



Review Article

Modulation of host immunity by tick saliva



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ABSTRACT

Next generation sequencing and proteomics have helped to comprehensively characterize gene expression in tick salivary glands at both the transcriptome and the proteome level. Functional data are, however, lacking. Given that tick salivary secretions are critical to the success of the tick transmission lifecycle and, as a consequence, for host colonization by the pathogens they spread, we thoroughly review here the literature on the known interactions between tick saliva (or tick salivary gland extracts) and the innate and adaptive vertebrate immune system. The information is intended to serve as a reference for functional characterization of the numerous genes and proteins expressed in tick salivary glands with an ultimate goal to develop novel vector and pathogen control strategies.

Significance: We overview all the known interactions of tick saliva with the vertebrate immune system. The provided information is important, given the recent developments in high-throughput transcriptomic and proteomic analysis of gene expression in tick salivary glands, since it may serve as a guideline for the functional characterization of the numerous newly-discovered genes expressed in tick salivary glands.

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List of abbreviations: Akt, protein kinase B; BMDMs, bone marrow-derived macrophages; BSA, bovine serum albumin; cAMP, cyclic adenosine monophosphate; CCL, chemokine (C–C motif) ligand; CCR, C–C motif receptor; CD, cluster of differentiation; ConA, concanavalin A; CTL, cytotoxic T lymphocytes; CXCL, chemokine (C–X–C motif) ligand; DC, dendritic cell; ERK, extracellular signal-regulated kinase; IDO, indoleamine 2,3 deoxygenase; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IRAK, interleukin-1 receptor-associated kinase; LC, Langerhans cell; LFA-1, leukocyte function-associated antigen-1; LPS, lipopolysaccharide; MC, mast cell; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; NET, neutrophil extracellular trap; NF-κB, nuclear factor kappa light chain-enhancer of activated B cells; NK, natural killer; NO, nitric oxide; PBL, peripheral blood leukocytes; PGE₂, prostaglandin E₂; PI3k, phosphatidylinositol-3 kinase; PMNs, polymorphonuclear lymphocytes; RANTES, regulated upon activation, normal T cell expressed and secreted; ROS, reactive oxygen species; SGE, salivary gland extract; STAT, signal transducer and activator of transcription; sTNFR1, soluble TNF receptor I; TGF, transforming growth factor; Th, helper T cell; TLR, toll-like receptor; TNF, tumor necrosis factor; VLA-4, very late activation-4.

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1. Introduction

Ticks are obligatory blood-feeding arthropods that belong to the subclass *Acari*, order *Ixodida*, and three families: *Ixodidae* (hard ticks), *Argasidae* (soft ticks), and *Nuttalliellidae*. Soft ticks feed repeatedly for minutes to hours, while hard ticks usually stay attached to their hosts and feed for several days or even weeks, but only once in each life stage [1,2]. The amount of blood ingested is species and life-stage specific, with females of some tick species increasing their volume up to 200 times by the end of blood feeding [3].

Ticks are important vectors that transmit a wide range of pathogens. The most common tick-borne pathogens are viruses and bacteria, but fungi, protozoa, and helminths can also be transmitted [4]. Clinically and epidemiologically, the most important tick-borne diseases are: tick-borne encephalitis (TBE), caused by the TBE virus; Lyme disease, caused by spirochetes belonging to the *Borrelia burgdorferi* sensu lato complex in Europe and *B. burgdorferi* sensu stricto in the USA; tick-borne spotted fever, caused by *Rickettsia* spp.; anaplasmosis, caused by *Anaplasma* spp.; and babesiosis, caused by *Babesia* spp. protozoa [5,6]. Pathogens have different life cycles, but the transmission usually begins with a tick biting an infected vertebrate host and pathogen uptake by the tick in the blood meal. Pathogens, e.g. *Borrelia* spp. spirochetes then stay in the midgut and wait until next feeding, which triggers their proliferation and migration through the midgut wall to hemocoel and, ultimately, to the salivary glands. Moreover, spirochetes interact with some midgut and salivary components that induce *Borrelia* proliferation or increase their infectious potential [7]. When the tick bites its next vertebrate host, pathogens are transmitted via tick saliva. In some tick species the pathogens are transmitted transovarially from the female to laid eggs, thus keeping the level of prevalence in the tick population [8]. Tick saliva has been shown to facilitate pathogen transfer to the vertebrate host by virtue of its pharmacological properties, including modulation of the vertebrate immune system [9–11]. Moreover, tick saliva contains toxins belonging to families also found in venomous animals, such as spiders or snakes, and that can induce paralysis and other toxicoses [12].

To secure uninterrupted blood uptake, ticks suppress and evade the complex physiological host immune and homeostatic responses that are raised against them. Hemostasis, which includes coagulation, vasoconstriction, and platelet aggregation, is the first innate host defense mechanism against the mechanical injury caused by intrusion of tick mouthparts into the host skin. This early vertebrate host response further includes complement activation and inflammation, with the host inflammatory response including, among other factors, rapid leukocyte infiltration after skin injury [13]. Keratinocytes, endothelial cells, and resident leukocytes such as mast cells, dendritic cells, and macrophages make immediate contact with tick saliva or the tick hypostome and are activated. Pro-inflammatory chemokines and cytokines including interleukin-8 (IL-8), tumor necrosis factor (TNF), and IL-1 β are released to recruit neutrophils and other inflammatory cells to the area of tick infestation [14]. Following tick feeding, there is activation of both the cellular and humoral branches of vertebrate adaptive immunity [15]. Activated memory T and B cells (in the case of secondary infestation) amplify the host inflammatory response to ticks by releasing specific cytokines and producing antibodies that target tick salivary or mouthpart-derived antigens to activate complement or sensitize mast cells and basophils [9,14,15]. The strength and specificity of the host immune response and its effect on tick physiology depend on the host and tick species, the host's health, and its genotype [16]. The same is true for

tick defense mechanisms, since both tick salivary components and host immune mechanisms have been co-evolving. As a result, the tick–host interaction can be considered an “arms race” between the new defense mechanisms developed by the host and the evasion strategies developed by ticks [17]. As an adaptation to blood feeding, ticks secrete a complex mixture of immunomodulatory substances in their saliva that suppress both innate and adaptive host immune responses that can cause pain, itch, blood flow disruption in the tick feeding cavity, or even direct damage to the tick, thereby subverting tick rejection and death [18–20]. Despite the specificity of tick salivary component targets, there is also redundancy at the molecular, cellular, and functional level [9, 13]. The richness and diversity of tick salivary compounds have been established in several transcriptomic studies over the last 15 years and, more recently, by next generation sequencing (NGS) studies.

The rapid developments in NGS and proteomics are reflected in the recent progress made in tick research, in which several transcriptomic and proteomic studies have been published over the last few years. These studies represent a rich data source that provides the basis for functional studies and investigation of gene expression dynamics during tick feeding and different physiological states. For instance, significant differences in the salivary proteome of partially and fully engorged female *Rhipicephalus (Boophilus) microplus* ticks have been described [21]. More recently, a transcriptomic study described over 800 immuno-proteins in *Amblyomma americanum* saliva during 24–48 h of feeding [22]. A transcriptomic analysis of *Dermacentor andersoni* salivary glands resulted in over 500 singletons and 200 clusters in which a number of sequences with similarity to mammalian genes associated with immune response regulation, tumor suppression, and wound healing were identified [23]. By combining transcriptomic and proteomic approaches, nearly 700 proteins were identified in *D. andersoni* saliva after 2 and 5 days of feeding, from which 157 were postulated to be involved in immunomodulation and blood feeding [24]. Schwarz and colleagues performed a comprehensive study of *Ixodes ricinus* salivary and midgut transcriptomes and proteomes and found that the transcriptomic and proteomic dynamics did not 100% overlap in different tick tissues [25]. A recent study by Kotsyfakis and colleagues characterized transcriptional dynamics in the *I. ricinus* female and nymph salivary glands and midguts at various feeding time points [26], and established that some gene families show stage- and time-specific expression, possibly via epigenetic control. In addition, the genes encoding secreted proteins exhibited a high mutation rate, possibly representing a mechanism of antigenic variation, and analysis of the midgut transcriptome revealed several novel enzymes, transporters, and antimicrobial peptides [26]. A transcriptomic analysis of *Amblyomma maculatum* salivary glands revealed almost 3500 contigs with a secretory function [27]. Another sialome (salivary gland transcriptome) of *Amblyomma* ticks was published by Garcia and colleagues [28]: the authors analyzed samples from *Amblyomma triste* nymphs and females, *Amblyomma cajennense* females, and *Amblyomma parvum* females and focused on putative transcripts encoding anticoagulants, immunosuppressants, and anti-inflammatory molecules. A further study characterized *A. americanum* nymph and adult proteomes and compared the data with other *Amblyomma* species [29]. A *Rhipicephalus pulchellus* tick sialome study revealed differences between males and females [30], with the sequences identified used for a preliminary proteomic study to identify 460 male and over 2000 female proteins. A sialomic study was also performed in *Haemaphysalis flava* that revealed tens of thousands of genes, some of which were putative secreted salivary proteins thought to be involved with blood feeding and ingestion [31].

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