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Review

Sialomes and Mialomes: A Systems-Biology View of Tick Tissues and Tick–Host Interactions

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Tick saliva facilitates tick feeding and infection of the host. Gene expression analysis of tick salivary glands and other tissues involved in host–pathogen interactions has revealed a wide range of bioactive tick proteins. Transcriptomic analysis has been a milestone in the field and has recently been enhanced by next-generation sequencing (NGS). Furthermore, the application of quantitative proteomics to ticks with unknown genomes has provided deeper insights into the molecular mechanisms underlying tick hematophagy, pathogen transmission, and tick–host–pathogen interactions. We review current knowledge on the transcriptomics and proteomics of tick tissues from a systems-biology perspective and discuss future challenges in the field.

Ticks, Hosts, and Pathogens

Ticks are obligatory ectoparasitic blood feeders that parasitize reptiles, birds, and mammals. Ticks are medically important because they transmit a plethora of pathogenic agents that cause human diseases, including anaplasmosis, ehrlichiosis, babesiosis, rickettsiosis, and others (www.cdc.gov/ticks/diseases/). Lyme borreliosis is a common tick-borne disease worldwide, while tick-borne encephalitis is a public health concern in Europe and Asia (http://ecdc.europa.eu/en/healthtopics/emerging_and_vector-borne_diseases/tick_borne_diseases/tick_borne_encephalitis/pages/index.aspx). Ticks are divided into two major groups: soft ticks (family Argasidae) and hard ticks (family Ixodidae), which differ in their life cycles and blood-feeding strategies [1,2] and, as a consequence, are exposed to different host homeostatic responses. Hemostasis and acute inflammation are common responses to both groups of ticks and form the basis of the host anti-tick response. Hard ticks, however, must also counteract chronic inflammatory responses and specific humoral and cellular immunity [3].

Bellum Omnium Contra Omnes

Dynamic, multi-directional interactions occur between ticks, hosts, and transmitted pathogens in both the tick and host environments, affecting all three members (Figure 1). These can be regarded as a continuous *bellum omnium contra omnes*, or war of all against all. When a tick ingests host blood, hemoglobin is digested and detoxified in the tick gut [4–6], and proteases of host or pathogenic origin are neutralized [7]. Tick midgut proteins and cells interact with ingested tick-borne pathogens, which migrate via the midgut and haemocoel [8–10] to invade the salivary

Trends

The development of high-throughput NGS methodologies has revolutionized research at the vector–pathogen–host interface.

The decrease in sequencing costs and in the quantity of required starting material, as well as higher transcriptome coverage, have improved drastically our understanding of gene expression regulation in tick tissues involved (or not) in pathogen transmission.

High-throughput quantitative proteomics are now feasible even for disease vectors with an unknown genome and have provided deeper insights into the molecular mechanisms underlying hematophagy, pathogen transmission, and tick–pathogen–host interactions.

Emerging high-throughput gene sequencing methodologies and other 'omics' methodologies, such as metabolomics, may soon be applied to this field.

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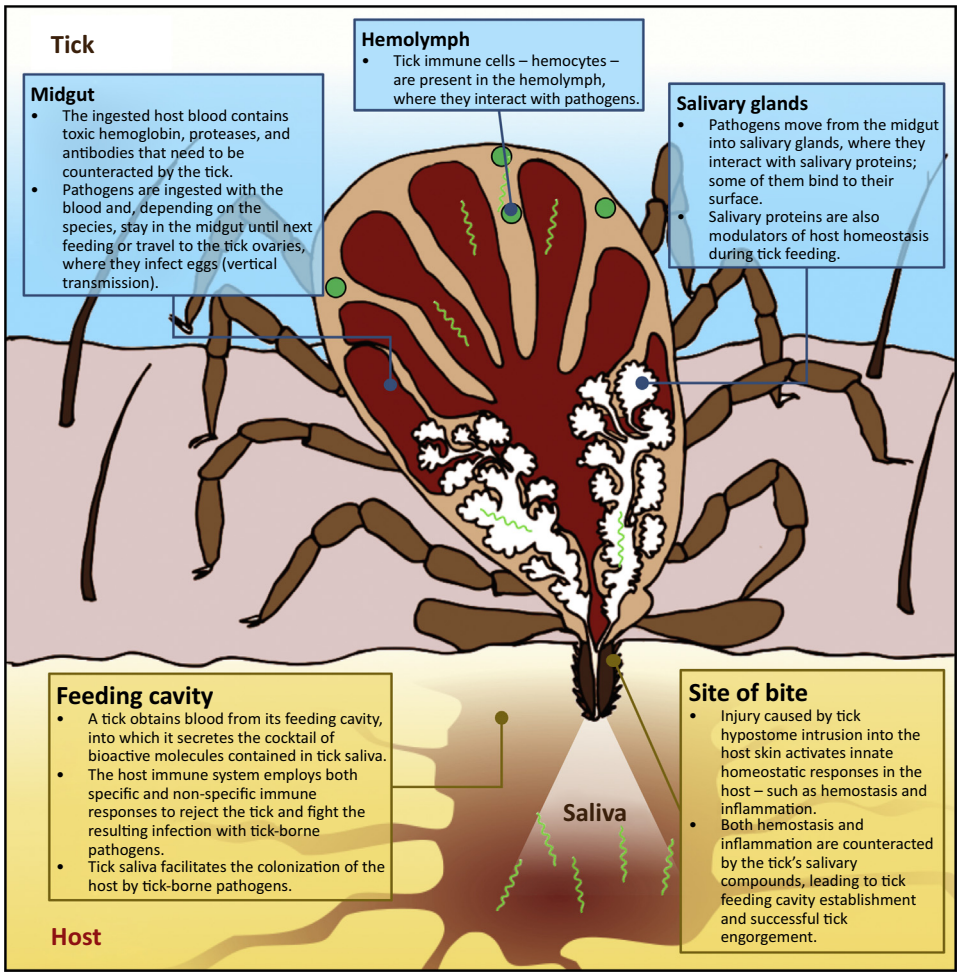

Figure 1. The Complex Interactions Between Ticks, Hosts, and Tick-Borne Pathogens. In ticks, the toxic properties of hemoglobin and the deleterious activities of leukocyte-derived proteins are attenuated by protease inhibition, enzymatic digestion of hemoglobin, and toxic iron scavenging [4,7,76]. Ingested pathogens interact with midgut proteins [11,12] and host blood-derived factors before migrating through the tick midgut and hemolymph to interact with the innate immune system of the tick [8,9]. Next, the pathogens migrate to the tick salivary glands, where they proliferate and acquire salivary proteins on their surface [13,14]. Pathogens are then injected into the host along with tick saliva, and tick salivary components begin to suppress the local host homeostatic response that is immediately raised against the tick bite-induced injury, the 'foreign' tick salivary antigens, and the tick-borne pathogens [3,3,16,19,77]. The overall outcome is facilitation of tick feeding and pathogen colonization of the tick, the host, or both.

glands, proliferate, and acquire salivary proteins on their surface. For example, the midgut proteins TROSPA (tick receptor for ospA) and Ixofin3D (*Ixodidae* fibronectin type III domain-containing tick gut protein) bind to *Borrelia* spirochetes and facilitate midgut colonization and subsequent pathogen transmission to the host [11,12]. Proteins of the Salp15 (salivary protein 15)-like multigene family are produced in the tick salivary glands and bind to *Borrelia* spirochetes to modulate host immunity, thus facilitating infection of the host [13,14]. Tick saliva secreted into the host suppresses local host immune responses, primarily to enable blood acquisition; however, the resulting host immunosuppression facilitates host infection [15–18]. Because tick salivary secretions are the main mediators of host immunosuppression or immunomodulation, salivary composition plays a crucial role in tick-borne pathogen transmission and represents a major topic of interest to researchers in the field [3].

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