, *I. scapularis* (Say, 1821) and *I. pacificus* (Cooley and Kohls, 1943) (Hahn et al. 2016).

A typical manifestation of the disease is a migratory and gradually increasing inflammatory spot—erythema migrans in the skin around the tick bite area. However, 30% of people with LB do not develop erythema (Marques 2015). Therefore, the diagnosis and subsequent treatment are more difficult. Up to 20% of people have symptoms that persist for up to a year after overcoming the disease (Marques 2008). Multisystemic inflammatory symptoms of the disease begin 2 to 30 days after infection.

From a diagnostic point of view, serological determination is not possible at an early stage. The only indicators are clinical manifestations of the disease and a positive tick-bite history. However, the later stages can be determined from intrathecal fluids and blood. In the case of early treatment, treatment with doxycycline, penicillin antibiotics, or azithromycin is possible (Steere 2001) If left untreated, severe heart, CNS, and bone-joint problems develop within a few years (Steere 2001; Steere et al. 2016). If the nervous system is affected, intravenous treatment with Ceftriaxone for 2.5 weeks is recommended. Geographically, symptoms are different in Europe from the US due to the occurrence of different *Borrelia* genotypes on different continents (Steere 2001; Fingerle et al. 2008). In Europe, reservoir hosts of *B. burgdorferi* s.l. include hares, rodents (especially for *B. afzelii*), and insectivores, as well as several species of birds (especially for *B. garinii*) (Gern 2008). Spirochetes are inactive in the tick during the entire fasting period; however, after feeding, they multiply in the midgut, from where they migrate within 48 h from the start of feeding to salivary glands (Piesman and Dolan 2002; Wormser et al. 2007).

With early removal of the tick, no significant disease transmission has been demonstrated. Preventive treatment is only used for patients with ticks removed more than 24 h after attachment. Standard anti-*Borrelia* vaccines are based on an immunogenic protein of the bacterium and are therefore geographically linked due to the diversity of *Borrelia* genotypes and cannot be used anywhere in the world.

After infection of *I. scapularis* larvae, the spirochetes migrate to the midgut. The transfer of *Borrelia* and its establishment in the gut is enabled by the interaction of the

outer-surface protein A (OspA) of *Borrelia* with the tick receptor for outer surface protein A (TROSPA) (Pal et al. 2004). From the midgut, spirochetes are transported to the salivary glands and subsequently to the host (Dunham-Ems et al. 2009). The transmission of the genospecies *B. afzelii* in *I. ricinus* has not yet been clearly elucidated (Pospisilova et al. 2018, 2019). Expression of Salp15, OspA, TSLPI, and tHRF proteins in the tick ensure spirochete transmission and survival in the host (Wagemakers et al. 2016). A candidate for vaccine production is the salivary gland protein Salp15, which binds to the outer surface protein C (OspC) found on the surface of *B. burgdorferi* (Ramamoorthi et al. 2005). Salp15 has been shown to promote *B. burgdorferi* infection (Dai et al. 2009). Salp15 homologues identified in *I. ricinus* do not have the same function to increase the infectivity of *B. afzelii* and *B. garinii* (Hovius et al. 2008a, b). Administration of Salp15 antiserum has been shown to provide significant protection against *Borrelia* in mice. The combination of Salp15 and OspA increases the effectiveness of immunization (Dai et al. 2009). Salp15 inhibits T cell activation by binding to the CD4 co-receptor on host T cells. Subsequently, calcium flux induced by IL-2 and TCR production is repressed (Garg et al. 2006; Boulanger 2018; Wen et al. 2020).

An OspA-based vaccine was developed by LYMErix TM (Fikrig et al. 1990), but was later withdrawn from the market due to its epitope with lymphocyte function-associated antigen 1 (LFA1). Subsequently, vaccines lacking the described epitope have been developed (Comstedt et al. 2017).

The most modern approach in vaccination against LB is a six-component vaccine based on OspA-ferritin nanoparticles, which was developed by Czech scientists in 2020 and partially prevents the transmission of *B. afzelii* and *B. burgdorferi* sensu stricto. Its efficacy has been tested and demonstrated in mice (Kamp et al. 2020).

At the same time, the possibilities of limiting the transmission of the pathogen by influencing the metabolic pathways of the tick are being investigated. A tick mannose-binding lectin inhibitor (TSLPI) has been identified in the salivary glands of *I. scapularis* (Schuijt et al. 2011). A TSLPI homologue in *I. ricinus* has also been identified (Wagemakers et al. 2016). TSLPI inhibits mannose binding lectin (MBL) activity. Decreased TSLPI expression or immunization caused a significant reduction in *Borrelia* host infection (Schuijt et al. 2011). Therefore, anti-TSLPI antibodies are considered effective in combating this spirochete infection (Hofhuis et al. 2017).

A possibility to influence the transmission of *Borrelia* from ticks to the host is the histamine release factor (tHRF), which is located in the salivary glands and the midgut of *I. scapularis* (Dai et al. 2010). The tick produces this factor to reduce the itching of the attachment site, thereby making it inconspicuous to the host. Histamine causes the activation of pro-inflammatory cells after the tick has attached. Its level at the site of attachment decreases along with the degree of tHRF expression (Monteiro and Bechara 2008). Treatment using RNAi of tHRF has been shown to reduce the weight of the feeding ticks (taking up less blood) while reducing *B. burgdorferi* infection. A similar result has previously been achieved by active immunization of mice using recombinant tHRF and passive transmission of tHRF antiserum (Dai et al. 2010; Wada et al. 2010).

In recent years, studies have been performed on the relationship between *B. afzelli* infection and the salivary molecules such as Ixodegrin, lipocalin, and basic tail protein. Although these molecules have been shown to be associated with *B. afzelli* infectivity, no significant reduction in infection has been demonstrated in mice when vaccinated with their recombinant forms (Trentelman et al. 2020).

Anaplasmosis

Granulocytic ehrlichiosis, later called human granulocytic anaplasmosis (HGA), is caused by the bacterium *Anaplasma phagocytophilum* (Foggie, 1949) (Rickettsiales). There are very few cases of anaplasmosis in humans in Europe, and more in the United States. In Europe, the bacterium is important especially from a veterinary point of view, as it causes the so-called tick-borne fever in cattle. (Stuen et al. 2013).

HGA is manifested by vomiting, fever, urinary truss, but also by neurological disorders and heart rhythm disorders as well. The disease occurs 10 to 12 days after infection. The bacterium attacks neutrophils and causes thrombocytopenia, leukopenia, and increases in liver enzymes GOT and GPT (Bakken and Dumler 2000, 2015). Death has been observed mainly in immunodeficient patients (Bakken and Dumler 2000; Dumler et al. 2001; de la Fuente et al. 2016).

Ixodes ricinus is the vector for *A. phagocytophilum* in Europe (Heyman et al. 2010), *I. scapularis* in America (Turck et al. 2019) and *I. persulcatus* and other *Ixodes* spp. in Asia (Dugat et al. 2015). In most cases, the nymph stage is responsible for the transmission of this disease (Gray 2002). The characteristic transmission of *A. phagocytophilum* is horizontal, i.e. from the infected host to the tick, where it passes from the gut to the salivary glands and subsequently infects a new host (Telford et al. 1996). There are many strains of the bacterium in Europe, having many different animal species as their reservoirs, however, the competence of rodents as reservoirs is questionable. It has been proven that reservoirs in an urban environment can be, e.g., domestic dogs and birds (Silaghi et al. 2008; Massung et al. 2006; Paulauskas et al. 2009). *Anaplasma phagocytophilum* can infect domesticated and wild animals and was detected in cattle and deer (de la Fuente et al. 2005a, b; Naranjo et al. 2006). Some strains are pathogenic to carnivores, others

to cattle or sheep, but most are not pathogenic to humans. That is why the number of cases of human anaplasmosis in Europe is so low compared to the USA (Stuen et al. 2013). In the United States, the *Peromyscus leucopus* (Rafinesque, 1818) mouse is the reservoir for the pathogenic strain of the bacterium and the deer *Odocoileus virginiansus* (Zimmermann, 1780) is the reservoir for the non-human pathogenic bacterial strain (Massung et al. 2005).

In the USA, the infection has a mortality rate of 9%, while no deaths have been documented in Europe (Bakken and Dumler 2000, 2015). The reason for this difference is still unclear, despite frequent serological evidence of the disease in European residents (van Dobbenburgh et al. 1999; von Loewenich et al. 2003; Amiel et al. 2004; Heyman et al. 2010). Interestingly, in acute European cases, the presence of morulae in granulocytes (a hallmark of patients in the USA) has been reported in only 30% of patients (Heyman et al. 2010). The infection may be persistent in patients (Dumler and Bakken 1996). Symptomatic patients suspected of having HGA should receive immediate antibiotic therapy with Doxycycline (Wormser et al. 2007).

There is currently no vaccine (Table 1) against diseases caused by *A. phagocytophilum* (Stuen et al. 2015). However, an outer membrane protein (OmpA) of the bacterium has been detected. Antigen therapy against OmpA has shown reduced ability of *A. phagocytophilum* to infect host cells (Ojogun et al. 2012). The invasive proteins, AipA and Asp14, which provide permeability of the host cell, were also detected. The use of antisera against these proteins has significantly reduced the infectivity of the bacterial culture (Seidman et al. 2014).

The peptides, Salp16, P11, and lipocalins, which were detected in the salivary glands and gut of *I. scapularis* and are involved in the tick-pathogen interaction ensuring the survival of *A. phagocytophilum*, have also been described relatively well and could serve as perspective vaccine targets. Expression of Salp16 is induced in the salivary glands of the tick after interaction with *A. phagocytophilum*. The bacterium migrates from the infected host to the gut of the tick and subsequently to the salivary glands, from where it can infect the new host. By suppressing Salp16 expression, bacteria are unable to infect the salivary glands of *I. scapularis* and subsequently the host (Sultana et al. 2010). The peptide P11 has been shown to improve the uptake of *A. phacocytophilum* by *I. scapularis* haemocytes. Infected haemocytes are subsequently transported to the salivary glands (Liu et al. 2011). Lipocalins, which include inhibitors of the lectin pathway of the complement, have also been discovered in recent years in saliva of *I. scapularis* and a homologue was discovered in *I. ricinus* (Beaufays et al. 2008; Schwarz et al. 2013). Lipocalins are a family of proteins that play an important role in tick feeding. They are excreted in saliva. By binding to histamine or serotonin, they protect ticks from host immune and inflammatory reactions (Paesen et al. 2000; Valdés 2014). The expression of lipocalins is associated with tick infectivity, yet the exact mechanism of action is still unknown (Contreras et al. 2017).

Tick-borne rickettsioses

Rickettsia are intracellular alpha-proteobacteria transmitted to humans by arthropod vectors, predominantly fleas and hard ticks (Portillo et al. 2015; Eremeeva and Dasch 2015). The most known disease caused by *Rickettsia* is endemic typhus (*R. typhi*) (Wolbach and Todd, 1920), which is transmitted to humans from rodents by fleas (Robinson et al. 2003). In addition to typhus, pathogenic *Rickettsia* transmitted by ticks cause spotted fever in humans. Many other *Rickettsia* and *Rickettsia*-like species have been identified in tick organs, but their pathogenicity is still unknown (Parola et al. 2005).

Depending on the locality in which the spotted fever was identified, an adjective was added to the disease, e.g., Mediterranean fever, African fever, Rocky mountain fever, and so on. The vectors of these pathogens are, e.g., *Dermacentor variabilis* (Say, 1821), *Dermacentor andersoni* Stiles, 1908, *Rhipicephalus sanguineus* (Latreille, 1806) and *Amblyomma americanum* (Linnaeus, 1758), in which transovarial transmission of the pathogens occurs (de la Fuente et al. 2017a, b). Due to the significant difference in genotypes across geographical locations, it is necessary to specify the type of disease in patients according to their travel history before further treatment (De Sousa et al. 2003).

Spotted fever is a disease accompanied by fever, lymphadenopathy, and numerous rashes all over the body. Symptoms start on the tenth day after the tick bites. Mortality from the disease has previously been studied in Portugal in a study of 105 patients and accounted for up to 32% (De Sousa et al. 2003). Serological examination can determine the presence of the disease up to two weeks after infection. The diagnosis is therefore based on clinical signs at an early stage.

In the case of *Rickettsia*, the tick is not only a vector, but also a permanent reservoir. Therefore, since there is no effective vaccine against the disease, prevention and the use of antibiotics are the most important options (Botelho-Nevers et al. 2012; Sahni et al. 2013). Standard treatment involves high doses of doxycycline or tetracycline (Dantas-Torres 2007). Mortality increases with delay in treatment and is caused by multiorgan failure. It has been shown that it is possible to acquire infection with several species of *Rickettsia* from one vector; however, one species of *Rickettsia* can block another one in the host during the disease (Macaluso et al. 2002).

Attempts to develop a vaccine against *R. rickettsii,* the causative agent of Rocky Mountain spotted fever, based on killed bacteria did not reduce indicators of mortality from

this disease (Walker 2009). *Rickettsia rickettsii* infect cells by endocytosis (Petchampai et al. 2015) through actin-based motility (Ireton 2013). Potential new vaccination options are being studied on the actin-related protein 2/3 complex (Arp2/3), which is part of the actin cytoskeleton of eukaryotic cells (Petchampai et al. 2015). It is this complex that is involved in the interaction and infection with various *Rickettsia* species (Petchampai et al. 2014).

Protozoan diseases

Babesiosis

Babesiosis is a very common disease in livestock, but disease in humans in Europe is rare (Hunfeld et al. 2008). *Babesia divergens* (M'Fadyean and Stockman, 1911) is transmitted from natural reservoirs to humans mainly by *I. ricinus* (Zintl et al. 2003; Bock et al. 2004); however, humans are not their natural hosts (Yabsley and Shock 2012). In contrast, in the USA human babesiosis is common and is caused mainly by *Babesia microti* (Franca, 1910), with *I. scapularis* as its main vector (Yang et al. 2021). In subtropical and tropical regions, *Babesia bovis* V. Babes, 1888 and *B. bigemina* (Smith and Kilborne, 1893) Wenyon, 1926 causing disease in cattle, are mainly transmitted by *Rhipicephalus* spp. (Wise et al. 2014).

The causative agents of the disease are single-cell blood parasites—babesiae (Apicomplexa, Sporozoea, Piroplasmida, Babesiidae), which mainly attack the red blood cells of the host, as well as other cells of the reticuloendothelial system. *Babesia bovis,* for example, accumulates and multiplies in the lumen of the tick gut (Piesman et al. 1986). In the case of penetration into erythrocytes of the vertebrate host, they multiply asexually (Mehlhorn and Shein 1984).

Since babesiosis occurs in both humans and cattle, it is considered a medical threat and an economic danger to the agricultural industry (Bock et al. 2004). *Babesia bovis* causes the greatest loss to meat and milk production (Gohil et al. 2013).

The severity of the disease in humans varies significantly, depending on the type of babesia. The disease can be asymptomatic to fatal, depending on the patient's immunity and comorbidities (Zintl et al. 2005; Gray 2006). A severe form with concomitant fever, jaundice, and haemolytic anaemia is symptomatic of malaria. Despite being a rare disease in Europe, it has gained scientific interest through high mortality (Vannier et al. 2015).

The onset of infection is manifested by fatigue, headache, fever, and gastrointestinal problems (Hunfeld et al. 2008). With the progressive destruction of erythrocytes, haemoglobinuria to hepatitis can also occur (Gray 2006). In the more severe forms, renal dysfunction, myocardial infarction, disseminated intravascular coagulation, or acute respiratory failure may occur as well. Transmission of the parasite is also possible within the tick from a fertilized female to eggs (transovarian transmission) (Zintl et al. 2003).

At present, there is no vaccination against babesia (Table 1). The only currently- available method of protection against babesiosis in cattle is the Gavac™ vaccine (see above) against the tick, *R. microplus*, which reduces tick infestations by reducing the ability to feed, as well as preventing females from reproducing (de la Fuente et al. 1999). However, the general efficacy of a vaccine based on Bm86 varies and depends on the heterogeneity of the Bm86 gene between strains of *R. microplus* (Kaewmongkol et al. 2015). Subsequent experiments have shown that the Bm86 homologue in *I. ricinus* is not a suitable target for vaccine design as it did not provide any adequate immune response (Coumou et al. 2015). This is explained by the fact that *R. microplus* and *I. ricinus* ticks have different life cycles and susceptibility to gut damage (de la Fuente et al. 2007).

Theileriosis

Although theileriosis is not a disease of medical concern, it is a very important veterinary problem. Tropical theileriosis is a disease caused by the pathogens *Theileria annulata* (Dchunkowsky and Luhs, 1904) and *Theileria parva* (Theiler, 1904) (Bettencourt, Franca & Borges, 1907) and the vectors of these pathogens are ticks of the genera *Rhipicephalus* and *Hyalomma* (Ouhelli and Pandey 1982; Mustafa et al. 1983; Ouhelli 1985). In ticks of the genus *Hyalomma*, *Theilleria* pass transstadial transmission, from the larva to the adult tick (Bhattacharyulu et al. 1975). Theileriosis causes serious economic problems not only in African but also in Asian countries (Minjauw and Mcleod 2003; Cicek 2009; Gharbi et al. 2011). *Theileria parva* causing East Coast fever occurs in Sub-Saharan Africa and its main vector is *R. appendiculatus* (Dolan 1989). *Theileria annulata* causing tropical theileriosis occurs in northern Africa, southern Europe, the Middle, East, South and some parts of Asia and is transmitted mainly by *Hyalomma* species (George et al. 2015; Kumar et al. 2016; Dandasena et al. 2018).

Theileria go through three stages in their life cycle and each developmental stage elicits a different specific immune response (Pipano and Shkap, 2000). Sporozoites of *T. annulata* occur in salivary glands of ticks, schizonts are found in monocytes (macrophages) and lymphocytes (Sager et al. 1998), and merozoites in erythrocytes of the vertebrate hosts (Pipano and Shkap 2006). The most serious damage to cattle is caused by the schizont stage. The schizonts react with the microtubules of the host cells and divide with the host cell during mitosis, thus ensuring the persistence of the infection. In the case of long-term cultivation of lymphoid cells that are infected with schizonts, their virulence is lost, i.e.

schizonts from the blood elicit a stronger immune response than cultured ones (Pipano and Shkap 2000). It is against this stage that attenuated vaccines have been developed in many countries around the world (Gupta et al. 1998; Darghouth 2008). *Theilleria annulata* affects livestock, mainly cattle and buffaloes (Darghouth et al. 2011). For example, in untreated calves, daily live weight gain was found to be reduced by 14.7% and milk yields of only 0.7 L per day were also registered (Gharbi et al. 2011).

Currently, acaricides as well as vaccination with attenuated *T. annulata*-infected cell lines are used to control the spread of infected ticks (Gharbi et al. 2011; Darghouth et al. 2011; Mhadhbi et al. 2010; Bilgic et al. 2019). For example, the attenuation of the Tunisian cell line infected with *T. annulata* schizonts protected almost 90% of Holstein cattle (Darghouth 2008). Although attenuated vaccines may even have an efficacy of about 100% in homologous parasites, their efficacy decreases in heterogeneous ones (Darghouth et al. 1996). Veal breeds in Sudan immunized with attenuated *T. annulata* only protected cattle from possible death (El Hag 2010). Importantly, not all live vaccines can eliminate the infection, they can only reduce the risk of tropical theileriosis (Gharbi et al. 2020).

Both *Theileria* species mentioned above are transmitted through tick saliva, infect lymphocytes and form macroschizonts in the vertebrate host. This causes uncontrolled cell proliferation and immortalization (Spooner et al. 1989; Zweygarth et al. 2020). The disease they cause has the same or similar phenotypic characteristics as cancer (Tretina et al. 2015). Parvaquone, later Buparvaquone (McHardy and Morgan 1985; Kinabo and Bogan 1988) was initially used to treat the disease, with an efficacy of 88.7%. Parvaquone had an efficiency of 60.7% (Hashemi-Fesharki 1991). However, currently development of resistance to this drug has been observed (Mhadhbi et al. 2010, 2015; Marsolier et al. 2015; Chatanga et al. 2019). Infection caused by *T. parva* is controlled with the help of the mentioned drugs but also with the help of vaccines. One of them is the life sporozoite vaccine cocktail Mugaga. This vaccine is a combination of three parasite isolates (Mugaga, Serengeti and Kiambu 5) that should produce immunity in cattle (Hemmink et al. 2016). However, the efficacy of this vaccine was not sufficiently high (Sitt et al. 2015). This may be due to the limited diversity of the vaccine (Hemmink et al. 2016; Steinaa et al. 2018; Bilgic et al. 2019; Roy et al. 2019, 2021).

Ticks and COVID-19 transmission

In December 2019, a serious pneumonia disease, SARS-CoV-2, developed in *Rhinolophus affinis* (Horsfield, 1823) bats and spread around the world in a short time. Ticks have been suggested as one of the vectors of this disease (Aghajani et al. 2020; Villar et al. 2020). They could, for example, transmit the virus to pets, dogs, or cats. However, these pets are dead-end hosts and do not pose any risk of transmitting this pathogen to humans. Ectoparasitic cat fleas could be another SARS-CoV-2 rescuer (Villar et al. 2020). Other results suggest that passive transmission of the virus is also possible by contact with surfaces that are contaminated with SARS-CoV-2 (Lam et al. 2021). This is also due to the stability of the virus (Goldman, 2020; Fernández-de-Mera et al. 2021).

To date, however, there is no reliable evidence that ticks or other ectoparasitic arthropods are involved in transmission of COVID-19 coronavirus infection (Wormser et al. 2021).

Potential targets exprimed in tick digestive system for novel vaccine research

Understanding the regulation of the tick's digestive mechanisms is currently the most powerful tool for combating the tick as a parasite. For example, the *B. burgdorferi* spirochaete is a highly motile pathogen that is able to move through host tissues and fluids (Nakamura 2020). If ticks are feeding on an infected host, the pathogens use chemotaxis and migrate toward or away from a chemical stimulus and as a result, transmission of the infection occurs (Murfin et al. 2019). It is the tick gut that is the primary site of pathogen colonization (Sharma et al. 2019) and can avoid the immune response of ticks and other hosts (Smith et al. 2016; Shaw et al. 2017). The spirochetes remain in the gut lumen during tick feeding and subsequently pass into the salivary glands (De Silva and Fikrig 1995).

Tick salivary gland secretions are essential for suppressing host immune responses (Bishop et al. 2002; Trimnell et al. 2005). The salivary glands form clusters of three types of acini: the agranular acini type I, which do not change in size during food intake and the granular acini type II and III, which increase in size with food intake. They are involved in the synthesis of bioactive components and the excretion of excess water and ions (Binnington 1978; Krolak et al. 1982). Saliva production is regulated by central neuropeptides present in innervation of the salivary glands from the synganglion (Šimo et al. 2013, 2014).

Neuropeptides

Neuropeptides and peptide hormones belong to the signalling molecules that control cellular communication in all multicellular organisms (Garczynski et al. 2019). Neuropeptide production begins with the synthesis of an inactive precursor molecule in the endoplasmic reticulum. Subsequently, this precursor is transported to the Golgi

apparatus and secretory granules are formed there. These secretory granules are transported from the Golgi apparatus by endocytosis. Secretory vesicles contain precursor proteins with convertases that cleave bioactive peptides from the precursor molecule (Hökfelt et al. 2000). The finished signalling molecules act on target cells through interaction with specific membrane receptors, for example G-protein coupled receptors (GPCRs) (Hewes and Taghert 2001). Tick neuropeptides are suitable target molecules for the design of vaccines or drugs that regulate the transmission of pathogens into the host's blood. However, because some arthropod neuropeptide sequences are similar to those in mammals, it is necessary to exclude the effects of antibodies to the homologous sequences of mammalian peptides when selecting a target antibody to a particular tick neuropeptide. In ticks, neuropeptides are produced by neurosecretory cells, interneurons of the central nervous system (CNS), as well as motor and sensory neurons, but also by endocrine cells of the intestine and cells of other peripheral organs (Schoofs et al. 2017). Insects temporarily store neuropeptides in their neurohermal organs of the retrocerebral complex: *corpora cardiaca* (CC) and *corpora allata* (CA) and transverse nerves from where they are secreted into the haemolymph (Stay and Tobe 2007). They are produced in the form of prepropeptide precursors that are post-translationally cleaved and modified in the endoplasmic reticulum (Baggerman et al. 2005). The size of mature peptides in insects is 5 to 80 amino acids.

The regulation of cellular mechanisms by neuropeptides is complex. One neuropeptide can perform multiple functions. Conversely, multiple neuropeptides may be involved in the regulation of a single process (Schoofs et al. 2017). For a closer look, some immunoreactive neuropeptides found in various species of ticks are further described, which are also studied as potential "target" molecules for defence against the transmission of pathogens to the host. Initial application studies of neuropeptides in vaccine production were performed by Almazán et al. (2020). The effect of multiple antigen peptide (MAP) was tested based on the neuropeptides MIP and SIFamide, on the fitness and development of *I. ricinus* and on the transmission of pathogens. However, at first, it is necessary to find out where and how these neuropeptides are expressed. Most neuropeptides are produced by specific neurons in the synganglion, but a few regulatory peptides are also produced by enteroendocrine cells in the midgut (Šimo et al. 2009b, 2014). Specific peptidergic neurons innervate the salivary glands or hindgut and regulate activity of these organs during feeding of the tick on the host (Šimo et al. 2009a, b, 2012; Šimo and Park 2014; Roller et al. 2015; Kim et al. 2019). Anti-MIP antibodies can affect the moulting of *I. ricinus* larvae to nymphs (Almazán et al. 2020). Appropriate modulation of neuropeptide signalling may be an effective strategy for tick control (Ogden et al. 2007). We propose that the following neuropeptides might be involved in this research.

Allatotropin

Allatotropin (AT) has been identified in vitro as a stimulator of juvenile hormone (JH) biosynthesis in corpora allata (CA) in adult pharate females of *Manduca sexta* (Linnaeus, 1763) (Manse) (Kataoka et al. 1989). In addition to acting on CA, it accelerates the heart rate (cardioaccelerator function) (Koladich et al. 2002), stimulates the vibration of the ventral membrane, regulates movement, prevents ion transport through the middle intestinal epithelium and controls the release of digestive enzymes in the insect's midgut (Truesdell et al. 2000; Elekonich and Horodyski 2003; Weaver and Audsley 2007) and many others. AT and related neuropeptides regulate myoactive functions, development, food intake, muscle contractions, cardiovascular functions, circadian rhythms and inhibit ions (Bednár et al. 2017). AT has a myostimulatory effect at low concentrations and increase the amplitude of peristaltic movements (Duve et al. 1999). The pleiotropic function of AT peptides is indicated by the expression profile of the allatotropin receptor (ATR). ATR is highly expressed in the insect CA. The effect of AT on CA is mediated by Ca^{2+} phosphoinositide signalling (Rachinsky and Tobe 1996). To date, AT was found to elicit immune responses in two important vectors of pathogens, mosquitoes *Aedes aegypti* (Linnaeus, 1762) and *Anopheles albimanus* (Wiedemann, 1821) (Hernández-Martínez et al. 2017). The role of AT signalling may be expected in blood feeding ticks as well. AT immunoreactivity has been detected in the tick *R. appendiculatus* (Table 2, Fig. 1) in a number of synganglion neurons, as well as in peripheral nerves (Šimo et al. 2009a). A gene encoding ATs was identified in the genome of *I. scapularis* (Table 2, Fig. 1) (Šimo et al. 2014).

Allatostatin A

The main roles of insect allatostatins-A (AST-A) are myoinhibitory effects on internal organs, inhibition of endocrine functions and suppression of feeding (Duve et al. 1999; Bendena et al. 1999; Hergarden et al. 2012). Allatoregulatory peptides, including allatostatin A, B and C, are involved in the process of regulating tick feeding through the regulation of juvenile hormone in insects (Aguilar et al. 2003; Stay et al. 1992). AST-A in ticks was detected (Table 2) in peptidergic neurons in the synganglion and enteroendocrine cells in the midgut (Šimo et al. 2014). Some of the neurons (OsHG) innervate the hindgut of *R. appendiculatus* (Šimo and Park 2014). AST-A was also detected in *Dermacentor variabilis* (Say, 1821) (Zhu and Oliver 2001), *I. scapularis* (Fig. 1) and *R. microplus* (Donohue et al. 2010). In the genome of *I. scapularis*, four predicted and closely related AST-A receptor

Table 2 Localization and function of neuropeptides found in different tick species

Neuropeptide	Species of tick	Organ localization	Function
Allatostatin-A (AST-A)	*D. variabilis* (Zhu and Oliver 2001) *R. appendiculatus* (Šimo et al.2009a) *R. microplus* (Donohue et al. 2010) *I. scapularis* (Šimo et al. 2014)	A large number of peptidergic neurons in the synganglion (Šimo et al. 2009a; Zhu and Oliver 2001), innervation of hindgut probably from the OsHG neuron (Šimo et al. 2014)	Expected function based on known properties in insects—myoinhibitory effect on movements of the gut or ovaries (Duve et al. 1999; Teal 2002)
Allatotropin (AT)	*R. appendiculatus* (Šimo et al. 2009a)	A large number of peptidergic neurons in the synganglion and peripheral nerves (Šimo et al. 2009a),	Expected function based on known properties in insects—myostimulatory effect on peristaltic bowel movements or ovaries (Duve et al. 1999; Čižmár et al. 2019)
Pigment dispersing factor (PDF)	*R. appendiculatus* (Šimo et al. 2009a)	Small neurons in the synganglion, innervation of SG type II acini from the neurons OsSG1,2 (Šimo et al. 2009a, b)	Currently unknown function
Myoinhibitory peptide (MIP)	*R. appendiculatus* (Šimo et al. 2009a) *I. scapularis* (Šimo et al. 2009b, 2014)	Neurons in the synganglion, innervation of the SG acini type II, III by PcSG neuron (Šimo et al. 2009a, b), innervation of the rectal sac from PoHG1,2 neurons (Šimo et al. 2013, 2014)	SIFamide antagonist—reduces SIFα-activated hindgut motility (Šimo and Park 2014)
Tachykinin (TK/TK-like)	*R. appendiculatus* (Šimo et al. 2009a) *I. scapularis* (Mateos-Hernández et al. 2021)	Neurons in the synganglion which innervate its surface (Šimo et al. 2009a), and ducts in salivary glands (Mateos-Hernández, et al. 2021)	Currently unknown function
SIF amide (SIFa)	*R. appendiculatus* (Šimo et al. 2009a) *I. scapularis* (Šimo et al. 2009b, 2014)	Peptidergic neurons in the synganglion, innervation of the SG acini type II and III by PcSG neuron (Šimo et al. 2009a, b), innervation of the rectal sac from PoHG1,2 neurons (Šimo et al. 2013, 2014)	MIP antagonist, stimulates hindgut activity (Šimo and Park 2014)
Insulin- like peptide (ILP)	*O. parkeri (*Zhu and Oliver 1991) *D. variabilis* (Altschul et al. 1997) *I. scapularis* (Egekwu et al. 2014)	Neurosecretory cells and inervation in the synganglion (Zhu et Oliver 1991; Altschul et al. 1997; Egekwu et al. 2014)	The function of insulins is not yet known, the most detailed functions are described in insects, where they perform many physiological functions (Antonova et al. 2012; Strand et al. 2016; Nässel and Broeck 2016; Colombani, et al. 2012; Nuss and Brown 2018)
Elevenin (Elev)	*I. scapularis* (Kim et al. 2018)	PcSG neurons in the synganglion, innervation of SG acini type II, III (Kim et al. 2018)	May regulate salivary gland function associated with feeding (Kim et al. 2018)

Peptide	Sequence	Source
Allatotropin (AT)	MAALGRTSALVAAALFLCLAAAGSETPEASDRQHRGGFQKLRLSTARGFGKRIPPGLAFLRQRNQEPADPIIKKGFR KMKISTARGFGKREDPDLSFLLENEDIDPVDLKEKRGIRRLSLSTARGFGKRMSPGFSDDQGPSDAGQSGSGWLAE EIAKVADISDDGLAYQDSF	IscW_ISCW017791
Allatostatin A (AST-A)	MDMRRSPCTVSRFMRPCPVTCLLLLFMLAAQYCRAEDASPAQLQENDKRRPPAAMYGFGLGKRAPFLFLADDA AEQAAERAEAEDEDPDLNYLDKRGERPQHPLRYGFGLGKRLDRDGNYPGSIDHNRRERHRFGFGLGKRGKKSEIE DFMKRRYNFGLGKRSAYGGDDGERWKRSLASDHN*	XP_029848989.1
SIFamide (SIFa)	MNSWKAFFMFGTLLVMAVMMNMACAAYRKPPFNGSIFGKRSRADLNNADVKYAMCEAVNDTCTQWFPITQ DGAQ*	Šimo et al. (2009)
Myoinhibitory peptide (MIP)	MSPVESSRHAGRRPVVATYGESGRTATSAVVLSRSLLVLLVLAALLCCSAAEPQPQGGDWNALSGMWGKRASD WNRLSGMWGKRAGAYGPYQALLRAEESNDGAGHGISARAAPPGSPRENHWNDLSGYWG*	Šimo et al. (2009)
Elevenin (Elev)	MKRTCIQALVGVPFFAALVHQLHAELDCRKYPFYYRCRGISAKRSFAPITKMEAMSLKELYEDDDGRKNRRRPADA VLGWVRNKYGDDIFDPDEPLDATRGSFERKELY*	Kim et al. (2018)
Insulin-like peptide 1 (ILP1)	MGPPVAGQTAAPMVSWALNTVVVALVAASALVAPAAAGSGRRCGKILLEFMEFVCEGEFYDPYENTGPKRSLIG QRLFPLVSPGIENTDKAPASGFLRAESASQLLRKRNFQGGIVFECCYKACSIMEAQSYCPS*	Sharma et al. (2019)
Insulin-like peptide 3 (ILP3)	MNAAVLLLLCATALLSSHRGASARSSVEKRNNRYCGSNLNRVLDFLCEEYYDPTQKRHTGYRPAHDLPAALPVWF PVLDANGDSKLGFMEAKAALQLLRPSVHYGRHTRGIVEECCHKSCSTLELLAYCKTPRNNADLQVSSDDNTA	Sharma et al. (2019)
Insulin-like peptide 4 (ILP4)	MALARHAAVLVALVLAGAWTSFVDLVEARPASSGASTSSSSSTVRLCGPRLVDLVWMLCMDRGGVHSHMDRR ALGAPRARPQQPFVIYRPSLPRPDGQEDEDSGSSERGTTATSIAANTYHHSSGHSNGGGIVDECCRKACSFATLASY CARPSAGSSLDAFNMLLASPADEARSSESAMQGDQAVEPTTEAPSPVESHVQHAQEVNREHNEVERTGPAAERS RGDGVSTGRVLIPGANFLRSPEEDTAFGPRVRIGTFSRHRPFFYVVQAAFNGDTEEALDA	Sharma et al. (2019)
Insulin-like peptide 5 (ILP5)	MLRCAAVWLVVSAVMDLASGTADTPNWEEIFRNRNDEDWARVVWHVERHRRCYHQLVSHMNLVCREDIYKLSR RRRDVAADKDPEMTDLFLKPEAALGVLTGKLSKRRVTQHNIRTRSIIDECCDTEVGCSWEEYAEYCPANRRMRNR KR	Sharma et al. (2019)
Tachykinín (TK)	MDHPEMKVVALWSLVLLLTLSSVRTASFQSSEVGNEPEVGEVSLVEKLGWDGGLDGGDDLEIAAAADDEKRAFH AMRGKKDDPSLDWDEADKRAFHAMRGKRLLAPASVDSFIAQLRRAVLQGKRGSGFFGMRGKRMSRTPGKEHP RSTFVATRGRRSVLSEAESRPYY*	Šimo et al. (2019)

Fig. 1 An overview of selected *Ixodes scapularis* peptides. Accession numbers: AT (172aa), AST A (182 aa) XP_029848989.1; SIFa (74 aa) ADD92393.1;; MIP (131 aa); Elev (109 aa) AXL48134.1; ILP1 (135 aa) QDB63964.1; ILP3 (147 aa) QDB63965.1; ILP4 (284 aa) QDB63966.1; ILP5 (149 aa) QDB63967.1; TK (169 aa) EL516783.1. The sequence of MIP1 N-termini is unknown and the C-termini of the MIP3 is with missing amidation signal incomplete. Signal peptide is in the sequences underlined; yellow are A-chains of ILPs and turquoise are B-chains of ILPs; predicted dibasic cleavage sites are red; green are the sequences of mature neuropeptides and the asterisks stand for STOP codon

sequences (FGLa / ASTRs) were discovered (Šimo and Park 2014). Their sequences are similar as they contain a characteristic structure and seven transmembrane domains as well as all GPCR receptors (Šimo and Park 2014).

SIFamide

SIFamide (SIFa) immunoreactivity was observed (Table 2, Fig. 1) in several neurons in the synganglion of *I. scapularis* and *R. appendiculatus* (Šimo et al. 2009a; Šimo and Park 2014). The most prominent PcSG neurons innervate acini type II and III of the SGs. Other neurons producing SIFamide (PoHG1, 2) project axons through the opistosomal nerves (OsN) to the hindgut surface (Šimo and Park 2014). In vitro assay showed that application of SIFamide stimulated hindgut contractions. Increased gut motility may suggest the role of SIFa in ion and water transport (Šimo and Park 2014). The identified putative receptor for SIFamide is expressed in the synganglion, salivary glands and gut (Šimo et al. 2013).

Myoinhibitory peptide

Myoinhibitory peptide (MIP) is a neuropeptide that inhibits visceral muscle contractions (Table 2) (Šimo and Park 2014). MIP was subsequently detected in *I. scapularis* (Fig. 1) and *R. appendiculatus* (Šimo et al. 2009a, b; Šimo and Park 2014). In all these ticks, MIP is expressed in PcGS synganglion neurons and passes into the SGs where the neurons innervate acini type II and III. It is acini type II and III that have specific cuticular valvae that open when ticks feed (Binnington 1978). Myoepithelial cells then push the ingested fluid into the salivary gland ducts (Coons et al. 1994; Lamoreaux et al. 2000). Available studies suggest that MIP could regulate salivary gland valve opening as well as myoepithelial cell function during tick feeding (Šimo

et al. 2013). MIP-immunoreactivity was also detected in the hindgut inervation from $PoHG_{1,2}$ neurons via opistosomal nerves, where it is colocalised with SIFamide (Šimo et al. 2014). Receptors specific for MIP were also identified (Šimo et al. 2013; Šimo and Park 2014). Because MIP and SIFamide are colocalized in terminal axons in acini type II and III in SG, we can assume that MIP will have an antagonistic effect on SIFamide-mediated increased motility. Following stimulation with SIFamide, the inhibitory effect of certain neuropeptides was tested. Only MIP was able to reduce intestinal motility by approximately 65% (Šimo and Park 2014). Based on described functions in insects and localization of MIP in ticks, we can assume that it has an inhibitory role in the tick salivary gland and gut (Šimo and Park 2014).

Elevenin

Elevenin (Elev) was first detected in the abdominal ganglia of *Aplysia californica* (Cooper, 1863) sea slugs, in the neuron L11 (Taussig et al. 1984). Its homologous peptides have also been identified in other molluscs and insects (Tanaka et al. 2014). In *Nilaparvata lugens* (Stal, 1854) (Insecta: Hemiptera) Elev was detected in the CNS and SGs (Uchiyama et al. 2018). It also plays an important role in cuticle melanisation and stimulates the production of intracellular cAMP (Uchiyama et al. 2018). Peptide elevenin (IsElev) and its two receptors, IsElevR1 and IsElevR2, were characterized in *I. scapularis* (Table 2, Fig. 1). The sensitivity of IsElevR1 to IsElev has been shown to be 560-fold higher than to IsElevR2 (Bauknecht and Jekely 2015; Kim et al. 2018). The gene encoding Elev peptide is expressed most abundantly in the synganglion and salivary glands of *I. scapularis*. In the synganglion of starving females, Elev was detected in PcSG neurons, which innervate the salivary gland acini type II and III (Kim et al. 2018). By qPCR IsElavR1 was detected in synganglion, salivary glands and ovary. The second receptor, IsElevR2 was detected in synganglion and ovary, but not in salivary glands (Kim et al. 2018). Based on immunoreactivity and expression levels in specific tissues, we can assume that Elev participates in processes in the tick salivary glands through its receptors and regulates the initial control of egg development processes.

Insulin

The insulin-like peptide (ILP) was detected by immunohistochemistry (Table 2) in the synganglion of the tick *Ornithodoros parkeri* (Cooley, 1936) (Zhu and Oliver 1991) and subsequently by BLAST search (Altschul et al. 1997) in several tick species (Šimo et al. 2014). Subsequently, a putative insulin transcript (IsILP1) was identified in *I. scapularis* (Egekwu et al. 2014) and similar is in *D. variabilis* (Donohue et al. 2010; Bissinger et al. 2011). Subsequently, other IsILP3, 4, and 5 were identified in *I. scapularis* (Fig. 1) (Sharma et al. 2019). IsILP5 and IsILP1 are expressed only in the synganglion and the highest level of IsILP3 and IsILP4 expression was detected in the salivary glands (Sharma et al. 2019). The insulin receptor IsInR in *I. ricinus* was detected especially in the ovaries, and knock-down of this receptor together with IrAKT and IrTOR reduced the amount of blood taken and reduced reproductive capacity (Kozelková et al. 2021). In nymphs, the expression of IsILP3 and IsILP4 increases upon detachment from the host. Increased expression after detachment suggests that it plays an important role during development of this stage to a higher instar (Sharma et al. 2019). Knockdown of the Insulin-like Growth Factor Binding Protein (IGFBP) prevented fully-engorgement of females *A. americanum* (Mulenga and Khumthong 2010). Interestingly, each insulin is characterized by a specific expression pattern (Sharma et al. 2019). The function of insulins in ticks is not yet known; however, the most detailed functions are described in insects, where they control many physiological functions (Antonova et al. 2012; Colombani et al. 2012; Strand et al. 2016; Nässel and Broeck 2016; Nuss and Brown 2018).

Tachykinin

Tachykinins (TKs) are widely distributed pleiotropic neuropeptides, which are present in vertebrates, and invertebrates (Nässel et al. 2019). Overexpression of human TK receptors (TKR) is connected to many diseases, such as depression, stress, cardiovascular diseases, Parkinson's disease, and others (Feickert and Burckhardt 2019). TKs (Table 2, Fig. 1) are commonly expressed in the CNS and midgut enteroendocrine cells of insects and vertebrates (Nässel et al. 2019), but are also produced by the venom glands of wasps (Yoon et al. 2020; Arvidson et al. 2016). Interestingly, the salivary glands of the mosquito *A. aegypti* and octopus *Octopus vulgaris* (Cuvier, 1797) produce TK peptides with the FXGLMamide motif (Steinhoff et al. 2014; Nässel et al. 2019), related to vertebrate substance P derived from the preprotachykinin A precursor. It would be interesting to determine if ticks, as blood-feeding parasitic organisms, produce similar peptides in the salivary glands. TK immunoreactivity was observed in the synganglion and in the ducts of the salivary glands of *R. appendiculatus* (Šimo et al. 2009a) and a precursor encoding IscapTKs has been identified in the genome of *I. scapularis* (Šimo et al., 2014). Furthermore, infection of the ISE6 tick cell line with *A. phagocytophilum* led to strain-dependent changes in the TK expression (Mateos-Hernández et al. 2021). Possible involvement of TKs in the

tick-pathogen interactions make them even more interesting as neuropeptides for future studies.

Conclusions

The most appropriate strategy used to control the life cycle of ticks is to identify molecules that control feeding and digestion, as well as regulate complex interactions between ticks, pathogens and their hosts. This could provide efficient tools for interruption of pathogen transmission. Neuropeptides and their receptors participate in important signalling pathways which control crucial processes during feeding and associated transmission of pathogens. Recent data indicate that the feeding activity of the tick is under control of neuropeptide signalling that requires neuroendocrine interactions between the synganglion, salivary glands and gut. As the incidence of known tick-borne diseases is increasing from year to year, identification of bioactive molecules and their signalling pathways in ticks are essential for the targeted preparation of vaccines against ticks and tick-borne diseases.

Acknowledgements This study was supported by Slovak grant agencies, Agentúra na podporu výskumu a vývoja, (APVV-16-0395 and APVV-18-0201) and Vedecká grantová agentúra (VEGA 2/0080/18).

Declarations

Conflict of interest The authors declare no competing interests.

References

Abbas RZ, Zaman MA, Colwell DD, Gilleard J, Iqbal Z (2014) Acaricide resistance in cattle ticks and approaches to its management: the state of play. Vet Parasitol 203:6–20. https://doi.org/10.1016/j.vetpar.2014.03.006

Aguilar R, Maestro J, Vilaplana L, Pascual N, Piulachs M, Bellés X (2003) Allatostatin gene expression in brain and midgut and activity of synthetic allatostatins on feeding-related processes in the cockroach *Blattella germanica*. Regul Pept 115:171–177. https://doi.org/10.1016/S0167-0115(03)00165-4

Aghajani J, Farnia P, Ayoubi S, Farnia P, Ghanavi J, Velayati AA (2020) Can animals like bats, pangolins, and ticks would be considered as long-term reservoirs of severe acute respiratory syndrome coronavirus 2. Biomed Biotechnol Res J 4(5):3–12. https://doi.org/10.4103/bbrj.bbrj_120_20

Aljamali M, Sauer J, Essenberg R (2002) RNA interference: applicability in tick research. Exp Appl Acarol 28:89–96. https://doi.org/10.1023/a:1025346131903

Almazán C, Šimo L, Fourniol L, Rakotobe S, Borneres J, Cote M et al (2020) Multiple antigenic peptide-based vaccines targeting *Ixodes ricinus* neuropeptides induce a specific antibody response but do not impact tick infestation. Pathogens 9:900. https://doi.org/10.3390/pathogens9110900

Altschul S, Madden T, Schäffer A, Zhang J, Zhang Z, Miller W, Lipman DJ (1997) Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. Nucl Acids Res 25:3389–3402. https://doi.org/10.1093/nar/25.17.3389

Amicizia D, Domnich A, Panatto D, Lai PL, Cristina ML, Avio U, Gasparini R (2013) Epidemiology of tick-borne encephalitis (TBE) in Europe and its prevention by available vaccines. Human Vaccines & Immunotherapeutics 9(1163–1171):1. https://doi.org/10.4161/hv.23802

Amiel C, Abadia G, Choudat D (2004) Human granulocytic ehrlichiosis in Europe. Med Mal Infect 34:11–122

Anderson J, Magnarelli LA (2008) Biology of ticks. Infect Dis Clin North Am 22(2):195–215. https://doi.org/10.1016/j.idc.2007.12.006

Andreotti R (2006) Performance of two Bm86 antigen vaccine formulation against tick using crossbreed bovines in stall test. Braz J Vet Parasitol 15:97–100

Anguita J, Ramamoorthi N, Hovius JW, Das S, Thomas V, Persinski R et al (2002) Salp15 an *Ixodes scapularis* salivary protein inhibits CD4(+) T cell activation. Immunity 16:849–859. https://doi.org/10.1016/s1074-7613(02)00325-4

Antonova Y, Arik A, Moore W, Riehle M, Brown M (2012) Insulin-like peptides: structure signaling and function. Insect Endocrinol 2:63–92. https://doi.org/10.1016/B978-0-12-384749-2.10002-0

Antunes S, Couto J, Ferrolho J, Sanches GS, Charrez JOM, De la Cruz HN et al (2019) Transcriptome and proteome response of *Rhipicephalus annulatus* tick vector to *Babesia bigemina* infection. Front Physiol 10:318. https://doi.org/10.3389/fphys.2019.00318

Arvidson R, Kaiser M, Pan SQ, Libersat F, Adams ME (2016) Bioinformatic and functional analysis of venom from the jewel wasp *Ampulex compressa*. FASEB J 30:819–821

Baggerman G, Liu F, Wets G, Schoofs L (2005) Bioinformatic analysis of peptide precursor proteins. Ann NY Acad Sci 1040:59–65. https://doi.org/10.1196/annals.1327.006

Bakken JS, Dumler JS (2015) Human granulocytic anaplasmosis. Infect Dis Clin North Am 29:341–355. https://doi.org/10.1016/j.idc.2015.02.007

Bakken JS, Dumler JS (2000) Human granulocytic ehrlichiosis. Clin Infect Dis 31:554–560

Bauknecht P, Jekely G (2015) Large-scale combinatorial deorphanization of platynereis neuropeptide GPCRs. Cell Rep 12:684–693. https://doi.org/10.1016/j.celrep.2015.06.052

Beaufays J, Benoît A, Decrem Y, Prévôt P-P, Santini S, Brasseur R et al (2008) *Ixodes ricinus* tick lipocalins: identification cloning phylogenetic analysis and biochemical characterization. PLoS ONE 3:e3941. https://doi.org/10.1371/journal.pone.0003941

Bednár B, Roller L, Čižmár D, Mitrová D, Žitňan D (2017) Developmental and sex-specific differences in expression of neuropeptides derived from allatotropin gene in the silkmoth *Bombyx mori*. Cell Tiss Res 368:259–275. https://doi.org/10.1007/s00441-016-2556-x

Bendena WG, Donly BC, Tobe SS (1999) Allatostatins: a growing family of neuropeptides with structural and functional diversity. Ann NY Acad Sci 891:311–329

Bhattacharyulu Y, Chaudhri RP, Gill BS (1975) Transstadial transmission of *Theileria annulata* through common ixodid ticks infesting Indian cattle. Parasitology 71:1–7. https://doi.org/10.1017/s0031182000053087

Bilgic HB, Aksulu A, Bakırcı S, Unlu AH, Kose O, Hacılarlıoglu S et al (2019) Infection dynamics of *Theileria annulata* over a disease season following cell line vaccination. Vet Parasitol 265:63–73. https://doi.org/10.1016/j.vetpar.2018.11.012

Binnington K (1978) Sequential changes in salivary gland structure during attachment and feeding of the catle tick *Boophilus microplus*. Int J Parasitol 8:97–115. https://doi.org/10.1016/0020-7519(78)90004-8

Bishop R, Lambson B, Wells C, Pandit PJO, Nkonge C, Morzaria S et al (2002) A cement protein of the tick *Rhipicephalus appendiculatus* located in the secretory e cell granules of the type III salivary gland acini induces strong antibody responses in cattle. Int J Parasitol 15:833–842. https://doi.org/10.1016/s0020-7519(02)00027-9

Bissinger BW, Donohue KV, Khalil SM, Grozinger CM, Sonenshine DE, Zhu J, Roe RM (2011) Synganglion transcriptome and developmental global gene expression in adult females of the American dog tick, *Dermacentor variabilis* (Acari: Ixodidae). Insect Mol Biol 20:465–491. https://doi.org/10.1111/j.1365-2583.2011.01086.x

Bock R, Jackson L, de Vos A, Jorgensen W (2004) Babesiosis of cattle. Parasitology 129:S247–S269. https://doi.org/10.1017/s0031182004005190

Botelho-Nevers E, Socolovschi C, Raoult D, Parola P (2012) Treatment of *Rickettsia* spp infections: a review. Expert Rev Anti Infect Ther 10:1425–1437. https://doi.org/10.1586/eri.12.139

Boulanger N (2018) Rôle immunomodulateur de la salive de tique dans la transmission d'agents infectieux [Immunomodulatory effect of tick saliva in pathogen transmission]. Biol Aujourd`hui 212(3–4):107–117. https://doi.org/10.1051/jbio/2019001

Brites-Neto J, Duarte KM, Martins TF (2015) Tick-borne infections in human and animal population worldwide. Vet World 8:301–315. https://doi.org/10.14202/vetworld.2015.301-315

Burt F, Swanepoel R, Shieh W, Smith J, Leman P, Greer P et al (1997) Immunohistochemical and in situ localization of Crimean-Congo hemorrhagic fever (CCHF) virus in human tissues and implications for CCHF pathogenesis. Arch Pathol Lab Med 121/8:839–846

Chatanga E, Mosssad E, Abdo Abubaker H, Amin Alnour S, Katakura K, Nakao R, Salim B (2019) Evidence of multiple point mutations in *Theileria annulata* cytochrome b gene incriminated in buparvaquone treatment failure. Acta Trop 191:128–132. https://doi.org/10.1016/j.actatropica.2018.12.041

Chmelař J, Kotál J, Kopecký J, Pedra J, Kotsyfakis M (2016) All for one and one for all on the tick-host battlefield. Trends Parasitol 32:368–377. https://doi.org/10.1016/j.pt.2016.01.004

Chumakov M (1949) A new virus – Crimean hemorrhagic fever. Nov Med 4:9–11

Cicek E (2009) 9th International Ecology and Environment Congress. Bull Ecol Soc Amer 90(3):318. https://doi.org/10.1890/0012-9623-90.3.318

Colombani J, Andersen D, Léopold P (2012) Secreted peptide Dilp8 coordinates *Drosophila* tissue growth with developmental timing. Science 336:582–585

Comstedt P, Schüler W, Meinke A, Lundberg U (2017) The novel Lyme borreliosis vaccine VLA15 shows broad protection against *Borrelia* species expressing six different OspA serotypes. PLoS ONE 12:e0184357. https://doi.org/10.1371/journal.pone.0184357

Contreras M, Alberdi P, Fernández De Mera IG, Krull C, Nijhof A, Villar M, de la Fuente J (2017) Vaccinomics approach to the identification of candidate protective antigens for the control of tick vector infestations and *Anaplasma phagocytophilum* infection. Front Cell Infect Microbiol 7:360. https://doi.org/10.3389/fcimb.2017.00360

Coons L, Lessman C, Ward M, Berg R, Lamoreaux W (1994) Evidence of a myoepithelial cell in tick salivary glands. Int J Parasitol 24:551–562

Coumou J, Wagemakers A, Trentelman JJ, Nijhof AM, Hovius JW (2015) Vaccination against Bm86 homologues in rabbits does not impair *Ixodes ricinus* feeding or oviposition. PLoS ONE 10:e0123495. https://doi.org/10.1371/journal.pone.0123495

Čižmár D, Roller L, Pillerová M, Sláma K, Žitňan D (2019) Multiple neuropeptides produced by sex-specific neurons control activity of the male accessory glands and gonoducts in the silkworm *Bombyx mori*. Sci Rep 9:2253. https://doi.org/10.1038/s41598-019-38761-x

Dai J, Narasimhan S, Zhang L, Liu L, Wang P, Fikrig E (2010) Tick histamine release factor is critical for *Ixodes scapularis* engorgement and transmission of the Lyme disease agent. PLoS Pathog 6:e1001205. https://doi.org/10.1371/journal.ppat.1001205

Dai J, Wang P, Adusumilli S, Booth CJ, Narasimhan S, Anguita J, Fikrig E (2009) Antibodies against a tick protein Salp15 protect mice from the Lyme disease agent. Cell Host Microbe 6:482–492. https://doi.org/10.1016/j.chom.2009.10.006

Dandasena D, Bhandari V, Sreenivasamurthy GS, Murthy S, Roy S, Bhanot V et al (2018) A Real-time PCR based assay for determining parasite to host ratio and parasitaemia in the clinical samples of bovine theileriosis. Sci Rep 8(1):15441. https://doi.org/10.1038/s41598-018-33721-3

Dantas-Torres F (2007) Rocky Mountain spotted fever. Lancet Infect Dis 7:724–732

Dantas-Torres F, Lia R, Capelli G, Otranto D (2012) Efficiency of flagging and dragging for tick collection. Exp Appl Acarol 61:119–127. https://doi.org/10.1007/s10493-013-9671-0

Dantas-Torres F, Oliveira-Filho E, Soares F, Souza B, Valenca R, Sa F (2008) Ticks infesting amphibians and reptiles in Pernambuco Northeastern Brazil. Rev Bras Parasitol Vet 17:218–221. https://doi.org/10.1590/S1984-29612008000400009

Darghouth MA, Ben Miled L, Bouattour A, Melrose TR, Brown CG, Kilani M (1996) A preliminary study on the attenuation of Tunisian schizont-infected cell lines of *Theileria annulata*. Parasitol Res 82(7):647–655. https://doi.org/10.1007/s004360050179

Darghouth MA, Preston P, Kilani M, Bouattour A (2011) Theileriosis. In: Keerthi S (ed) Infectious and parasitic diseases of livestock, Vol. 2, Lavoisier Editions, Cachan, France, pp 1839–1866

Darghouth MA (2008) Review on the experience with live attenuated vaccines against tropical theileriosis in Tunisia: considerations for the present and implications for the future. Vaccine 26(Suppl 6):G4–G10. https://doi.org/10.1016/j.vaccine.2008.09.065

de la Fuente J, Rodríguez M, Montero C, Redondo M, García-García JC, Méndez L et al (1999) Vaccination against ticks (*Boophilus* spp.): the experience with the Bm86-based vaccine Gavac. Genet Anal 15(3-5):143–8. https://doi.org/10.1016/s1050-3862(99)00018-2.

de la Fuente J, Torina A, Caracappa S, Tumino G, Furlá R, Almazán C, Kocan KM (2005a) Serologic and molecular characterization of *Anaplasma* species infection in farm animals and ticks from Sicily. Vet Parasitol 133:357–362. https://doi.org/10.1016/j.vetpar.2005.05.063

de la Fuente J, Torina A, Naranjo V, Caracappa S, Vicente J, Mangold AJ et al (2005b) Genetic diversity of *Anaplasma marginale* strains from cattle farms in the province of Palermo Sicily. J Vet Med B Infect Dis Vet Publ Health 52:226–229. https://doi.org/10.1111/j.1439-0450.2005.00851.x

de la Fuente J, Almazán C, Canales M, Pérez de la Lastra JM, Kocan KM, Willadsen P (2007) A ten-year review of commercial vaccine performance for control of tick infestations on cattle. Anim Health Res Rev 8:23–28. https://doi.org/10.1017/s1466252307001193

de la Fuente J, Estrada-Pena A, Venzal JM, Kocan KM, Sonenshine DE (2008a) Overview: Ticks as vectors of pathogens that cause disease in humans and animals. Front Biosci 13:6938–6946

de la Fuente J, Ruiz-Fons F, Naranjo F, Torina A, Rodriguez O, Gortazar C (2008b) Evidence of *Anaplasma* infections in European roe deer *(Capreolus capreolus)* from southern Spain. Res Vet Sci 84:382–386. https://doi.org/10.1016/j.rvsc.2007.05.018

de la Fuente J, Estrada-Peña A, Cabezas-Cruz A, Kocan KM (2016) *Anaplasma phagocytophilum* uses common strategies for infection of ticks and vertebrate hosts. Trends Microbiol 24:173–180. https://doi.org/10.1016/j.tim.2015.12.001

de la Fuente J, Antunes S, Bonnet S, Cabezas-Cruz A, Domingos AG, Estrada-Peña A et al (2017a) Tick-pathogen interactions and vector competence: identification of molecular drivers for tick-borne diseases. Front Cell Infect Microbiol 7:114. https://doi.org/10.3389/fcimb.2017.00114

de la Fuente J, Contreras M, Estrada-Peña A, Cabezas-Cruz A (2017b) Targeting a global health problem: Vaccine design and challenges for the control of tick-borne diseases. Vaccine 35:5089–5094. https://doi.org/10.1016/j.vaccine.2017.07.097

de Sousa R, Nobrega S, Bacellar F, Torgal J (2003) Mediterranean spotted fever in Portugal: risk factors for fatal outcome in 105 hospitalized patients. Ann NY Acad Sci 990:285–294

De Silva A, Fikrig E (1995) Growth and migration of *Borrelia burgdorferi* in *Ixodes* ticks during blood feeding. Am J Trop Med Hyg 53(4):397–404. https://doi.org/10.4269/ajtmh.1995.53.397

Decrem Y, Mariller M, Lahaye K, Blasioli V, Beaufays J, Zouaoui Boudjeltia KZ et al (2008) The impact of gene knock-down and vaccination against salivary metalloproteases on blood feeding and egg laying by *Ixodes ricinus*. Int J Parasitol 38:549–560. https://doi.org/10.1016/j.ijpara.2007.09.003

Dolan TT (1989) Theileriasis: a comprehensive review. Rev Sci Techn 8(1):11–78. https://doi.org/10.20506/rst.8.1.398

Donohue K, Khalil SM, Grozinger C, Sonenshine D, Roe R (2010) Neuropeptide signaling sequences identified by pyrosequencing of the American dog tick synganglion transcriptome during blood feeding and reproduction. Insect Biochem Mol Biol 40:79–90. https://doi.org/10.1016/j.ibmb.2009.12.014

Dugat T, Lagrée AC, Maillard R, Boulouis HJ, Haddad N (2015) Opening the black box of *Anaplasma phagocytophilum* diversity: current situation and future perspectives. Front Cell Infect Microbiol 14:61. https://doi.org/10.3389/fcimb.2015.00061

Dumler JS, Bakken JS (1996) Human granulocytic ehrlichiosis in Wisconsin and Minnesota: a frequent infection with the potential for persistence. J Infect Dis 173:1027–1030. https://doi.org/10.1093/infdis/173.4.1027

Dumler JS, Barbet AF, Bekker CP, Dasch GA, Palmer GH, Ray SC et al (2001) Reorganization of genera in the families Rickettsiaceae and Anaplasmataceae in the order Rickettsiales: unification of some species of *Ehrlichia* with *Anaplasma*, *Cowdria* with *Ehrlichia* and *Ehrlichia* with *Neorickettsia*, descriptions of six new species combinations and designation of *Ehrlichia equi* and "HGE agent" as subjective synonyms of *Ehrlichia phagocytophila*. Int J Syst Evol Microbiol 51:2145–2165. https://doi.org/10.1099/00207713-51-6-2145

Dumpis U, Crook D, Oksi J (1999) Tick-borne encephalitis. Clin Infect Dis 28:882–890. https://doi.org/10.1086/515195

Dunham-Ems SM, Caimano MJ, Pal UW, Eggers CH, Balic A, Radolf JD (2009) Live imaging reveals a biphasic mode of dissemination of *Borrelia burgdorferi* within ticks. J Clin Invest 119:3652–3665. https://doi.org/10.1172/jci39401

Duve H, East P, Thorpe A (1999) Regulation of lepidopteran foregut movement by allatostatins and allatotropin from the frontal ganglion. J Comp Neurol 413:405–416

Egekwu N, Sonenshine D, Bissinger B, Roe R (2014) Transcriptome of the female synganglion of the black-legged *tick Ixodes scapularis* (Acari: Ixodidae) with comparison between Illumina and 454 Systems. PLoS ONE 9:1–24. https://doi.org/10.1371/journal.pone.0102667

El Hag L M (2010) Studies on the epidemiology and control of *Theileria annulata* in Khartoum State using macroschizont-infected attenuated cell culture vaccine. Ph.D Thesis. Sudan Academy of Sciences, Khartoum, Sudan

Elekonich MM, Horodyski FM (2003) Insect allatotropins belong to a family of structurally-related myoactive peptides present in several invertebrate phyla. Peptides 24(10):1623–1632. https://doi.org/10.1016/j.peptides.2003.08.011

Eremeeva ME, Dasch GA (2015) Challenges posed by tick-borne rickettsiae: eco-epidemiology and public health implications. Front Publ Health 21:55. https://doi.org/10.3389/fpubh.2015.00055

Ergonul O (2006) Crimean-Congo haemorrhagic fever. Lancet Infect Dis 6:203–214. https://doi.org/10.1016/s1473-3099(06)70435-2

Ergonul O, Celikbas A, Baykam A, Eren S, Dokuzoguz B (2006) Analysis of risk-factors among patients with Crimean-Congo haemorrhagic fever virus infection: severity criteria revisited. Clin Microbiol Infect 12:551–554. https://doi.org/10.1111/j.1469-0691.2006.01445.x

Feickert M, Burckhardt BB (2019) Substance P in cardiovascular diseases - A bioanalytical review. Clin Chim Acta 495:501–506. https://doi.org/10.1016/j.cca.2019.05.014

Fernández-de-Mera IG, Rodríguez Del-Río FJ, de la Fuente J, Pérez-Sancho M, Hervás D, Moreno I et al (2021) Detection of environmental SARS-CoV-2 RNA in a high prevalence setting in Spain. Transbound Emerg Dis 68(3):1487–1492. https://doi.org/10.1111/tbed.13817

Fikrig E, Barthold SW, Kantor FS, Flavell RA (1990) Protection of mice against the Lyme disease agent by immunizing with recombinant OspA. Science 250:553–556. https://doi.org/10.1126/science.2237407

Fingerle V, Schulte-Spechtel U, Ruzic-Sabljic ESLS, Hofmann H, Weber K, Pfister K (2008) Epidemiological aspects and molecular characterization of *Borrelia burgdorferi* sl from southern Germany with special respect to the new species *Borrelia spielmanii* sp. nov. Int J Med Microbiol 298(3–4):279–290. https://doi.org/10.1016/j.ijmm.2007.05.002

Garczynski SF, Hendrickson C, Harper A, Unruh T, Dhingra A, Ahn S, Choi M (2019) Neuropeptides and peptide hormones identified in codling moth *Cydia pomonella* (Lepidoptera: Tortricidae). Arch Insect Biochem Physiol 101:e21587. https://doi.org/10.1002/arch.21587

Garg R, Juncadella IJ, Ramamoorthi N, Ashish AS, Thomas V, Rincón M et al (2006) Cutting edge: CD4 is the receptor for the tick saliva immunosuppressor Salp15. J Immunol 177:6579–6583. https://doi.org/10.4049/jimmunol.177.10.6579

Gaudreault NN, Madden DW, Wilson WC, Trujillo JD, Richt JA (2020) African swine fever virus: An emerging DNA arbovirus. Front Vet Sci 7:215. https://doi.org/10.3389/fvets.2020.00215

George N, Bhandari V, Reddy DP, Sharma P (2015) Molecular and phylogenetic analysis revealed new genotypes of *Theileria annulata* parasites from India. Parasit Vectors 8:468. https://doi.org/10.1186/s13071-015-1075-z

Gern L (2008) *Borrelia burgdorferi* sensu lato the agent of lyme borreliosis: life in the wilds. Parasite 15:244–247. https://doi.org/10.1051/parasite/2008153244

Gharbi M, Touay A, Khayeche M, Laarif J, Jedidi M, Sassi L, Darghouth M A (2011) Ranking control options for tropical theileriosis in at-risk dairy cattle in Tunisia, using benefit-cost analysis. Rev Sci Techn 30(3):763–778. https://doi.org/10.20506/rst.30.3.2074

Gharbi M, Darghouth MA, Elati K, Al-Hosary A, Ayadi O, Salih DA et al (2020) Current status of tropical theileriosis in Northern Africa: A review of recent epidemiological investigations and implications for control. Transbound Emerg Dis 67(Suppl 1):8–25. https://doi.org/10.1111/tbed.13312

Gohil S, Herrmann S, Günther S, Cooke BM (2013) Bovine babesiosis in the 21st century: advances in biology and functional genomics. Int J Parasitol 43:125–132. https://doi.org/10.1016/j.ijpara.2012.09.008

Goldman E (2020) Exaggerated risk of transmission of COVID-19 by fomites. Lancet Infect Dis 20(8):892–893. https://doi.org/10.1016/S1473-3099(20)30561-2

Gray J (2002) Biology of *Ixodes* species ticks in relation to tick-borne zoonoses. Wien Klin Wochenschr 114:473–478
Gray J (2006) Identity of the causal agents of human babesiosis in Europe. Int J Med Microbiol 296:131–136. https://doi.org/10.1016/j.ijmm.2006.01.029
Gresikova M, Kaluzova M (1997) Biology of tick-borne encephalitis virus. Acta Virol 41:115–124
Gupta SK, Sharma RD, Rakha NK, Sudhan NA, Nichani AK (1998) Immune response to *Theileria annulata* (Hisar) cell culture vaccine under the field conditions in bovines. Indian Vet J 75:405–411
Hahn MB, Jarnevich CS, Monaghan AJ, Eisen RJ (2016) Modeling the geographic distribution of *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae) in the contiguous. United States J Med Entomol 53:1176–1191. https://doi.org/10.1093/jme/tjw076
Hannier S, Liversidge J, Sternberg JM, Bowman AS (2004) Characterization of the B-cell inhibitory protein factor in *Ixodes ricinus* tick saliva: a potential role in enhanced *Borrelia burgdoferi* transmission. Immunology 113:401–408. https://doi.org/10.1111/;j.1365-2567.2004.01975.x
Hashemi-Fesharki R (1991) Chemotherapeutic value of parvaquone and buparvaquone against *Theileria annulata* infection of cattle. Res Vet Sci 50(2):204–207. https://doi.org/10.1016/0034-5288(91)90107-y
Hemmink JD, Weir W, MacHugh ND, Graham SP, Patel E, Paxton E et al (2016) Limited genetic and antigenic diversity within parasite isolates used in a live vaccine against *Theileria parva*. Int J Parasitol 46(8):495–506. https://doi.org/10.1016/j.ijpara.2016.02.007
Hergarden AC, Tayler TD, Anderson DJ (2012) Allatostatin-A neurons inhibit feeding behavior in adult *Drosophila*. Proc Natl Acad Sci USA 109(10):3967–3972. https://doi.org/10.1073/pnas.1200778109
Hernández-Martínez S, Sánchez-Zavaleta M, Brito K, Herrera-Ortiz A, Ons S, Noriega F (2017) Allatotropin: A pleiotropic neuropeptide that elicits mosquito immune responses. PLoS ONE 124:e0175759. https://doi.org/10.1371/journal.pone.0175759
Hewes RS, Taghert PH (2001) Neuropeptides and neuropeptide receptors in the *Drosophila melanogaster* genome. Genome Res 11(6):1126–1142. https://doi.org/10.1101/gr.169901
Heyman P, Hofhuis A, Cochez C, Sprong H (2010) A clear and present danger: Tick-borne diseases in Europe. Exp Rev Anti Infect Ther 8:33–50. https://doi.org/10.1586/eri.09.118
Hofhuis A, van de Kassteele J, Sprong H, van den Wijngaard CC, Harms MG, Fonville M et al (2017) Predicting the risk of *Lyme borreliosis* after a tick bite using a structural equation model. PLoS ONE 12:e0181807. https://doi.org/10.1371/journal.pone.0181807
Hoogstraal H (1979a) The epidemiology of tick-borne Crimean-Congo hemorrhagicfever in Asia Europe and Africa. J Med Entomol 15:307–417. https://doi.org/10.1093/jmedent/15.4.307
Hoogstraal H (1979b) Ticks and spirochetes. Acta Trop 36:133–136
Hoogstraal H (1981) Changing patterns of tickborne diseases in modern society. Annu Rev Entomol 26:75–99. https://doi.org/10.1146/annurev.en.26.010181.000451
Hovius JW, de Jong MA, den Dunnen J, Litjens M, Fikrig E, van der Poll T et al (2008a) Salp15 binding to DC-SIGN inhibits cytokine expression by impairing both nucleosome remodeling and mRNA stabilization. PLoS Pathog 4:e31. https://doi.org/10.1371/journal.ppat.0040031
Hovius JW, Schuijt TJ, de Groot KA, Roelofs JJ, Oei GA, Marquart JA et al (2008b) Preferential protection of *Borrelia burgdorferi* sensu stricto by a Salp15 homologue in *Ixodes ricinus* saliva. J Infect Dis 198:1189–1197
Hökfelt T, Broberger C, Xu ZQ, Sergeyev V, Ubink R, Diez M (2000) Neuropeptides–an overview. Neuropharmacolog 39(8):1337–1356. https://doi.org/10.1016/s0028-3908(00)00010-1
Hunfeld KP, Hildebrandt A, Gray JS (2008) Babesiosis: recent insights into an ancient disease. Int J Parasitol 38:1219–1237. https://doi.org/10.1016/j.ijpara.2008.03.001
Ireton K (2013) Molecular mechanisms of cell-cell spread of intracellular bacterial pathogens. Open Biol 3:130079. https://doi.org/10.1098/rsob.130079
Jonsson NN, Matschoss AL, Pepper P, Green PE, Albrecht MS, Hungerford J, Ansell J (2000) Evaluation of tickGARD(PLUS: a novel vaccine against *Boophilus microplus* in lactating Holstein-Friesian cows. Vet Parasitol 88:275–285
Kaewmongkol S, Kaewmongkol G, Inthong N, Lakkitjaroen N, Sirinarumitr T, Berry CM (2015) Variation among Bm86 sequences in *Rhipicephalus (Boophilus) microplus* ticks collected from cattle across Thailand. Exp Appl Acarol 66:247–256. https://doi.org/10.1007/s10493-015-9897-0
Kamp HD, Swanson KA, Wei RR, Dhal PK, Dharanipragada R, Kern A et al (2020) Design of a broadly reactive Lyme disease vaccine. NPJ Vaccines 1:33. https://doi.org/10.1038/s41541-020-0183-8
Kataoka H, Toschi A, Li JP, Carney RL, Schooley DA, Kramer SJ (1989) Identification of an allatotropin from adult *Manduca sexta*. Science 243:1481–1483
Kemp D, Pearson R, Gough J, Willadsen P (1989) Vaccination against *Boophilus microplus*: localization of antigens on tick gut cells and their interaction with the host immune system. Exp Appl Acarol 7:43–58
Kim D, Šimo L, Park Y (2018) Molecular characterization of neuropeptide elevenin and two elevenin receptors IsElevR1 and IsElevR2 from the blacklegged tick *Ixodes scapularis*. Insect Biochem Mol Biol 101:66–75. https://doi.org/10.1016/j.ibmb.2018.07.005
Kim D, Šimo L, Vancová M, Urban J, Park Y (2019) Neural and endocrine regulation of osmoregulatory organs in tick: Recent discoveries and implications. Gen Comp Endocrinol 278:42–49. https://doi.org/10.1016/j.ygcen.2018.08.004
Kinabo LD, Bogan JA (1988) Parvaquone and buparvaquone: HPLC analysis and comparative pharmacokinetics in cattle. Acta Trop 45(1:87–94
Koladich PM, Cusson M, Bendena WG, Tobe SS, McNeil JN (2002) Cardioacceleratory effects of *Manduca sexta* allatotropin in the true armyworm moth. *Pseudaletia unipuncta*. Peptides 23(4):645–651. https://doi.org/10.1016/s0196-9781(01)00658-1
Kozelková T, Doležel D, Grunclová L, Kučera M, Perner J, Kopáček P (2021) Functional characterization of the insulin signaling pathway in the hard tick *Ixodes ricinus*. Ticks Tick Borne Dis 12(4):101694. https://doi.org/10.1016/j.ttbdis.2021.101694
Krasilnikov IV, Mischenko IA, Sharova OI, Bilalova G, Atavaskaya H, Vorobeva M et al (2004) Vaccine -protection between European and Far Eastern subtypes. "EnceVir": development in implementaiton in pracitcal use. Biopreparations 2:21–24
Krolak JM, Ownby C, Sauer J (1982) Alveolar structure of salivary glands of the lone star tick *Amblyomma americanum* (L): unfed females. J Parasitol 68:61–82
Kumar B, Maharana BR, Prasad A, Joseph JP, Patel B, Patel JS (2016) Seasonal incidence of parasitic diseases in bovines of south western Gujarat (Junagadh), India. J Parasit Dis 40(4):1342–1346. https://doi.org/10.1007/s12639-015-0686-9
Kunz C (2003) TBE vaccination and the Austrian experience. Vaccine 1:S50–S55. https://doi.org/10.1016/s0264-410x(02)00813-7
Kunz C, Hofmann H, Stary A (1976) Field studies with a new tick-borne encephalitis (TBE) vaccine. Zentralbl Bakteriol Orig A 234:141–144
Kurokawa C, Lynn GE, Pedra J, Pal U, Narasimhan S, Fikrig E (2020) Interactions between *Borrelia burgdorferi* and ticks.

Nat Rev Microbiol 18(10):587–600. https://doi.org/10.1038/s41579-020-0400-5
Labuda M, Randolph S (1999) Survival strategy of tick-borne encephalitis virus: cellular basis and environmental determinants. Zentralbl Bakteriol 289:513–524. https://doi.org/10.1016/s0934-8840(99)80005-x
Labuda M, Trimnel AR, Lickova M, Kazimírová M, Davies GM, Lissina O et al (2006) An antivector vaccine protects against a lethal vector-borne pathogen. PLoS Pathog 2:e26. https://doi.org/10.1371/journal.ppat.0020027
Lam SD, Ashford P, Díaz-Sánchez S, Villar M, Gortázar C, de la Fuente J, Orengo C (2021) Arthropod ectoparasites have potential to bind SARS-CoV-2 via ACE. Viruses 13(4):708. https://doi.org/10.3390/v13040708
Lamoreaux W, Needham G, Coons L (2000) Evidence that dilation of isolated salivary ducts from the tick *Dermacentor variabilis* (Say) is mediated by nitric oxide. J Insect Physiol 46:959–964
Leboulle G, Crippa M, Decrem Y, Mejri N, Brossard M, Bollen A, Godfroid E (2002) Characterization of a novel salivary immunosuppressive protein from *Ixodes ricinus* ticks. J Biol Chem 277:10083–10089. https://doi.org/10.1074/jbc.m111391200
Lindquist L, Vapalahti O (2008) Tick-borne encephalitis. Lancet 371:1861–1871. https://doi.org/10.1016/s0140-6736(08)60800-4
Liu L, Narasimhan S, Dai J, Zhang L, Cheng G, Fikrig E (2011) *Ixodes scapularis* salivary gland protein P11 facilitates migration of *Anaplasma phagocytophilum* from the tick gut to salivary glands. EMBO Rep 12:1196–1203. https://doi.org/10.1038/embor.2011.177
Loew-Baselli A, Konior R, Pavlova BG, Fritsch S, Poellabauer E, Maritsch F et al (2006) Safety and immunogenicity of the modified adult tick-borne encephalitis vaccine FSME-IMMUN: results of two large phase 3 clinical studies. Vaccine 24:5256–5263. https://doi.org/10.1016/j.vaccine.2006.03.061
Loew-Baselli A, Poellabauer EM, Pavlova BG, Fritsch S, Firth C, Petermann R et al (2011) Prevention of tick-borne encephalitis by FSME-IMMUN vaccines: review of a clinical development programme. Vaccine 29:7307–7319. https://doi.org/10.1016/j.vaccine.2011.07.089
Macaluso K, Sonenshine D, Ceraul S, Azad A (2002) Rickettsial infection in *Dermacentor variabilis* (Acari: Ixodidae) inhibits transovarial transmission of a second *Rickettsia*. J Med Entomol 39:809–813. https://doi.org/10.1603/0022-2585-39.6.809
Marsolier J, Perichon M, DeBarry JD, Villoutreix BO, Chluba J, Lopez T et al (2015) *Theileria* parasites secrete a prolyl isomerase to maintain host leukocyte transformation. Nature 520(7547):378–382. https://doi.org/10.1038/nature14044
Marques AR (2008) Chronic Lyme disease: a review. Infect Dis Clin North Am 22:341–348. https://doi.org/10.1016/j.idc.2007.12.011
Marques AR (2015) Laboratory diagnosis of Lyme disease: advances and challenges. Infect Dis Clin North Am 29:295–307.https://doi.org/10.1016/j.idc.2015.02.005
Massung R, Courtney J, Hiratzka S, Pitzer V, Smith G, Dryden R (2005) *Anaplasma phagocytophilum* in white-tailed deer. Emerg Infect Dis 11:1604–1606
Massung R, Levin M, Miller N, Mather T (2006) Reservoir competency of goats for *Anaplasma phagocytophilum*. Ann NY Acad Sci 1078:476–478. https://doi.org/10.1196/annals.1374.088
Mateos-Hernández L, Pipová N, Allain E, Henry C, Rouxel C, Lagrée A et al (2021) Enlisting the *Ixodes scapularis* embryonic ISE6 cell line to investigate the neuronal basis of tick-pathogen interactions. Pathogens 10:70. https://doi.org/10.3390/pathogens10010070
Mazzola LT, Kelly-Cirino C (2019) Diagnostic tests for Crimean-Congo haemorrhagic fever: a widespread tickborne disease. BMJ Glob Health 4(Suppl 2):e001114. https://doi.org/10.1136/bmjgh-2018-001114
McHardy N, Morgan DW (1985) Treatment of *Theileria annulata* infection in calves with parvaquone. Res Vet Sci 39(1):1–4
Medlock JM, Hansford K, Bormane A, Derdakova M, Estrada-Peña A, George J et al (2013) Driving forces for changes in geographical distribution of *Ixodes ricinus* ticks in Europe. Parasit Vectors 6:1. https://doi.org/10.1186/1756-3305-6-1
Mehlhorn H, Shein E (1984) The piroplasms: life cycle and sexual stages. Adv Parasitol 23:37–103. https://doi.org/10.1016/S0065-308X(08)60285-7
Mhadhbi M, Chaouch M, Ajroud K, Darghouth MA, BenAbderrazak S (2015) Sequence polymorphism of cytochrome b gene in *Theileria annulata* Tunisian isolates and its association with buparvaquone treatment failure. PLoS ONE 10(6):e0129678. https://doi.org/10.1371/journal.pone.0129678
Mhadhbi M, Naouach A, Boumiza A, Chaabani MF, BenAbderazzak S, Darghouth MA (2010) In vivo evidence for the resistance of *Theileria annulata* to buparvaquone. Vet Parasitol 169(3–4):241–247. https://doi.org/10.1016/j.vetpar.2010.01.013
Mickiene A, Laiskonis A, Gunther G, Vene S, Lundkvist A, Lindquist L (2002) Tickborne encephalitis in an area of high endemicity in lithuania: disease severity and long-term prognosis. Clin Infect Dis 35:650–658. https://doi.org/10.1086/342059
Minjauw B, Mcleod A (2003) Tick-borne diseases and poverty. The impact of ticks and tick-borne diseases on the livelihood of small scale and marginal livestock owners in India and eastern and southern Africa. Research report, Edinburgh, UK: DFID Animal Health Programme, Centre for Tropical Veterinary Medicine, University of Edinburgh, pp 59– 60
Monteiro GE, Bechara GH (2008) Cutaneous basophilia in the resistance of goats to *Amblyomma cajennense* nymphs after repeated infestations. Ann N Y Acad Sci 1149:221–225. https://doi.org/10.1196/annals.1428.026
Muhanguzi D, Byaruhanga J, Amanyire W, Ndekezi C, Ochwo S, Nakamwesiga J et al (2020) Invasive cattle ticks in East Africa: Morphological and molecular confirmation of the presence of *Rhipicephalus microplus* in south-eastern Uganda. Parasit Vectors 13:165. https://doi.org/10.1186/s13071-020-04043-z
Mulenga A, Khumthong R (2010) Silencing of three *Amblyomma americanum* (L) insulin-like growth factor binding protein-related proteins prevents ticks from feeding to repletion. J Exp Biol 231:1153–1161. https://doi.org/10.1242/jeb.035204
Murfin KE, Kleinbard R, Aydin M, Salazar SA, Fikrig E (2019) *Borrelia burgdorferi* chemotaxis toward tick protein Salp12 contributes to acquisition. Ticks Tick Borne Dis 10(5):1124–1134. https://doi.org/10.1016/j.ttbdis.2019.06.002
Mustafa Uel-H, Jongejan, F, Morzaria SP (1983) Note on the transmission of *Theileria annulata* by *Hyalomma* ticks in the Sudan. Vet Q 5(3):112–113. https://doi.org/10.1080/01652176.1983.9693883
Nakamura S (2020) Spirochete flagella and motility biomolecules 10(4):550. https://doi.org/10.3390/biom10040550
Naranjo V, Ruiz-Fons F, Höfle U, de Mera I, Villanúa D, Almazán C et al (2006) Molecular epidemiology of human and bovine anaplasmosis in southern Europe. Ann N Y Acad Sci 1078:95–99. https://doi.org/10.1196/annals.1374.013
Nässel DR, Broeck J (2016) Insulin/IGF signaling in *Drosophila* and other insects: factors that regulate production release and post-release action of the insulin-like peptides. Cell Mol Life Sci 73:271–290. https://doi.org/10.1007/s00018-015-2063-3
Nässel DR, Zandawala M, Kawada T, Satake H (2019) Tachykinins: neuropeptides that are ancient diverse widespread and functionally pleiotropic. Front Neurosci 13:1262. https://doi.org/10.3389/fnins.2019.01262
Ndawula CJ, Tabor A (2020) Cocktail anti-tick vaccines: The unforeseen constraints and approaches toward enhanced efficacies. Vaccine 8(3):457. https://doi.org/10.3390/vaccines8030457

Nuss AB, Brown M (2018) Isolation of an insulin-like peptide from the Asian malaria mosquito *Anopheles stephensi* that acts as a steroidogenic gonadotropin across diverse mosquito taxa. Gen Comp Endocrinol 258:140–148. https://doi.org/10.1016/j.ygcen.2017.05.007

Nuttall P, Labuda M (2008) Saliva-assisted transmission of tick-borne pathogens In: Bowman AS Nuttall PA (eds) Ticks: Biology, Disease and Control, Cambridge University Press, Cambridge, pp 205-219. https://doi.org/10.1017/CBO9780511551802.011

Ogden NH, Bigras-Poulin M, O'callaghan CJ, Barker IK, Kurtenbach K, Lindsay LR et al (2007) Vector seasonality host infection dynamics and fitness of pathogens transmitted by the tick *Ixodes scapularis*. Parasitology 134:209–227

Ojogun N, Kahlon A, Ragland SA, Troese MJ, Mastronunzio JE, Walker NJ et al (2012) *Anaplasma phagocytophilum* outer membrane protein A interacts with sialylated glycoproteins to promote infection of mammalian host cells. Infect Immun 80:3748–3760. https://doi.org/10.1128/iai.00654-12

Ouhelli H, Pandey VS (1982) Prevalence of cattle ticks in Morocco. Trop Anim Health Prod 14(3):151–154. https://doi.org/10.1007/BF02242145

Ouhelli H (1985) Theileriose bovine à *Theileria annulata* (Dschunkowsky and Luhs, 1904): recherche sur la biologie des vecteurs (*Hyalomma* spp.) et sur les interactions hôte-parasite. PhD. Thesis. Institut National Polytechnique de Toulouse, Toulouse, France

Paesen GC, Adams PL, Nuttall PA, Stuart DL (2000) Tick histamine-binding proteins: lipocalins with a second binding cavity. Biochim Biophys Acta 1482:92–101. https://doi.org/10.1016/S0167-4838(00)00168-0

Pal U, Li X, Wang T, Montgomery RR, Ramamoorthi N, DeSilva AM et al (2004) TROSPA an *Ixodes scapularis* receptor for *Borrelia burgdorferi*. Cell 119:457–468. https://doi.org/10.1016/j.cell.2004.10.027

Parola P, Raoult D (2001) Ticks and tickborne bacterial diseases in humans: an emerging infectious threat. Clin Infect Dis 32:897–928. https://doi.org/10.1086/319347

Parola P, Paddock C, Raoult D (2005) Tick-borne borne rickettsioses around the world: emerging diseases challenging old concepts. Clin Microbiol Rev 18:719–756. https://doi.org/10.1128/CMR.18.4.719-756.2005

Paulauskas A, Radzijevskaja J, Rosef O (2009) *Anaplasma* in ticks feeding on migrating birds and questing ticks in Lithuania and Norway. Clin Microbiol Infect 2:34–36. https://doi.org/10.1111/j.1469-0691.2008.02164.x

Paules CI, Marston HD, Bloom ME, Fauci AS (2018) Tickborne diseases - confronting a growing threat. N Engl J Med 379:701–703. https://doi.org/10.1056/nejmp1807870

Petchampai N, Sunyakumthorn P, Banajee KH, Verhoeve VI, Kearney MT, Macaluso KR (2015) Identification of host proteins involved in rickettsial invasion of tick cells. Infect Immun 83:1048–1055. https://doi.org/10.1128/IAI.02888-14

Petchampai N, Sunyakumthorn P, Guillotte ML, Verhoeve VI, Banajee KH, Kearney MT et al (2014) Novel identification of *Dermacentor variabilis* Arp2/3 complex and its role in rickettsial infection of the arthropod vector. PLoS ONE 9:e93768. https://doi.org/10.1371/journal.pone.0093768

Piesman J, Dolan M (2002) Protection against lyme disease spirochete transmission provided by prompt removal of nymphal *Ixodes scapularis* (Acari: Ixodidae). J Med Entomol 39:509–512. https://doi.org/10.1603/0022-2585-39.3.509

Piesman J, Karakashian SJ, Lewengrub S, Rudzinska MA, Spielmank A (1986) Development of *Babesia microti* sporozoites in adult *Ixodes dammini*. Int J Parasitol 16:381–385. https://doi.org/10.1016/0020-7519(86)90118-9

Pipano E, Shkap V (2000) Vaccination against tropical theileriosis. Ann N Y Acad Sci 916:484–500. https://doi.org/10.1111/j.1749-6632.2000.tb05328.x

Plentz A, Jilg W, Schwarz TF, Kuhr HB, Zent O (2009) Long-term persistence of tick-borne encephalitis antibodies in adults 5 years after booster vaccination with Encepur Adults. Vaccine 27:853–856. https://doi.org/10.1016/j.vaccine.2008.11.082

Pogodina V, Bochkova N, Karan L, Frolova M, Trukhina A, Malenko G et al (2004) Comparative analysis of virulence of the Siberian and Far-East subtypes of the tick-born encephalitis virus. Vopr Virusol 49:24–30

Portillo A, Santibáñez S, García-Álvarez L, Palomar AM, Oteo JA (2015) Rickettsioses in Europe. Microbes Infect 17:834–838. https://doi.org/10.1016/j.micinf.2015.09.009

Pospisilova T, Urbanova V, Hes O, Kopacek P, Hajdusek O, Sima R (2018) Tracking *Borrelia afzelii* from infected *Ixodes ricinus* nymphs to mice suggests a direct 'gut-to-mouth' route of Lyme disease transmission. BioRxiv 87:e00896-e918. https://doi.org/10.1101/316927

Pospisilova T, Urbanova V, Hes O, Kopacek P, Hajdusek O, Sima R (2019) Tracking of *Borrelia afzelii* transmission from infected *Ixodes ricinus* nymphs to mice. Infect Immun 87(6):e00896-e918. https://doi.org/10.1128/IAI.00896-18

Prevot PP, Adam B, Boudjeltia KZ, Brossard M, Lins L, Cauchie P et al (2016) Anti-hemostatic effects of a serpin from the saliva of the tick *Ixodes ricinus*. J Biol Chem 281:26361–26369. https://doi.org/10.1074/jbc.m604197200

Prymula R, Pöllabauer EM, Pavlova BG, Löw-Baselli A, Fritsch S, Angermayr R et al (2012) Antibody persistence after two vaccinations with either FSME-IMMUN® Junior or ENCEPUR® Children followed by third vaccination with FSME-IMMUN® Junior. Human Vaccines & Immunotherapeutics 8:736–742. https://doi.org/10.4161/hv.20058

Rachinsky A, Tobe S (1996) Role of second messengers in the regulation of juvenile hormone production in insects with particular emphasis on calcium and phosphoinositide signaling. Arch Insect Biochem Physiol 33:259–282. https://doi.org/10.1002/(SICI)1520-6327(1996)33:3/4%3C259::AID-ARCH7%3E3.0.CO;2-N

Ramamoorthi N, Narasimhan S, Pal U, Bao F, Yang XF, Fish D et al (2005) The Lyme disease agent exploits a tick protein to infect the mammalian host. Nature 436:573–577. https://doi.org/10.1038/nature03812

Rand K, Moore T, Sriskantha A, Spring K, Tellam R, Willadsen P et al (1989) Cloning and expression of a protective antigen from the cattle tick *Boophilus microplus*. Proc Natl Acad Sci USA 86:9657–9661. https://doi.org/10.1073/pnas.86.24.9657

Rego R, Trentelman J, Anguita J, Nijhof AM, Sprong H, Klempa B et al (2019) Counterattacking the tick bite: towards a rational design of anti-tick vaccines targeting pathogen transmission. Parasit Vectors 12:229. https://doi.org/10.1186/s13071-019-3468-x

Rizzoli A, Hauffe H, Carpi G, Vourc´h GI, Neteler M, Rosa R (2011) Lyme borreliosis in Europe Euro surveillance : bulletin Europeen sur les maladies transmissibles. Euro Surveill 16:19906

Rizzoli A, Silaghi C, Obiegala A, Rudolf I, Hubálek Z, Földvári G et al (2014) *Ixodes ricinus* and its transmitted pathogens in urban and peri-urban areas in Europe: new hazards and relevance for public health. Front Publ Health 2:251. https://doi.org/10.3389/fpubh.2014.00251

Robinson D, Leo N, Prociv P, Barker S (2003) Potential role of head lice *Pediculus humanus capitis* as vectors of *Rickettsia prowazekii*. Parasitol Res 90:209–211. https://doi.org/10.1007/s00436-003-0842-5

Rodríguez M., Montero C., Labarta V, de la Fuente J (1995) Effect of vaccination with GavacTM on the incidence of *Babesia bovis* infestations and the reduction in the number and frequency of acaricide treatments in cattle under production conditions in

Cuba. In: de la Fuente J (ed) Recombinant Vaccine for the Control of Cattle Tick, Elfos Scientiae, Havana, Cuba, pp 187–194
Rodríguez M, Penichet M, Mouris A, Labarta V, Luaces L, Rubiera R et al (1995b) Control of *B. microplus* populations in grazing cattle vaccinated with a recombinant Bm86 antigen preparation. Vet Parasitol 57:339–349. https://doi.org/10.1016/0304-4017(94)00678-6
Rodríguez M, Rubiera R, Penichet M, Montesinos R, Cremata J, Falcón V et al (1994) High level expression of the *B. microplus* Bm86 antigen in the yeast *P. pastoris* forming highly immunogenic particles for cattle. J Biotechnol 33:135–146. https://doi.org/10.1016/0168-1656(94)90106-6
Rodríguez M (2016) Developing anti-tick vaccines. Meth Mol Biol 1404:243–259. https://doi.org/10.1007/978-1-4939-3389-1_17
Rodriguez-Vivas RI, Jonsson NN, Bhushan C (2018) Strategies for the control of *Rhipicephalus microplus* ticks in a world of conventional acaricide and macrocyclic lactone resistance. Parasitol Res 117:3–29. https://doi.org/10.1007/s00436-017-5677-6
Roller L, Šimo L, Akira M, Slovák M, Park Y, Žitňan D (2015) Orcokinin-like immunoreactivity in central neurons innervating the salivary glands and hindgut of ixodid ticks. Cell Tissue Res 360:209–222. https://doi.org/10.1007/s00441-015-2121-z
Rosa PA, Tilly K, Stewart PE (2005) The burgeoning molecular genetics of the Lyme disease spirochaete. Nat Rev Microbiol 3:129–143. https://doi.org/10.1038/nrmicro1086
Roy S, Bhandari V, Dandasena D, Murthy S, Sharma P (2019) Genetic profiling reveals high allelic diversity, heterozygosity and antigenic diversity in the clinical isolates of the *Theileria annulata* from India. Front Physiol 10:673. https://doi.org/10.3389/fphys.2019.00673
Roy S, Bhandari V, Barman M, Kumar P, Bhanot V, Singh Arora J et al (2021) Population genetic analysis of the *Theileria annulata* parasites identified limited diversity and multiplicity of infection in the vaccine from India. Front Microbiol 11:579929. https://doi.org/10.3389/fmicb.2020.579929
Rumer L, Sheshukova O, Dautel H, Mantke OD, Niedrig M (2011) Differentiation of medically important Euro-Asian tick species *Ixodes ricinus, Ixodes persulcatus, Ixodes hexagonus* and *Dermacentor reticulatus* by polymerase chain reaction. Vector Borne Zoonot Dis 11:899–905. https://doi.org/10.1089/vbz.2009.0191
Sager H, Bertoni G, Jungi TW (1998) Differences between B cell and macrophage transformation by the bovine parasite, *Theileria annulata*: a clonal approach. J Immunol 161(1):335–341
Sahni SK, Narra HP, Sahni A, Walker DH (2013) Recent molecular insights into rickettsial pathogenesis and immunity. Future Microbiol 8:1265–1288. https://doi.org/10.2217/fmb.13.102
Seidman D, Ojogun N, Walker NJ, Mastronunzio J, Kahlon A, Hebert KS et al (2014) *Anaplasma phagocytophilum* surface protein AipA mediates invasion of mammalian host cells. Cell Microbiol 16:1133–1145. https://doi.org/10.1111/cmi.12286
Sharma A, Pooraiiouby R, Guzman B, Vu P, Gulia-Nuss M, Nuss AB (2019) Dynamics of insulin signaling in the black-legged tick, *Ixodes scapularis*. Front Endocrinol 21:292. https://doi.org/10.3389/fendo.2019.00292
Sherrard-Smith E, Sala KA, Betancourt M, Upton LM, Angrisano F, Morin MJ et al (2018) Synergy in anti-malarial pre-erythrocytic and transmission-blocking antibodies is achieved by reducing parasite density. Elife 7:e35213. https://doi.org/10.7554/elife.35213
Schneider H (1931) Über epidemische akute Meningitis serosa. Wien Klin Wochenschr 44:350–352
Schöndorf I, Beran J, Cizkova D, Lesna V, Banzhoff A, Zent O (2007) Tick-borne encephalitis (TBE) vaccination: applying the most suitable vaccination schedule. Vaccine 25:1470–1475. https://doi.org/10.1016/j.vaccine.2006.10.028
Schoofs L, De Loof A, Van Hiel M (2017) Neuropeptides as regulators of behavior in insects. Annu Rev Entomol 31:35–52. https://doi.org/10.1146/annurev-ento-031616-035500
Schuijt TJ, Narasimhan S, Daffre S, De Ponte K, Hovius JW, Van't Veer C et al (2011) Identification and characterization of *Ixodes scapularis* antigens that elicit tick immunity using yeast surface display. PLoS ONE 6:e15926. https://doi.org/10.1371/journal.pone.0015926
Schwarz A, von Reumont BM, Erhart J, Chagas AC, Ribeiro JM, Kotsyfakis M (2013) De novo *Ixodes ricinus* salivary gland transcriptome analysis using two next-generation sequencing methodologies. FASEB J 27:4745–4756. https://doi.org/10.1096/fj.13-232140
Shaw DK, Wang X, Brown LJ, Chávez AS, Reif KE, Smith AA et al (2017) Infection-derived lipids elicit an immune deficiency circuit in arthropods. Nat Commun 8:14401. https://doi.org/10.1038/ncomms14401
Shaw MK (2003) Cell invasion by *Theileria sporozoites*. Trends Parasitol 19(1):2–6. https://doi.org/10.1016/s1471-4922(02)00015-6
Silaghi C, Gilles J, Hohle M, Fingerle V, Just F, Pfister K (2008) *Anaplasma phagocytophilum* infection in *Ixodes ricinus,* Bavaria Germany. Emerg Infect Dis 14:972–974
Silatsa B, Simo G, Githaka N, Mwaura S, Kamga R, Oumarou F et al (2019) A comprehensive survey of the prevalence and spatial distribution of ticks infesting cattle in different agro-ecological zones of Cameroon. Parasit Vectors 12:489. https://doi.org/10.1186/s13071-019-3738-7
Sitt T, Poole EJ, Ndambuki G, Mwauraa S, Njorogea T, Omondi GP et al (2015) Exposure of vaccinated and naive cattle to natural challenge from buffalo-derived *Theileria parva*. Int J Parasitol Parasit Wildl 4(2):244–251. https://doi.org/10.1016/j.ijppaw.2015.04.006
Smith AA, Navasa N, Yang X, Wilder CN, Buyuktanir O, Marques A, Anguita J, Pal U (2016) Cross-species interferon signaling boosts microbicidal activity within the tick vector. Cell Host Microbe 20(1):91–98. https://doi.org/10.1016/j.chom.2016.06.001
Spooner RL, Innes EA, Glass EJ, Brown CG (1989) *Theileria annulata* and *T. parva* infect and transform different bovine mononuclear cells. Immunology 66(2): 284–288
Sprong H, Azagi T, Hoornstra D, Nijhof AM, Knorr S, Baarsma ME et al (2018) Control of Lyme borreliosis and other *Ixodes ricinus*-borne diseases. Parasit Vectors 11:145. https://doi.org/10.1186/s13071-018-2744-5
Stay B, Tobe S (2007) The role of allatostatins in juvenile hormone synthesis in insects and crustaceans. Annu Rev Entomol 52:277–299. https://doi.org/10.1146/annurev.ento.51.110104.151050
Stay B, Chan KK, Woodhead AP (1992) Allatostatin-immunoreactive neurons projecting to the corpora allata of adult *Diploptera punctata*. Cell Tissue Res 270:15–23. https://doi.org/10.1007/BF00381875
Steinaa L, Svitek N, Awino E, Njoroge T, Saya R, Morrison I, Toye P (2018) Immunization with one *Theileria parva* strain results in similar level of CTL strain-specificity and protection compared to immunization with the three-component Muguga cocktail in MHC-matched animals. BMC Vet Res 14(1):145. https://doi.org/10.1186/s12917-018-1460-x
Steinhoff MS, von Mentzer B, Geppetti P, Pothoulakis C, Bunnett NW (2014) Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. Physiol Rev 94(1):265–301. https://doi.org/10.1152/physrev.00031.2013
Steere A (2001) Lyme disease. N Engl J Med 345:115–125
Steere A, Strle F, Wormser GP, Hu LT, Branda JA, Hovius JW et al (2016) Lyme borreliosis. Nat Rev Dis Primers 2:16090. https://doi.org/10.1038/nrdp.2016.90

Strand M, Brown M, Vogel K (2016) Mosquito peptide hormones: diversity production and function. Adv Insect Physiol 51:145–188. https://doi.org/10.1016/bs.aiip.2016.05.003

Stuen S, Granquist EG, Silaghi C (2013) *Anaplasma phagocytophilum* - a widespread multi-host pathogen with highly adaptive strategies. Front Cell Infect Microbiol 3:31. https://doi.org/10.3389/fcimb.2013.00031

Stuen S, Okstad W, Artursson K, Al-Khedery B, Barbet A, Granquist EG (2015) Lambs immunized with an inactivated variant of *Anaplasma phagocytophilum*. Acta Vet Scand 57:40. https://doi.org/10.1186/s13028-015-0131-1

Sultana H, Neelakanta G, Kantor FS, Malawista SE, Fish D, Montgomery RR, Fikrig E (2010) *Anaplasma phagocytophilum* induces actin phosphorylation to selectively regulate gene transcription in *Ixodes scapularis* ticks. J Exp Med 207:1727–1743. https://doi.org/10.1084/jem.20100276

Süss J (2011) Tick-borne encephalitis 2010: epidemiology risk areas and virus strains in Europe and Asia-an overview. Ticks Tick Borne Dis 2:2–15. https://doi.org/10.1016/j.ttbdis.2010.10.007

Šimo L, Park Y (2014) Neuropeptidergic control of the hindgut in the black-legged tick *Ixodes scapularis*. Int J Parasitol 44:819–826. https://doi.org/10.1016/j.ijpara.2014.06.007

Šimo L, Slovák M, Park Y, Žitňan D (2009a) Identification of a complex peptidergic neuroendocrine network in the hard tick *Rhipicephalus appendiculatus*. Cell Tissue Res 335:639–655. https://doi.org/10.1007/s00441-008-0731-4

Šimo L, Žitňan D, Park Y (2009b) Two novel neuropeptides in innervation of the salivary glands of the black-legged tick *Ixodes scapularis*: myoinhibitory peptide and SIFamide. J Comp Neurol 517:551–563. https://doi.org/10.1002/cne.22182

Šimo L, Žitňan D, Park Y (2012) Neural control of salivary glands in ixodid ticks. J Insect Physiol 58:459–466. https://doi.org/10.1016/j.jinsphys.2011.11.006

Šimo L, Koči J, Park Y (2013) Receptors for the neuropeptides myoinhibitory peptide and SIFamide in control of the salivary glands of the blacklegged tick *Ixodes scapularis*. Insect Biochem Mol Biol 43:376–387. https://doi.org/10.1016/j.ibmb.2013.01.002

Šimo L, Sonenshine DE, Park Y, Žitňan D (2014) Nervous and sensory systems: structure, function, genomics and proteomics. In: Sonenshine DE, Roe RM (eds) Biology of ticks. Oxford Univ Press, Oxford, pp 309–367

Šimo L, Kazimirova M, Richardson J, Bonnet SI (2017) The essential role of tick salivary glands and saliva in tick feeding and pathogen transmission. Front Cell Infect Microbiol 7:281. https://doi.org/10.3389/fcimb.2017.00281

Tanaka Y, Suetsugu Y, Yamamoto K, Noda H, Shinoda T (2014) Transcriptome analysis of neuropeptides and G protein-coupled receptors (GPCRs) for neuropeptides in the brown planthopper *Nilaparvata lugens*. Peptides 53:125–133. https://doi.org/10.1016/j.peptides.2013.07.027

Taussig R, Kaldany R, Scheller R (1984) A cDNA clone encoding neuropeptides isolated from *Aplysia* neuron L11. Proc Natl Acad Sci USA 81:4988–4992. https://doi.org/10.1073/pnas.81.15.4988

Teal P (2002) Effects of allatotropin and allatostatin on in vitro production of juvenile hormones by the corpora allata of virgin females of the moths of *Heliothis virescens* and *Manduca sexta*. Peptides 23:663–669. https://doi.org/10.1016/s0196-9781(01)00660-x

Telford SR, Dawson JE, Katavolos P, Warner CK, Kolbert CP, Persing DH (1996) Perpetuation of the agent of human granulocytic ehrlichiosis in a deer tick-rodent cycle. Proc Natl Acad Sci USA 93:6209–6214. https://doi.org/10.1073/pnas.93.12.6209

Ternovoi V, Protopopova E, Chausov E, Novikov D, Leonova G, Netesov S et al (2007) Novel variant of tickborne encephalitis virus Russia. Emerg Infect Dis 13:1574–1578. https://doi.org/10.3201/eid1310.070158

Tipih T, Burt F (2020) Crimean-Congo hemorrhagic fever virus: Advances in vaccine development. BioRes Open Access 9:137–150. https://doi.org/10.1089/biores.2019.0057

Trager W (1939) Acquired immunity to ticks. J Parasitol 25:57–81. https://doi.org/10.2307/3272354

Trentelman J, Sima R, Krezdorn N, Tomás-Cortázar J, Barriales D, Takumi K et al (2020) A combined transcriptomic approach to identify candidates for an anti-tick vaccine blocking *B. afzelii* transmission. Sci Rep 10:20061. https://doi.org/10.1038/s41598-020-76268-y

Tretina K, Gotia HT, Mann DJ, Silva JC (2015) Theileria-transformed bovine leukocytes have cancer hallmarks. Trends Parasitol 31(7):306–314. https://doi.org/10.1016/j.pt.2015.04.001

Trimnell AR, Davies GM, Lissina O, Hails R, Nuttall P (2005) A cross-reactive tick cement antigen is a candidate broad-spectrum tick vaccine. Vaccine 23:4329–4341. https://doi.org/10.1016/j.vaccine.2005.03.041

Trimnell A, Hails R, Nuttall P (2002) Dual action ectoparasite vaccine targeting "exposed" and "concealed" antigens. Vaccine 4:29–30. https://doi.org/10.1016/s0264-410x(02)00334-1

Turck JW, Taank V, Neelakanta G, Sultana H (2019) *Ixodes scapularis* Src tyrosine kinase facilitates *Anaplasma phagocytophilum* survival in its arthropod vector. Ticks Tick Borne Dis 10:838–847. https://doi.org/10.1016/j.ttbdis.2019.04.002

Truesdell PF, Koladich PM, Kataoka H, Kojima K, Suzuki A, McNeil JN et al (2000) Molecular characterization of a cDNA from the true armyworm *Pseudaletia unipuncta* encoding *Manduca sexta* allatotropin peptide(1). Insect Biochem Mol Biol 30:691–702. https://doi.org/10.1016/s0965-1748(00)00040-0

Uchiyama H, Maehara S, Ohta H, Seki T, Tanaka Y (2018) Elevenin regulates the body color through a G protein-coupled receptor NlA42 in the brown planthopper *Nilaparvata lugens*. Gen Comp Endocrinol 167:86–103. https://doi.org/10.1016/j.ygcen.2017.07.017

Valdés JJ (2014) Antihistamine response: a dynamically refined function at the host-tick interface. Parasit Vectors 7:491. https://doi.org/10.1186/s13071-014-0491-9

Valle M, Mèndez L, Valdez M, Redondo M, Montero-Espinosa C, Vargas M et al (2004) Integrated control of *Boophilus microplus* ticks in Cuba based on vaccination with the anti-tick vaccine Gavac. Exp Appl Acarol 34:375. https://doi.org/10.1023/B:APPA.0000049223.92326.02

Van Dobbenburgh A, Van Dam A, Fikrig E (1999) Human granulocytic ehrlichiosis in western Europe. N Engl J Med 340:1214–1216. https://doi.org/10.1056/nejm199904153401517

Vannier EG, Diuk-Wasser MA, Ben Mamoun C, Krause PJ (2015) Babesiosis. Infect Dis Clin North Am 29:357–370

Vayssier-Taussat M, Kazimirova M, Hubalek Z, Hornok S, Farkas R, Cosson JF et al (2015) Emerging horizons for tick-borne pathogens: from the 'one pathogen-one disease' vision to the pathobiome paradigm. Future Microbiol 10:2033–2043. https://doi.org/10.2217/fmb.15.114

Villar M, Fernández de Mera IG, Artigas-Jerónimo S, Contreras M, Gortázar C, de la Fuente J (2020) Coronavirus in cat flea: findings and questions regarding COVID-19. Parasit Vectors 13:409. Published 2020 Aug 10. https://doi.org/10.1186/s13071-020-04292-y

Von Loewenich F, Stumpf G, Baumgarten B, Rollinghoff M, Dumler J, Bogdan C (2003) Human granulocytic ehrlichiosis in Germany: evidence from serological studies tick analyses and a case of equine ehrlichiosis. Ann NY Acad Sci 990:116–117. https://doi.org/10.1111/j.1749-6632.2003.tb07348.x

Wada T, Ishiwata K, Koseki H, Ishikura T, Ugajin T, Ohnuma N et al (2010) Selective ablation of basophils in mice reveals their nonredundant role in acquired immunity against ticks. J Clin Invest 120:2867–2875. https://doi.org/10.1172/jci42680

Wagemakers A, Coumou J, Schuijt TJ, Oei A, Nijhof AM, van 't Veer C et al (2016) An *Ixodes ricinus* tick salivary lectin pathway inhibitor protects *Borrelia burgdorferi* sensu lato from human complement. Vector Borne Zoonot Dis 16:223–228. https://doi.org/10.1089/vbz.2015.1901

Walker DH (2009) The realities of biodefense vaccines against *Rickettsia*. Vaccine 4:D52–D55. https://doi.org/10.1016/j.vaccine.2009.07.045

Wen S, Wang F, Ji Z, Pan Y, Jian M, Bi Y et al (2020) Salp15 a multifunctional protein from tick saliva with potential pharmaceutical effects. Front Immunol 10:3067. https://doi.org/10.3389/fimmu.2019.03067

Weaver RJ, Audsley N (2007) Neuropeptides of the beetle, *Tenebrio molitor* identified using MALDI-TOF mass spectrometry and deduced sequences from the *Tribolium castaneum* genome. Peptides 29(2):168–178. https://doi.org/10.1016/j.peptides.2007.09.020

Willadsen P, Bird P, Cobon G, Hungerford J (1995) Commercialisation of a recombinant vaccine against *Boophilus microplus*. Parasitology 110:43–45. https://doi.org/10.1017/s0031182000001487

Wise LN, Pelzel-McCluskey AM, Mealey RH, Knowles DP (2014) Equine piroplasmosis. Vet Clin North Am Equine Pract 30:677–693

Wormser G, Dattwyler RJ, Shapiro E, Halperin J, Steere A, Klempner M et al (2007) The clinical assessment treatment and prevention of lyme disease human granulocytic anaplasmosis and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 41:941. https://doi.org/10.1086/508667

Wormser G, Jacobson E, Shanker E (2021) Negative impact of the COVID-19 pandemic on the timely diagnosis of tick-borne infections. Diagn Microbiol Infect Dis 99:115226. https://doi.org/10.1016/j.diagmicrobio.2020.115226

Yabsley MJ, Shock BC (2012) Natural history of zoonotic *Babesia*: Role of wildlife reservoirs. Int J Parasitol 2:18–31. https://doi.org/10.1016/j.ijppaw.2012.11.003

Yang Y, Christie J, Köster L, Du A, Yao C (2021) Emerging human babesiosis with "Ground Zero" in North America. Microorganisms 9:440. https://doi.org/10.3390/microorganisms9020440

Yoon KA, Kim K, Kim W, Bang W, Ahn N, Bae C et al (2020) Characterization of venom components and their phylogenetic properties in some aculeate bumblebees and wasps. Toxins 1:12. https://doi.org/10.3390/toxins12010047

Zent O, Bröker M (2005) Tick-borne encephalitis vaccines: past and present. Expert Rev Vaccines 4:747–755. https://doi.org/10.1586/14760584.4.5.747

Zhu XX, Oliver J (2001) Cockroach allatostatin-like immunoreactivity in the synganglion of the American dog tick *Dermacentor variabilis* (Acari: Ixodidae). Exp Appl Acarol 25:1005–1013

Zhu XX, Oliver J (1991) Immunocytochemical localization of an insulin-like substance in the synganglion of the tick *Ornithodoros parkeri* (Acari: Argasidae). Exp Appl Acarol 13:153–159

Zintl A, Gray S, Skerrett H, Mulcahy G (2005) Possible mechanisms underlying age-related resistance to bovine babesiosis. Parasite Immunol 27:115–120. https://doi.org/10.1111/j.1365-3024.2005.00748.x

Zintl A, Mulcahy G, Skerrett H, Taylor S, Gray J (2003) Babesia divergens a bovine blood parasite of veterinary and zoonotic importance. Clin Microbiol Rev 16:622–636. https://doi.org/10.1128/cmr.16.4.622-636.2003

Zweygarth E, Nijhof AM, Knorr S, Ahmed JS, Al-Hosary A, Obara I, Bishop RP, Josemans AI, Clausen PH (2020) Serum-free in vitro cultivation of *Theileria annulata* and *Theileria parva* schizont-infected lymphocytes. Transbound Emerg Dis 1:35–39. https://doi.org/10.1111/tbed.13348