



REVIEW ARTICLE

Roles of Tick Symbiotic Microorganisms in Pathogen Transmission

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Abstract

Ticks have garnered significant research interest owing to their ability to vector pathogens into humans and animals. The intricate symbiotic associations between ticks and tick microbiota substantially influence developmental processes, reproductive success, and potential to serve as vectors for tick-transmitted diseases. This paper reviews the epidemiology of diseases transmitted by ticks and delves into the composition and function of tick endosymbionts in transmission and infection. This review also highlights the role of tick immunity in maintaining gut homeostasis. Finally, tick symbiont-pathogen interactions and potential strategies for controlling tick-borne diseases by leveraging symbiotic relationships are discussed.

Keywords: tick, tick-borne pathogens, endosymbionts, symbiont-pathogen interactions, tick control strategies

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INTRODUCTION

Ticks, which are specialized blood-sucking parasites, widely infest a variety of hosts, including mammals, birds, reptiles, and amphibians. More than 907 species of ticks have been recorded globally with additional species yet to be discovered [1]. Ticks threaten humans and livestock through direct blood-sucking, secondary infections, and the transmission of a multitude of pathogens [2]. The emergence of new tick-borne diseases and the resurgence of existing diseases pose severe challenges to public health. For example, Lyme disease has spread across the United States, garnering widespread concern [3]. The distribution range of arthropods is expanding as a result of global climate change and human activities, leading to the expansion of tick-borne disease endemic areas [4,5]. Simultaneously, new tick-borne pathogens and diseases are

being identified [6,7]. Currently, progress on tick-borne pathogens has been made in pathogen detection, identification of pathogenic mechanisms, and predicting disease trends [8–11]. However, the mechanisms underlying interactions between ticks, pathogens, and hosts have not been completely elucidated [12]. Gaining insight into the molecular and cellular interactions at the tick-pathogen interface holds the potential to yield new targets and strategies, which can be harnessed to obstruct the transmission of tick-borne pathogens to hosts [13].

In addition to transmitting pathogens, ticks also carry a variety of non-pathogenic microorganisms, such as maternally inherited endosymbiotic microbes and environmentally acquired gut microbes (non-endosymbionts) [14–16]. These endosymbiotic microbes significantly impact survival adaptation, nutritional needs [17,18], growth and development [19,20],

reproductive capacity [21], the environmental stress response [22], immune defense [23], and disease transmission in ticks [24,25]. With the development of technology to detect symbionts, the infection status and functional mechanisms of tick endosymbionts are understood more thoroughly than ever before. For example, it has been shown that obligate endosymbionts present in various ticks, such as *Coxiella*- and *Francisella*-like endosymbionts (*Coxiella*-LEs and *Francisella*-LEs, respectively), provide essential nutrients during tick development. Thus, these endosymbionts may become new targets for tick control strategies in the future [26,27]. Comparative genomics and phylogenetic analysis have revealed the evolutionary connections between endosymbionts and pathogens, which may be crucial for understanding the basic biological characteristics of ticks and the prevention of tick-borne diseases [14]. This review determined the relationship and interactions between tick pathogens and endosymbionts to facilitate the development of strategies for tick-borne disease control.

Tick-borne pathogen diversity and hazards

Ticks serve as competent vectors mediating the transmission of diverse zoonotic pathogens encompassing viruses, bacteria, and parasites [28]. The remarkable environmental adaptability and long life cycles of ticks contribute to the sustained persistence of viable pathogens [29]. Notably, ticks can simultaneously carry multiple pathogens, which increases the risk of co-infections [30]. These biological characteristics establish ticks as highly pathogenic vectors posing a potential threat to humans and animals. Tick-borne viruses (TBVs) span five major families with representative pathogens including *Nairoviridae* (e.g., Crimean-Congo hemorrhagic fever virus [31]), *Phenuiviridae* (e.g., severe fever with thrombocytopenia syndrome virus [32]), *Flaviviridae* (e.g., tick-borne encephalitis virus [33–37] and Songling virus), *Orthomyxoviridae* (e.g., Thogoto virus [38–41]), and *Reoviridae* (e.g., Colorado tick fever virus [42]). Tick-borne bacteria primarily include the spotted fever group *Rickettsia* and *Borrelia*, especially *Borrelia burgdorferi*, which causes Lyme disease, the most prevalent tick-borne illness in the Northern Hemisphere. Relapsing fever-associated *B. miyamotoi* has recently been detected in southern China [43,44]. Additionally, emerging *Rickettsia* species (e.g., YN02/YN03 in Yunnan and *R. asembonensis* in Tibet) highlight expanding genetic diversity. *Anaplasma phagocytophilum* (*A. phagocytophilum*) [45] and *Francisella tularensis* further contribute to rising tick-borne bacterial threats, which are exacerbated by the expanding geographic distribution of tick habitats [46,47]. Tick-borne parasites predominantly involve *Babesia* and *Theileria*. Human babesiosis is mainly caused by *Babesia microti* and *B. divergens* with regional variants, like *B. venatorum* in China and Europe [48–51] and *B. motasi*-like organisms in South Korea [52]. *Theileria* infections in cattle and sheep drive economic losses worldwide [53–57]. Collectively, these tick-borne pathogens threaten global health, as detailed in Table 1.

Endosymbiotic microorganisms in ticks

In recent years next-generation sequencing technologies have been used to study the composition of the tick microbiome [96,97]. Ticks exhibit a rich diversity of microorganisms forming complex interaction networks. The endosymbiotic microorganisms of ticks have garnered increasing attention, including infection rates, tissue distribution, diversity, impact on the host, and mechanisms of action [98–100]. The endosymbiotic microorganisms in ticks are relatively diverse (Table 2), including *Coxiella*-LEs, *Francisella*-LEs, *Candidatus Midichloria mitochondrii* (*M. mitochondrii*), *Spiroplasma*, *Wolbachia*, and *R. buchneri* [111]. Endosymbiotic microorganisms have a pivotal role in enhancing the fitness and survival of ticks by providing essential nutritional support through unique metabolic capabilities [112–114]. For example, *Coxiella*-LEs, the genome of which encodes genes for vitamin B synthesis, effectively compensates for deficiency of these nutrients in host blood, thereby supplying critical nutritional supplementation to ticks [115]. *Coxiella*-LEs are distributed in the malpighian tubules and ovaries in *Rh. sanguineus*, yet *Coxiella*-LEs functions exhibit tissue-specific specialization. *Coxiella*-LEs in the malpighian tubules are primarily involved in cellular metabolism and stress responses, whereas *Coxiella*-LEs in the ovaries are closely associated with cell proliferation. This functional divergence underscores the tissue-specific roles of *Coxiella*-LEs and the close coordination with the physiologic demands of the tick [116]. Furthermore, the endosymbiont, *M. mitochondrii*, exhibits remarkable biological traits in *Ixodes ricinus*, including the ability to invade the mitochondria of tick ovarian cells and achieve 100% efficiency in transovarial transmission [106]. The distribution and functional roles of *M. mitochondrii* are dynamically regulated. Specifically, *M. mitochondrii* predominantly localizes to the ovaries and trachea in unfed female ticks, while the distribution expands to include the ovaries, malpighian tubules, and salivary glands in partially engorged females. Genomic analyses suggested that *M. mitochondrii* may have multifaceted roles in the tick antioxidant defense, energy metabolism, and osmoregulation, which significantly enhances the blood-feeding adaptability of ticks [117]. In summary, endosymbiotic microorganisms, through diverse metabolic functions and tissue-specific interactions, are indispensable to tick survival, reproduction, and pathogen transmission, highlighting the critical role in the biology of ticks and the epidemiology of tick-borne diseases.

The concept of transgenerational microbiomes was studied in *I. scapularis* by Brinkerhoff et al. [118]. Brinkerhoff et al. [118] reported that the microbial richness, diversity, and composition in adult female ticks and eggs were similar, with *Rickettsia* spp. being the dominant genus, indicating vertical transmission of *Rickettsia* spp. Similarly, Zhang et al. [119] demonstrated that the microbial communities in female *D. silvarum* and eggs presented high similarity. Bonnet et al. [111] reported that approximately two-thirds of ticks harbor *Coxiella*, *Rickettsia* and

TABLE 1 | Main tick-borne diseases, tick vectors, and geographic distribution worldwide.

Disease	Causative organism	Clinical features	Mortality rate (%)	Tick vector(s)	Area(s) of endemicity	Ref(s)
Virus						
Tick-borne encephalitis	Tick-borne encephalitis virus	Fever, headache, nausea, meningitis	0.5–35	<i>I. persulcatus</i> , <i>I. ricinus</i>	Europe, China, Mongolia, and parts of Russia and Scandinavia	[58]
Crimean-Congo hemorrhagic fever	Crimean-Congo hemorrhagic fever virus	High fever, headaches, nausea, vomiting, abdominal pain, thrombocytopenia, leukopenia, and elevated liver enzyme levels	3–40	<i>Hy. marginatum</i>	Asia, Africa, and Eastern Europe	[59–61]
Severe fever with thrombocytopenia syndrome	Severe fever with thrombocytopenia syndrome virus	High fever, thrombocytopenia, leukocytopenia, gastrointestinal symptoms, elevated liver enzymes, proteinuria, hematuria	5–40	<i>H. longicornis</i>	China, Japan, and South Korea	[62]
Heartland virus disease	Heartland virus	Fever, fatigue, anorexia, diarrhea, leukopenia, thrombocytopenia, elevated liver transaminases	12.5	<i>Amblyomma americanum</i> (A. americanum)	North America	[63]
Bourbon virus disease	Bourbon virus	Fever, leukopenia and thrombocytopenia	NA	<i>A. americanum</i>	Bourbon County, Kansas, USA	[64,65]
Powassan encephalitis	Powassan virus lineages 1 and 2	Headaches, mild fever, neurologic complications, cognitive deficits, memory impairment	10	<i>I. scapularis</i> and <i>I. cookei</i>	North America and the Russian Federation	[66]
Omsk hemorrhagic fever	Omsk hemorrhagic fever virus	High-grade fever, headaches, myalgias, moderate-to-severe hemorrhagic manifestations, pneumonia, nephrosis, and meningitis	0.5–3	<i>Dermacentor reticulatus</i> (D. reticulatus)	Western Siberian regions	[67–69]
Colorado tick fever	Colorado tick fever virus	Fever, headaches, muscle aches, fatigue	NA	<i>D. andersoni</i>	Western America, Canada	[70]
Kyasanur forest disease	Kyasanur forest disease virus	Endothelial damage and leakage, bleeding, organ damage, and even shock in severe cases. High fever (lasting 6–11 days), anorexia, abdominal pain, body aches, diarrhea, headaches, leukopenia, myalgia, thrombocytopenia, increased intravascular permeability	> 9000 cases have occurred between 1957 and 2017, 0.9%–33%.	<i>H. spinigera</i>	Southern India	[71–75]
Xue-Cheng virus disease	Xue-Cheng virus	Acute febrile, leukopenia, elevated serum hepatic aminotransferases, elevated lactate dehydrogenase, and elevated hypersensitive C-reactive protein	NA	<i>H. concinna</i> and <i>H. japonica</i>	Northeastern China, specifically the Mudanjiang region	[76]
Wetland virus disease	Wetland virus	Fever, headaches, malaise, myalgias, arthritis, leukopenia, thrombocytopenia, and elevated lactate dehydrogenase	NA	<i>H. concinna</i>	Northeastern China, including Inner Mongolia, Heilongjiang, Jilin, and Liaoning	[77]
Bacteria						
Tick-borne recurrent fever	<i>B. miyamotoi</i>	Recurrent bouts of fever, headaches, and malaise	NA	<i>Ornithodoros</i> and <i>Ixodes</i>	Worldwide, except for Antarctica and Australia	[78–80]

TABLE 1 | (Continued)

Disease	Causative organism	Clinical features	Mortality rate (%)	Tick vector(s)	Area(s) of endemicity	Ref(s)
Q fever	<i>Coxiella burnetii</i>	Febrile flu-like illness, pneumonia, and endocarditis	0.5–38	<i>Rhipicephalus</i> , <i>Dermacentor</i> , <i>Hyalomma</i> , <i>Haemaphysalis</i> and <i>Ixodes</i>	Worldwide	[81–83]
Mediterranean spotted fever	<i>Rickettsia conorii</i> (<i>R. conorii</i>)	Fever, headaches, arthralgias and myalgias, local lymphadenopathy, hepatomegaly, splenomegaly, and gastrointestinal symptoms	0–3	<i>Rhipicephalus sanguineus</i> (<i>Rh. sanguineus</i>)	Mediterranean basin, northern Africa and southern Europe	[84]
Tick-borne African fever	<i>R. africae</i>	Fever, headaches, and myalgias	NA	<i>Amblyomma</i>	Sub-Saharan Africa	[81]
Tick-borne lymphadenopathy	<i>R. slovaca</i> , <i>R. raoultii</i> , <i>R. rioja</i>	Fever, headaches, myalgias, and cervical adenopathy	NA	<i>Dermacentor</i>	Europe	[81]
Lyme diseases	<i>B. burgdorferi</i> sensu lato	Early stage: fever, chills, headaches, fatigue, muscle and joint aches, and one or more erythema migrans rashes. Early disseminated stage: fever, fatigue, headaches, myalgias, arthralgias, and carditis. Late-stage: arthritis, encephalopathy, and neuropathy	NA	<i>I. persulcatus</i> , <i>I. pacificus</i> , and <i>I. scapularis</i>	United States, Europe, Asia	[2,85,86]
Human granulocytic anaplasmosis	<i>A. phagocytophilum</i>	High fever, rigors, generalized myalgias, severe headaches, and gastrointestinal symptoms.	Fatality rate: 0.3% (based on data from 2008–2012)	<i>I. scapularis</i> , <i>I. pacificus</i>	Northeastern U.S.	[87]
Human ehrlichiosis	<i>Ehrlichia</i>	High fever, rigors, generalized myalgias, severe headaches, and gastrointestinal symptoms	3	<i>A. americanum</i> and <i>D. variabilis</i>	Northeastern mid-Atlantic and Midwest U.S.	[87]
Neorhlichiosis	<i>Candidatus</i> Neorhlichia mikurensis	Fever, myalgias, arthralgias, erythema nodosum, erysipelas-like rashes, and elevated C-reactive protein levels	NA	<i>I. Ricinus</i> and <i>I. granulatus</i>	Europe and Thailand	[88,89]
Tularemia	<i>Francisella tularensis</i>	Endotoxemia, sudden fever, chills, weakness, dry cough, diarrhea, headaches, erythematous papules at the inoculation site, swollen and painful lymph glands, acute pharyngotonsillitis with a sore throat, trouble breathing, and pneumonia	The overall mortality of an untreated tularemia infection is 5–15%	<i>D. variabilis</i> , <i>D. andersoni</i> and <i>A. americanum</i>	Worldwide	[90]
Parasites						
Babesiosis	<i>B. venatorum</i> , <i>B. microti</i> , and <i>B. divergens</i>	Fever, jaundice, anemia, and hemoglobinuria	Immunodeficient individuals (40% case fatality).	<i>I. ricinus</i> , <i>I. persulcatus</i> and <i>H. longicornis</i>	Europe and China	[81,91]
Theileriosis	<i>Theileria</i>	Fever, lymphadenopathy, and corneal opacity	5–100	<i>Hyalomma</i> , <i>Amblyomma</i> , <i>Haemaphysalis</i> , and <i>Rhipicephalus</i>	Worldwide	[92,93]
Hepatozoonosis	<i>Hepatozoon canis</i> and <i>Hepatozoon americanum</i>	Pyrexia, anemia, lethargy, severe myositis, and gait abnormalities	NA	<i>Rh. sanguineus</i>	Worldwide	[94,95]

NA, data not available.

TABLE 2 | Endosymbiotic microorganisms and functions.

Symbionts	Host(s)	Tissue distribution	Impact on hosts	Ref(s)
<i>Coxiella</i> -LEs	<i>Amblyomma</i> , <i>Haemaphysalis</i> , <i>Rhipicephalus</i> , <i>Ixodes</i> , and <i>Dermacentor</i>	Midgut, malpighian tubules, ovaries, and salivary glands	B vitamin supplementation, chorismate production, and reproductive fitness	[99-102]
<i>Francisella</i> -LEs	<i>Ornithodoros moubata</i> (<i>O. moubata</i>), <i>Amblyomma</i> , <i>Hyalomma</i> and <i>Haemaphysalis</i>	Midgut, malpighian tubules, ovaries, and salivary glands	Providing B vitamins	[103,104]
<i>Candidatus Midichloria mitochondrii</i>	<i>I. ricinus</i>	Ovaries	ATP source	[105,106]
<i>Spiroplasma</i>	<i>Ixodes</i> , <i>Dermacentor</i> , and <i>Rhipicephalus</i>	Salivary glands, midgut and ovaries	May be involved in immune regulation or microbial community interactions	[107,108]
<i>Wolbachia</i>	<i>Ixodes</i> , <i>Amblyomma</i> , and <i>Rhipicephalus</i>	Ovaries	Induction of reproductive incompatibility, parthenogenesis, and feminization, in addition to acting as defensive endosymbionts	[109]
<i>R. buchneri</i>	<i>I. scapularis</i>	Ovarian tissues and salivary glands	Inhibits infection and replication of <i>R. monacensis</i> and <i>R. parkeri</i> in tick cells	[110]

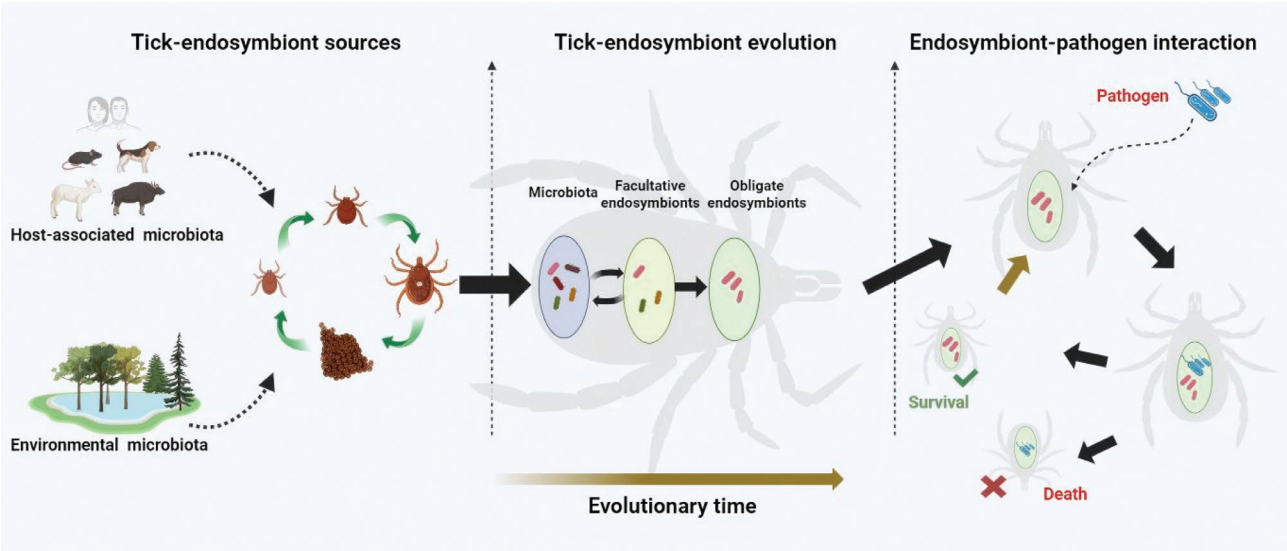


FIGURE 1 | Tick-endosymbiont sources [111], evolution [24], and interactions between endosymbionts and pathogens [121]. Tick-endosymbiont sources encompass host and environmental microorganisms, which evolve into facultative or obligate endosymbionts. The interactions with pathogens influence tick survival and fitness.

Francisella are also common infectious microorganisms in ticks. Co-infections with symbiotic microorganisms in ticks are common and involve complex infection types. Studies have shown that tick microbial communities are influenced by factors spanning organs, individuals, populations, environments, and spatiotemporal scales [120]. To decode the complex interactions among ticks, the microbiota, and pathogens, we propose an integrated eco-evolutionary model [24]. This model reveals that tick endosymbionts derive from host-associated and environmental

microbes, evolving into facultative or obligate forms. The interactions with pathogens drive selective outcomes, which determines tick survival or elimination (Fig 1). This framework advances our understanding of tick microbiota dynamics and the impact on pathogen transmission.

Tick innate immunity regulates gut microbiota homeostasis

The defense system of ticks is crucial for maintaining homeostasis between the internal symbiotic microbiota

and pathogens, which is vital for health and vector capabilities [8]. Ticks use a sophisticated defense mechanism that can recognize and combat a variety of pathogens, while selectively tolerating symbionts and influencing the structure and function of the gut microbiota [122,123]. During blood feeding, ticks form a peritrophic membrane (PM), which is a chitin- and protein-rich structure that acts as a molecular sieve and separates the intestinal lumen from the surrounding midgut space. This PM serves as a protective barrier for intestinal epithelial cells, offers resistance against abrasion from food and invasion by pathogens, and facilitates colonization by beneficial symbiotic microbiota [124,125].

The innate immune response in ticks involves several signaling pathways, including the Toll, immune deficiency (IMD), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, all of which are involved in the recognition and response to invading pathogens and regulation of symbiotic microbiota (Fig 2) [127–129]. The extracellular signaling molecule, Spätzle, is activated in response to microbial stimuli in the Toll pathway, and upon binding to the Toll

receptor, triggers a cascade of signal transduction leading to the production of antimicrobial peptides (AMPs) to counteract infection [130,131]. The IMD pathway is activated by bacterial peptidoglycan, which is recognized by peptidoglycan recognition proteins (PGRPs) and initiates a signaling cascade that results in the generation of AMPs [132,133]. The JAK-STAT pathway is activated by dual oxidase (DUOX) in response to microbial and pathogenic stimuli, producing reactive oxygen species (ROS) that help control pathogens and maintain a balance in the symbiotic microbiota. ROS also promote the release of a cytokine-like molecule, unpaired 3 (UPD), which activates the JAK-STAT signaling pathway upon binding to its receptor, DOME [134,135]. STAT factors are responsible for regulating the immune response, epithelial cell repair, and integrity of the peritrophic membrane. Transcription factors facilitate the synthesis of AMPs and other immune effector molecules upon entering the nucleus to defend against pathogen invasion and maintain stability of the microorganism community [136]. Collectively, these evolutionarily conserved pathways establish a multi-layered defense network in ticks that

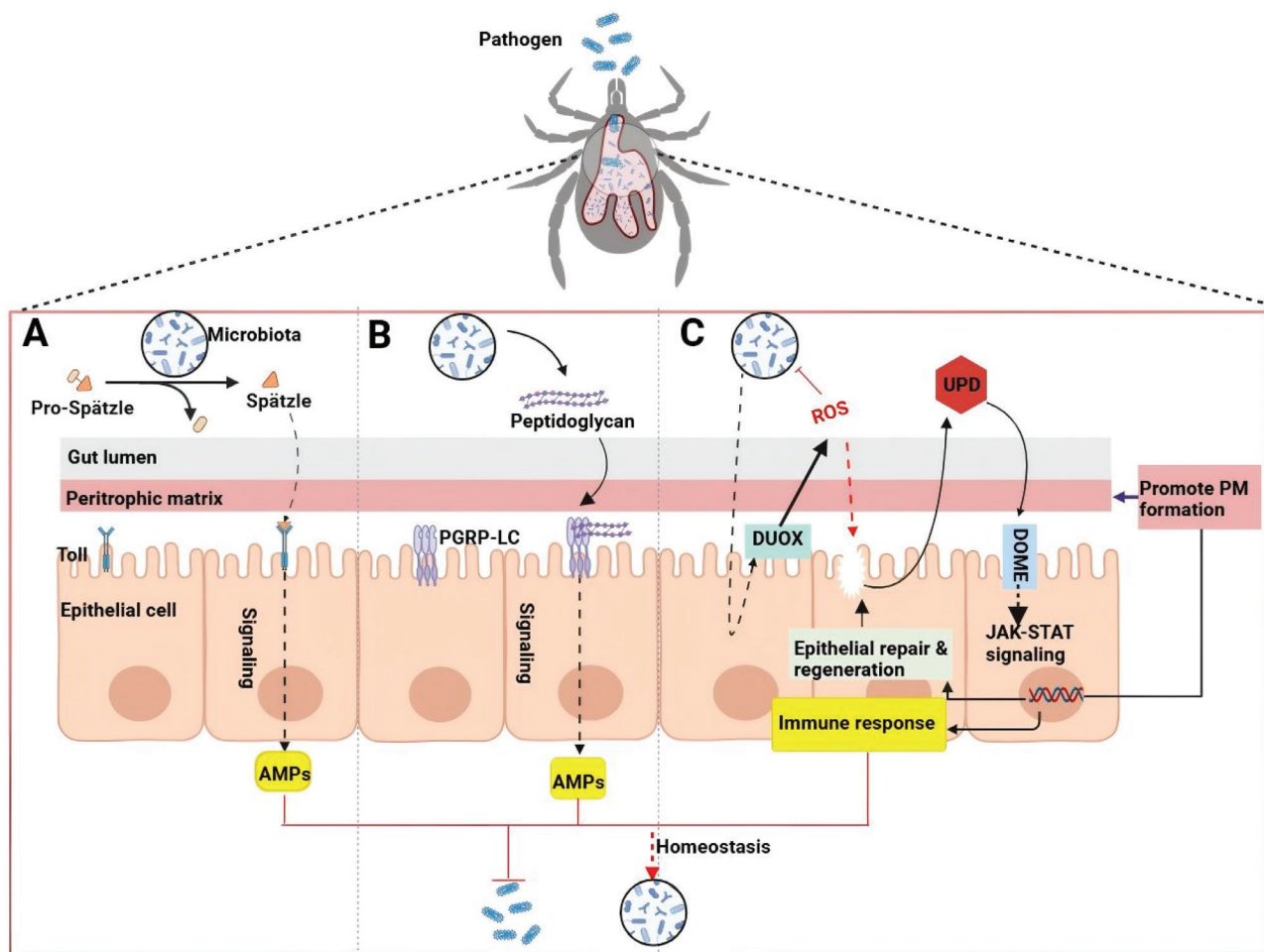


FIGURE 2 | The gut microbiota prevents pathogen invasion in ticks through the following three immune signaling pathways: A. Toll pathway, B. IMD pathway, and C. JAK/STAT pathway. (Based on citation [126]).

orchestrate pathogen clearance through AMPs synthesis, ROS-mediated microbicidal activity, and tissue barrier reinforcement, while dynamically balancing immune activation with symbiotic microbiota homeostasis, which is a critical equilibrium that influences vector fitness and pathogen transmission capacity.

Tick endosymbiont-pathogen interactions

The endosymbiotic microbiota of ticks has a critical role in determining vector competence, with intricate interactions between these microbes and tick-borne pathogens shaping disease transmission dynamics. The mechanisms underlying these interactions can be categorized into four primary dimensions. First, endosymbiotic microorganisms and pathogens engage in resource competition within the tick, which influences pathogen colonization and survival. For example, high abundances of *Coxiella*-LEs and *Francisella*-LEs in salivary glands are inversely correlated with *Rickettsia* spp. pathogen loads in *R. pulchellus* and *A. gemma*, a pattern that is also observed with *Pseudomonas* spp. dominance [137]. Notably, *D. andersoni* resistant to *Anaplasma marginale* exhibit elevated proportions of *Francisella*-LEs, *Rickettsia* spp., and *R. buchneri* compared to susceptible counterparts, which suggests competitive exclusion as a potential mechanism [138]. Second, endosymbiotic microorganisms can directly modulate pathogen proliferation through inhibitory or facilitative effects. *Wolbachia* enhances *A. phagocytophilum* replication in ISE6 cells [139]. *R. buchneri* suppresses pathogenic *Rickettsiaceae* and *A. phagocytophilum* through putative antibiotic synthesis, which is supported by the inhibitory activity of its lysate against *R. parkeri* [110]. Third, symbiotic microorganisms influence pathogen infectivity by regulating tick immune responses. Gut symbionts modulate the STAT pathway to upregulate peritrophin-1 expression in *I. scapularis*, thereby maintaining intestinal barrier integrity and facilitating *B. burgdorferi* colonization [123]. Fourth, endosymbionts participate in tick metabolic processes, which indirectly affects pathogen transmission. For example, *Francisella* F-Om supports B vitamin synthesis in *O. moubata* [140], while *Francisella*-LEs and *Midichloria* jointly fulfill this role in *H. marginatum* [20]. *Coxiella*-LEs contribute to *Rh. sanguineus* reproduction by synthesizing L-proline and B vitamins [21]. *Coxiella*-LEs-derived shikimate pathway metabolites enhance serotonin synthesis in *H. longicornis*, which promotes feeding behavior [99]. These metabolic interactions not only govern tick physiology but also indirectly influence vector capacity.

Pathogens can manipulate the tick microbiome to enhance their fitness. *A. phagocytophilum* induces *I. scapularis* antifreeze glycoprotein expression, which reshapes the gut microbiota to facilitate colonization [141], while *B. burgdorferi* alters the gut microbiome to create a favorable niche for its persistence [142]. Narasimhan et al. [143] used axenic tick rearing, antibiotic treatment, and RNA interference to modulate the microbiome of *I. scapularis*, yet observed no significant impact on *B. burgdorferi* migration

within *I. scapularis* or subsequent infectivity in mice. Similarly, Hamilton et al. [144] induced larval microbiota dysbiosis in *I. ricinus* through surface sterilization protocols, revealing no statistically significant alteration in nymphal *B. burgdorferi* acquisition rates or load. These findings underscore that alterations in the symbiotic microbiota do not significantly influence the dynamics of pathogen transmission, thus highlighting the inherent complexity and condition-mediated uniqueness associated with pathogen species and ways of symbiont interference in symbionts–pathogen interactions.

Pluri-competent vector (PCV) ticks exhibit distinct microbial signatures linked to the ability to transmit multiple pathogens. Mota et al. analysed 16S rRNA datasets from field-collected ticks, which revealed significantly higher microbial richness in PCV ticks (e.g., *I. Ricinus* and *H. longicornis*) compared to mono-competent vectors (MCV) (e.g., *D. silvarum* and *I. holocyclus*). Mota et al. identified *Rickettsia*, *Staphylococcus*, and *Corynebacterium* as key genera enriched in PCV ticks relative to MCV using linear models for differential abundance (LinDA). Functional profiling via PICRUSt2 demonstrated mycothiol biosynthesis with ROS detoxification and β -lactam resistance pathways as critical mechanisms facilitating multi-pathogen co-existence in PCV ticks [145]. These findings highlight the role of microbial community structure and function in shaping vector competence for diverse pathogens. Future research integrating climatic variables, host diversity, and pathogen dynamics will help elucidate the mechanisms of microbiome-driven pathogen transmission in ticks [97].

Strategies to control ticks and tick-borne diseases involving manipulation of symbionts

The pivotal role of symbiotic microbial communities in regulating arthropod metabolism and vector competence has emerged as a transformative intervention paradigm. Field studies of mosquitoes in Yunnan Province revealed that *Rosenbergiella*_YN46, a plant-derived commensal bacterium, acidifies mosquito midguts through glucose dehydrogenase secretion, effectively inactivating flaviviruses by inducing envelope protein denaturation. This natural symbiont distribution showed an 83% negative correlation with dengue prevalence in surveillance areas [146]. Furthermore, *Serratia* AS1-TK, a genetically modified commensal, utilizes blood meal-inducible LipA promoters to simultaneously express anti-plasmodial and anti-viral effectors. Semi-field trials demonstrated a 61.1% reduction in *Plasmodium* infection and a 54.4% decrease in Zika virus load in intervention groups [147]. This approach gained cross-species validation from recent breakthroughs in tick microbiome manipulation. Strategic targeting of keystone taxa (e.g., *Enterobacteriaceae* [148] and *Staphylococcus* [149]) not only restructured microbial networks but also simultaneously compromised tick fitness and pathogen transmission dynamics, which provided precise targets for intervention strategies. Notably, functional disruption

of essential endosymbiont activities, especially B vitamin biosynthesis pathways through vaccine-based approaches, could substantially impair tick survival while blocking transovarial transmission routes and establishing innovative strategies for integrated control of ticks and associated vector-borne diseases [150].

Traditional anti-tick vaccines are developed using antigens of ticks and the pathogens ticks harbor. In contrast, symbiotic microorganism vaccines modified through genetic engineering techniques provide an environmentally sustainable method for controlling tick-borne diseases [14,151,152]. We propose three potential strategies to control ticks and pathogens. First, adult *A. americanum* exhibits the ability to consume non-nutritive liquid water actively. This behavior can be exploited by introducing inorganic compounds or microorganisms into the water source, effectively delivering toxic

agents to the ticks and resulting in their mortality [153]. Furthermore, the strategic introduction of symbiotic microorganisms can disrupt the developmental and reproductive processes of ticks, leading to a reduction in the fitness and competitive ability of ticks (S+) that are colonized by these microorganisms to decrease the overall tick population and thereby reducing the risk of disease transmission (Fig 3A) [154,155]. Second, the Frankenbacteriosis approach involves genetically modifying symbiotic microorganisms, such as *Sphingomonas* spp., to express key surface proteins of *A. phagocytophilum*, including major surface protein 4 and heat shock protein 70. This creates 'Franken *Sphingomonas*,' which mimics the pathogen and competes with the pathogen for cellular resources, thereby reducing *A. phagocytophilum* infection in tick cells. This genetic manipulation not only reduces pathogen load but also enhances tick

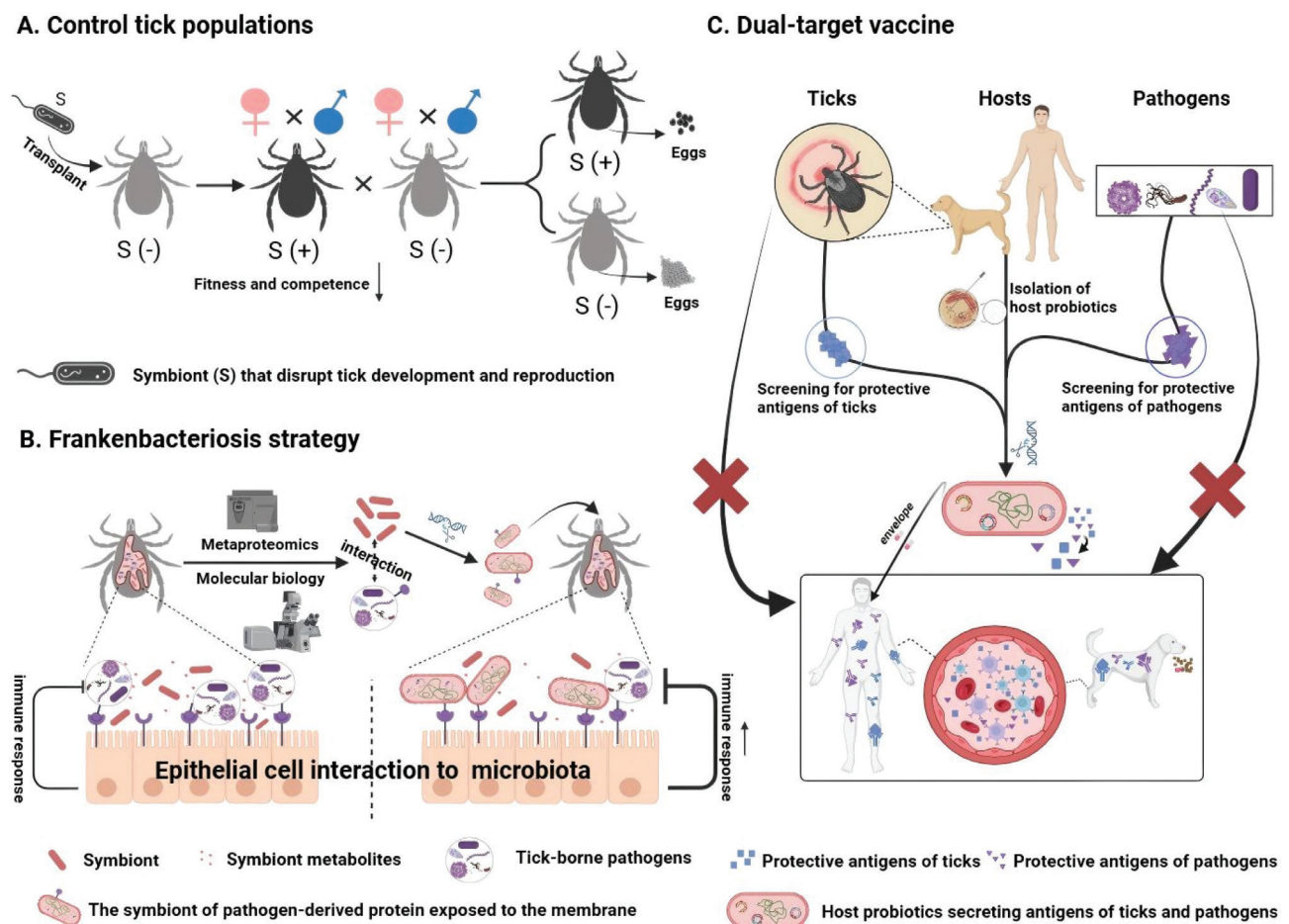


FIGURE 3 | Potential strategies of symbiotic microorganisms against ticks and tick-borne pathogens. A. Control tick populations. Transplanting a symbiont (S) that disrupts tick development and reproduction, allowing symbiont-positive (S(+)) and symbiont-negative (S(-)) ticks to propagate, and evaluating fitness and functionality to control tick populations. B. Frankenbacteriosis strategy. Advanced metaproteomic and molecular techniques decode epithelial-microbiota interactions, enabling symbionts to mimic pathogen effects and boost tick immunity. C. Dual-target vaccine. Oral symbiotic vaccines combine host probiotics as well as tick and pathogen antigens to induce dual immune responses. Probiotics isolated from the host are genetically engineered with screened protective antigens from ticks and pathogens, then orally administered to activate the vascular immune cells of hosts for antibody production, effectively blocking tick infestations and neutralizing tick-borne pathogens. The lower right panel illustrates immune cells (e.g., plasma cells) within the host blood vessel being activated to produce antibodies targeting tick and pathogen antigens.

fitness by altering the microbial community. (Fig 3B) [26,27]. Third, an oral symbiotic vaccine is simple to administer and can induce mucosal immunity compared to the traditional injection route, making the oral route a more ideal immunization route, especially for immunizing wild animals [156,157]. The development of oral vaccines that target ticks and the transmitted pathogens focuses on the identification and selection of protective antigens from ticks and pathogens [158], as well as isolating probiotics from the host [159]. Upon ingestion of oral vaccines, probiotics enhance gut-associated immune responses, stimulating immune cells to produce antibodies and cytokines. Antibodies elicited by the vaccine bind to critical tick proteins (e.g., the salivary protein, IpSAP [160] and the midgut protein, BM86 [161]), impairing the immunosuppressive function of ticks and nutrient absorption. Pathogen-specific antibodies simultaneously neutralize invading pathogens within the host, thus impeding transmission. (Fig 3C). Each strategy demonstrates unique advantages; specifically, population suppression offers species specificity, Frankenbacteriosis enables precision microbiome engineering, and dual-target oral vaccines provide dual protection for the host. The ultimate efficacy will likely depend on synergistic integration rather than standalone application. In addition, biosafety concerns should be fully considered, especially the potential consequences brought about by the ecologic disruption caused by genetically modified symbionts.

Prospects

Tick symbiotic microorganisms significantly influence physiologic processes and vector capabilities. This review systematically synthesizes significant advances in endosymbiont-pathogen interactions, with a brief discussion of non-endosymbiotic microorganisms. Subsequent studies should further investigate the composition of these microorganisms, with the prediction that non-endosymbiotic microorganisms may also play a role in pathogen transmission. Analyzing the detailed molecular links between the functions of symbiotic microorganisms and the interaction mechanisms with pathogens across different tick species remains a crucial future research direction. While conducting mechanistic studies, field trials and ecologic modeling should also be conducted to bridge gaps between laboratory findings and actionable public health solutions. These findings are expected to deepen our understanding of the complex biological interactions among ticks, pathogens, and symbiotic microorganisms, boost the development of anti-tick microbial vaccines, and hasten practical implementation.

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CONFLICTS OF INTEREST

We confirm and declare that the manuscript was prepared without any conflicts of interest or financial relationships.

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