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A Comprehensive Review of the Role of Tick-Associated Microbiota in Pathogen Acquisition, Survival, and Transmission

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ABSTRACT

There are many types of microbes in ticks, which help the ticks and play a significant role in the spread of certain diseases. The review consolidates existing information on tick-related microbiota, their roles, and their interactions with the environment, primarily focusing on the effects on diseases caused by Borrelia, Anaplasma, and Rickettsia. We study the range of microbes, including bacteria, fungi, viruses, protozoa, and archaea, in ticks at different points in their life and in all their habitats to find out how different aspects can affect their microbial communities. The review looks into the various ways that resident microbes can affect tick immunity, choose their habitats in ticks, and either resist or help pathogens to survive in ticks. To explain these complex interactions, two case studies of Borrelia burgdorferi in Ixodes ticks and Rickettsia spp. in Dermacentor ticks are examined. In the end, we study novel microbiota-aimed controls, including those that use symbionts, paratransgenesis, and microbial interference, as good replacements for common acaricides. Studying the connection between ticks and the microorganisms on them gives new ways to manage and treat tick-borne conditions.

INTRODUCTION

Ticks are blood-feeding parasites that must feed on hosts in order to stay alive. Such hosts are mammals, birds, and reptiles (1). Haemoprotozoan causes nation-level damages in the farming sector by killing and diminishing the farming performance, depriving the country of valuable resources (2). Ticks are vectors of some of the most serious zoonoses of the world, such as Lyme disease, anaplasmosis, babesiosis, or the Crimean-Congo hemorrhagic fever; pathogens include (Borrelia, Rickettsia, Anaplasma); protozoa (Babesia spp.); viruses (tick-borne encephalitis virus) (3). Historically, studies of tick-borne disease ecology have been based on the pathogen-tick-host triad, paying little attention to the microbiota that live within the tick (4). However, the indigenous microbiota comprising the symbiotic, commensal, and environmental bacteria of ticks constitutes a critical feature towards influencing vector competence through regulation of immune responses, provision of necessary nutrients, or direct interaction between such bacteria and invading pathogens. The structure of these microbial communities is very variable: environmental constraints are critical factors in their structure, as reflected in variation in bacterial diversity of laboratory-reared compared to wild ticks (5). The host ticks have less well-studied or understood microbial communities; these attract much less attention, yet are equally important. These communities include TBP, but also non-pathogenic microorganisms such as commensal and mutualistic microbes that are also plentiful in ticks (6). The recent advances in high-throughput sequencing have revealed a surprisingly diverse and dynamic tick microbiome that varies by species, developmental stage, region of origin, and status of blood-feeding (7). Endosymbionts, including *Coxiella*-like and *Rickettsiella*-like bacteria, in addition to compensating for a deficiency of blood meals on nutritional levels through the synthesis of B vitamins and cofactors, also modulate the expression of tick antimicrobial peptides and other immune effectors (8). These microbe-tick interactions can promote or

restrict pathogen uptake, persistence, and subsequent transfer to vertebrate hosts (9). Solving more intrinsic mechanistic understanding of Vector competence, but also for the development of microbiome-based interventions like paratransgenesis or microbiota-targeted vaccines, is more important (10). This review addresses the effect of microbiota on the tick pathogen relationship, its significance with regard to vector competence, pathogen transmission dynamics, and implications in disease control.

Composition of Tick Microbiota

The biodiversity of the tick microbial community is regulated by many factors such as the type of tick species, life stages, habitat, and positions that they feed on. Bacteria represent the most extensively studied component of the tick microbiota (1). These microorganisms may well be described as symbiotic, commensal, or pathogenic. Commonly, the *Rickettsia* species exist in ticks, and most of them are obligate intracellular bacteria of endosymbiotic nature (11, 12). Pathogenic species, including *Rickettsia rickettsii* (Rocky Mountain spotted fever), coexist with nonpathogenic strains that shape tick physiology and pathogen dynamics. (13) Non-pathogenic *Rickettsia* may aid in metabolism and even outcompete pathogenic strains, which will, in turn, influence vector competence (14). Tick-borne viruses are a less-studied but important part of the tick-borne pathogenic viruses, such as *Crimean-Congo hemorrhagic fever virus* (CCHFV) and *Tick-borne encephalitis virus* (TBEV), and are maintained in tick communities using vertical (transovarial) and horizontal transmission cycles (3). Species of fungi associated with ticks are comparatively least understood as compared to bacteria and viruses. Some of the fungal species may hold off the colonization of pathogenic bacteria or viruses through other species for resources or by producing antimicrobial compounds. Fungi may aid ticks in adaptation to environmental stress or exposure to soil. The *Metarhizium anisopliae* and *Beauveria bassiana*, which are also considered biocontrol agents against ticks (15). Protozoan microorganisms, including *Babesia* and *Theileria,* are well-known tick-borne pathogens (16). However, commensal or symbiotic protozoa in the tick microbiota are poorly studied. The least studied part of the tick microbiota, Archaea, has little evidence of their presence (17). Archaea primarily found in the gut of ticks are presumed to originate from environmental sources or the host's blood. Their roles can be involved in nutrient metabolism, although their exact effects on pathogen dynamics are yet to be determined (18). Tick species have unique microbiota because of genetic and physiological differences. For example, the genus Ixodes ticks are dominated by *Borrelia* and *Rickettsia,* and the *Rhipicephalus spp* are often infected by *Coxiella-like endosymbionts* (19). The microbial makeup varies as ticks develop from larvae through nymph to adult stages; the change indicates a change in environmental exposure and feeding behaviour (20). Depending on the type of habitat where ticks reside (forests, grasslands, or urban areas), they discover a variety of microbial communities (8). Soil microbes as well as microbiota in the host blood influence the gut microbiome of ticks, but the blood meal plays a large role in the microbiota, introducing new microbes from the host while changing the abundance of existing ones. Tick-specific microbiota may affect the survival of pathogens in the ticks (10). The tick microbiota is a diverse and changing community determined by a number of biological and environmental factors (10).

Role of Tick Microbiota in Pathogen Acquisition and Survival

The mechanism of pathogen acquisition by ticks is a complicated synergy between invasive pathogens and indigenous microbiota (symbiotic and non-pathogenic microflora) (13). Such interactions have the potential to significantly determine whether or not a pathogen establishes itself in the tick, an important step toward being transmitted to a new host. Resident microbiota is versatile in its roles, ranging from tick immune system modulation to competition for resources and ecological niches with the pathogens (9). Tick symbiotic endosymbionts, including *Coxiella-like endosymbionts (CLEs)*, are indispensable for tick survival and reproduction (8). Such bacteria deliver essential nutrients, including vitamins and cofactors that are lacking in the blood meal. Beyond their dietary purpose, symbiotic bacteria have also been seen to affect pathogen acquisition and persistence by changing the physiological and immunological settings inside the tick (21).

Symbiotic bacteria can manipulate the immune system of the tick such that a niche friendly to pathogen colonization. *CLEs* in *Rhipicephalus* ticks can inhibit antimicrobial or immune pathways, decreasing the capacity of the tick to kill incoming pathogens (22). Some symbiotic bacteria and pathogens develop mutualistic or neutral relationships, sharing the same niches, but competing almost insignificantly, relationships (23). *Coxiella-like endosymbionts* can also coexist with *Rickettsia* so as to exist both in the tick midgut and salivary glands (24). Metabolites or signaling molecules produced by symbiotic bacteria are likely to end up inadvertently helping the persistence of pathogen survival (25, 26). These interactions continue to be an active area of investigation and hope for the discovery of weaknesses in tick-pathogen systems. *Borrelia burgdorferi* (the causative agent of the disease), among other pathogens, must compete for nutrients and attachment sites in the tick midgut with resident gut microbes (27). Lack of behavior modification by resident bacteria better suited to the tick's environment may enable them to outcompete invading pathogens, thus reducing pathogen colonization success (28).

Nontoxic microbes fill ecological niches in the gut of the tick, its salivary glands, and the hemolymph, which have fewer places available for pathogen colonization (13). Some resident bacteria in humans exude antimicrobial peptides, toxins, or other molecules that help to prevent pathogenic growth. For example, there is evidence available on the fact that competition between *Borrelia burgdorferi* and native gut bacteria can impact the pathogen's ability to establish in the midgut of Ixodes tick species (29). The acquisition by Ixodes ticks of *Borrelia burgdorferi* constitutes a good model of the competition

between the pathogen and pathogens present in the microbiota (30). Borrelia uses a variety of strategies to combat competition, such as expression of cell surface proteins, which increase its adhesion to midgut epithelial cells. These proteins could assist the pathogen in occupying the roles of displacing or outcompeting resident microbes for colonization sites (31). Pathogens can use metabolites generated by symbiotic bacteria as nutrients/nutrition, or growth factors. For example, *Anaplasma spp* are capable of successful reproduction within ticks that have symbionts that produce nutrients. Pathogens may influence resident microbiota in order to curb the tick's immune defenses (32). The introduction or strengthening of competitive non-pathogenic microbes in ticks could inhibit pathogen colonization, hence paratransgenesis (33).

Ticks depend on their symbiotic microbiota to maintain their immune responses and hence achieve a balanced flora that may be beneficial to both the tick and its pathogens. Symbiotic bacteria such as *Coxiella-like endosymbionts (CLEs)* regulate the tick's immune pathway to downregulate antimicrobial responses (8). *CLEs* in *Rhipicephalus* ticks regulate the production of antimicrobial peptides (AMPs), essential molecules against invading pathogens (8). Lowered ability of AMP to function enables the surviving pathogens, such as *Rickettsia* and *Anaplasma,* to remain unidentified (34). The microbiota promotes the development of an immunotolerant state in ticks, especially in the gut and salivary glands, where the pathogens are located. This tolerance reduces inflammatory events that would be harmful to both microbiota and pathogen in turn (9).

Some pathogens take advantage of the immune modulation furnished by symbionts. *Borrelia* benefits from lowered immune activity in the midgut of Ixodes ticks, raising the chances of its survival and reproduction (29). Knowing the role of tick microbiota in pathogen survival is very useful in understanding vector competence, the ticks' ability to acquire, maintain, and transmit pathogens. These reflections open new opportunities for a targeted intervention on tick-borne diseases.

Role in Pathogen Transmission

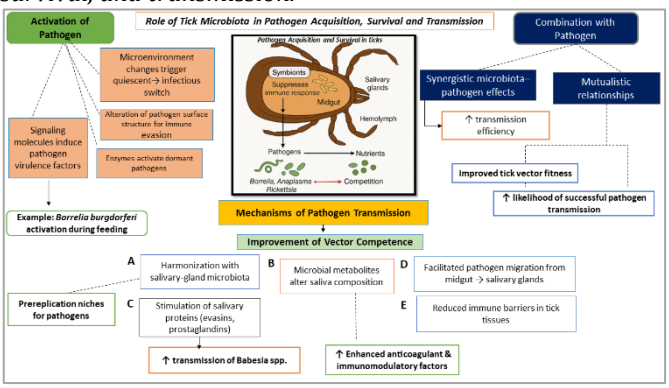
The microbiota of ticks is of great importance when it comes to aiding the positive spread of pathogens into the vertebrate hosts (Figure 1) (35). Mechanisms of pathogen transmission as a result of tick microbiota include activation of the pathogen, improvement of the vector competence, and combination with the pathogen (12). Some resident microbes in the tick gut or salivary glands produce signaling molecules that prescribe the expression of the virulence factors by pathogens. These switches ready the pathogen for successful colonization of the host, e.g., the switch that allows the *Borrelia burgdorferi* to change from a dormant stage in the tick midgut to an active invasive form during feeding is governed by the microbial environment (29). The microbiota may be producing enzymes that will activate dormant pathogens or alter the pathogen surface structure, enabling them to evade the host immune system. *Anaplasma spp*. The outer-membrane proteome can be dynamically altered through enzymatic actions in microbial metabolites by the tick (36). The presence of symbiotic bacteria has the potential to change the microenvironment of the tick, allowing for pathogens to switch between a quiescent and infectious form. This guarantees pathogens are prepared for transference in the apt situation; usually during tick feeding (25).

The term vector competence is referred to as the ability of a tick to pick up, maintain, and transmit pathogens (37). The pathogen transmission is an essential point of the salivary glands. Some microbes in the tick microbiota harmonize with the salivary gland environment and establish reinfections and prereplication microenvironments for pathogens (38). *Rickettsia* spp. Use the salivary gland-associated microbiota to increase rates of replication and transmission to the host (38). Microbial metabolites have the potential to change the makeup of tick saliva such that it enhances anticoagulant and immunomodulatory properties. This makes for a friendly establishment for pathogens to actually successfully be transmitted to the host (39).

Ticks that carry microbiota that stimulate the production of salivary proteins, evasins, and prostaglandins are more competent at transmitting diseases such as *Babesia spp*. Microbiota can modify the movement of pathogens from the midgut to salivary glands, which is a critical step of the transmission cycle (38, 39). The presence of symbiotic bacteria might decrease immune barriers in the tick, thus facilitating easier pathogen crossing of tissues. The interplay between the microbiota of ticks and pathogens most of the time has synergistic effects, which increase transmission efficiency (21). Mutualistic relationships of microbes with pathogens offer benefits to both, for functioning, survival, and dissemination. This may improve the tick as a vector in terms of fitness and also increase the possibility of the pathogen transmission to a successful level (40).

Figure 1

shows the role of tick microbiota in pathogen acquisition, survival, and transmission.



Microbiota-pathogen Interactions: Case Studies *Borrelia Burgdorferi* and *Ixodes* Ticks

The interaction between *Borrelia burgdorferi* and the microbiota of *Ixodes* ticks, such as *Ixodes scapularis* and *Ixodes ricinus,* acts as a model for studying how resident microbiota impact pathogen colonization and persistence in ticks (41). After consumption during the blood meal, *B. burgdorferi* enters mid midgut of *Ixodes* ticks where it has to adapt to compete with resident microbial communities. Research indicates that the gut environment can be altered

by the microbiota of the tick so as to favour the initial adhesion and colonization of *B. burgdorferi* (42). Not all commensal bacteria are harmless, as some produce antimicrobial peptides or occupy ecological niches, thus causing competition that may compromise *B. burgdorferi* proliferation (43). *B. burgdorferi* needs to survive in the tick through its various life stages: larva, nymph, and adult (25). The microbiota is involved in the maintenance of gut homeostasis, providing an indirect benefit by regulating immune responses and by establishing a microenvironment conducive for *B. burgdorferi* in its healthy state. Microbial biofilms in the gut of the tick may protect the organism *B. burgdorferi* from host defenses and external stressors. The microbiota promotes biofilm formation by either contributing to extracellular matrix components or by modifying local conditions, which promote biofilm stability (44).

Rickettsia spp. and *Dermacentor* Ticks

Dermacentor ticks contain many species of *Rickettsia*, which are both symbiotic and pathogenic. Interactions between these strains portray ways in which microbiota can promote or prevent pathogen colonisation and transmission (45). Symbiotic species of *Rickettsia,* including *R. peacockii,* live in *Dermacentor andersoni* ticks and perform fundamental functions that will facilitate tick survival and reproduction (12). Yet, these symbiotic strains can fight with pathogenic *Rickettsia* species, such as *Rickettsia rickettsii* (causative agent of Rocky Mountain spotted fever), to gain resources and their niches inside the tick (46). Symbiotic strains may compete and inhibit the pathogenic species of *Rickettsia* by competitive exclusion or by immune modification. The presence of *R. peacockii* in some tick populations correlates with fewer *R. rickettsii* cases (47, 48). In some cases, the presence of symbiotic *Rickettsia* might inadvertently aid pathogenic strains to persist in the tick by manipulating to immune responses of the tick or changing the physiology of the tick in ways that would support pathogen persistence (49). Geographically, interaction between symbiotic and pathogenic *Rickettsia* differs due to separate profiles in tick populations, in environmental aspects, and host availability. These dynamics determine rickettsia-associated diseases epidemiology (46).

Implications for Disease Control

Microbiota Manipulation

Manipulation of the microbiota of ticks by way of genetic manipulation or by means of microbial interference provides a revolutionary strategy to control vector competence (50). Symbiotic bacteria in ticks can be genetically engineered to turn out antimicrobial peptides or other molecules that prevent pathogen colonization or survival. Such engineered microbes can now be released to tick populations to minimize the effectiveness of their harboring and transmitting of pathogens (25). Utilizing the competitive exclusion by which non-pathogenic microbes outcompete pathogens for resources or niches, the pathogen colonization can thereby be limited. By using selective amplification of beneficial microbes, the composition of microbiota can be shifted to reduce pathogen fitness (51). Several studies have reported that some native bacteria can inhibit the colonization of *Borrelia burgdorferi* in Ixodes ticks and thus offer proof of concept for this approach (44, 52).

Symbiont-Targeted Interventions

Targeting critical symbiotic bacteria is an accurate strategy in terms of interrupting tick biology and pathogen survival (25). *Coxiella-like endosymbionts (CLEs)* play critical roles in the nutritional homeostasis of the tick. Manipulation of these symbionts using antimicrobial agents or inhibitors, or gene-targeting technologies, may impair tick survivability and reproduction, leading to a reduction in the transmission of associated pathogens (53). For example, tick fitness has been demonstrated to be reduced when *CLEs* are removed from Rhipicephalus ticks, which in turn makes them less effective vectors (54). Parasites are known to establish niches conducive for maintaining and exploiting pathogens, and their targeting, i.e., the disruption of CLE-mediated immune modulation, can reduce the pathogen load in ticks. This approach is especially effective against pathogens such as *Rickettsia* spp, whose survival and transmission depend on co-occurring symbionts (55). Schemes employing antibiotics or other kinds of interferences should be tailored to minimize the risk of resistance development, with a view to sustaining treatment effectiveness without encouraging resistance development of target and non-target organisms. In showing the introduction of non-pathogenic microbes into ticks in order to out-compete the pathogens in ticks suggests a promising, environmentally friendly control strategy (56). Pathogen microbes can be dispatched to tick populations by means of bait stations, acaricides, or by environmental application. These systems guarantee that a large percentage of ticks ingest the probiotics, therefore causing long-term changes in microbiota composition (57). This approach is responsive to integrated pest management (IPM) by reducing non-target effects and ecological disturbance. An enhanced level of awareness with regard to the interplay of microbiota, tick biology, and pathogens is key to developing applicable interventions. Spectral screening needs to be studied on a large scale in field trials to determine the feasibility and scale of effectiveness of such approaches. Changing the tick microbiota can be scary for unintentional ecological impacts (58). Development of standardized protocols would enhance more robust and reproducible findings and more clarity in understanding the ecological and functional role of tick microbiota.

CONCLUSIONS

Tick-associated microbiota have a key and complex role in determining the vector competence of ticks since they engage with pathogen acquisition, survival, and transmission. These microbial assemblages, consisting of bacteria, viruses, fungi, protozoa, and archaebacteria, not only facilitate tick physiology, yet engage pathogenically in varied manners to alter infection outcome. These interactions, when understood, expose the fundamental mechanisms by which pathogens remain and transmit in tick populations. Newcomers in research reveal the promising promise of microbiota-targeted strategies, including symbiont manipulation, paratransgenesis, and competitive exclusion as novel methods of tick-borne

disease control. However, applying such findings into real interventions, methods need to be standardized, ecological risk assessments, and the scale of delivery systems developed. The further study of tick-microbiota-pathogen relationships may deliver promise for the further scientific development and public health applications in vector control.

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