Tick Saliva in Anti-Tick Immunity and Pathogen Transmission

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ABSTRACT. When feeding on vertebrate host ticks (ectoparasitic arthropods and potential vectors of bacterial, rickettsial, protozoal, and viral diseases) induce both innate and specific acquired host-immune reactions as part of anti-tick defenses. In a resistant host immune defense can lead to reduced tick viability, sometimes resulting in tick death. Tick responds to the host immune attack by secreting saliva containing pharmacologically active molecules and modulating host immune response. Tick saliva-effected immunomodulation at the attachment site facilitates both tick feeding and enhances the success of transmission of pathogens from tick into the host. On the other hand, host immunization with antigens from tick saliva can induce anti-tick resistance and is seen to be able to induce immunity against pathogens transmitted by ticks. Many pharmacological properties of saliva described in ticks are shared widely among other blood-feeding arthropods.

Abbreviations

BP -binding protein
DbpA decorin-binding protein A
DTH delayed-type hypersensitivity
FXa coagulation factor Xa
HBP histamine-binding protein
IFN-γ interferon-γ
Ig immunoglobulin
IL interleukin
MIF macrophage migration inhibitory factor
NK natural killer cells
OsPA outer surface protein A
PGE2 prostaglandin E2
PGI2 prostaglandin I2
RGD Arg–Gly–Asp amino-acid ligand sequence
salp salivary proteins
SAT saliva-activated transmission
TAI tick-adhesion inhibitor
TAP tick anticoagulant peptide
TGF-β transforming growth factor β
T11 helper T cell subtype 1

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1 INTRODUCTION

Ticks are obligate, blood-feeding ectoparasites of vertebrates. They reside on the host only when feeding. Ixodidae and Argasidae are the two major tick families. Ixodidae are called “hard ticks” because of their sclerotized dorsal plate, and are the most important family in terms of numbers and medical importance. Argasidae are called “soft ticks” because of their flexible cuticle. Ixodids require days to complete feeding; during this time they remain firmly attached to the host, whereas Argasidae are rapid feeders, requiring a few hours or less for feeding to repletion, without firm attachment. Each feeding stage of ixodid life cycle may utilize a separate host, often of different species. An individual argasid, as a “nest parasite”, generally feeds on the same host or host species through its life span of one or more years (Bergman 1996; Parola and Raoult 2001).
2 MAIN FUNCTION OF TICK SALIVARY GLANDS IS TO RETURN EXCESS WATER AND SECRETE PHARMACOLOGICALLY ACTIVE MOLECULES INTO THE VERTEBRATE HOST

Salivary glands can be defined as organs that synthesize and secrete products which assist in the acquisition of food. When on the host, tick concentrates the blood nutrients by returning excess water and ions, two major constituents of tick saliva, from the blood meal via saliva back into the host. About 33–50 % of all fluid ingested is excreted back to the host via salivary glands (Bowman et al. 1997). When salivating into the feeding wound, pathogens presented in tick’s saliva are transmitted into the host; this is the most common route of tick-derived pathogen transmission (Stich et al. 1993). Salivary gland of ixodid tick synthesizes and secretes cement that firmly secures the tick to the host via mouthparts (Bishop et al. 2002). When off-host, salivary gland secretes hygroscopic solution that absorbs water from air and prevents the tick from dehydrating (Sauer et al. 1996; Meyer-Konig et al. 2001).

Ticks have to pierce their host’s skin to obtain their meal. This triggers several repair reactions in the host, including blood clotting, platelet aggregation, blood vessel contraction, increased vascular permeability, and leukocyte chemotaxis to the injury site. Pharmacological components in tick saliva (for a brief summary see Table I) facilitate feeding by antagonizing or modifying their host’s inflammatory response and hemostatic processes. When feeding, tick salivary glands enlarge their volume and become active. Enlargement and activation of salivary glands is supported by production of “feeding proteins” (Wang et al. 1999a). During attachment, the spectrum of proteins salivated into the wound changes (Sanders et al. 1996). Differences in protein production not only between different tick species, but also among individuals of the same species or developmental stage can be observed (Wang et al. 1999b; Lawrie and Nuttall 2001). Also the activity of tick-derived immunoactive factors can vary depending on the particular host species parasitized (Lawrie et al. 1999).

3 TICK SALIVARY FACTORS FACILITATE FEEDING BY PREVENTING THE HOST’S HEMOSTATIC PROCESS

As the tick feeds, blood vessels are ruptured, proceed to drain into the feeding lesion and provide the tick with a pool of blood from which to imbibe. Such blood flow is normally rapidly arrested by the host’s hemostatic process. This process, which could hinder tick feeding, involves hemostatic plug forming, activation of the plasma coagulation cascade and vessel contraction that can seal the injury site.

Hemostasis is initiated when platelets respond to subendothelial collagen exposed at the injury site and become activated. ADP is released from damaged cells and by activated platelets, thus amplifying further platelet attraction and causing platelet aggregation. Tick saliva contains apyrase inhibiting platelet aggregation by hydrolyzing ATP and ADP to AMP and monophosphate (Ribeiro et al. 1985; Titus and Ribeiro 1990; Mans et al. 2000). Tick salivary PG12 increases the concentration of cAMP in platelets, inhibits the secretion of ADP, and such inhibits aggregation and cause disaggregation of those platelets that have aggregated (Bowman et al. 1996; Pedibhotla et al. 1997).

Platelet activation and ADP release is followed by thrombin production and activation of the coagulation pathway. Blood coagulation (plug formation) occurs through intrinsic or extrinsic pathways and involves a series of proteolytic reactions that ultimately lead to the thrombin-catalyzed conversion of soluble fibrinogen into an insoluble fibrin mesh that holds the platelet plug in place. Tick saliva-derived anticoagulants TAP (Jordan et al. 1990; Waxman et al. 1990) and ixolaris (Francischetti et al. 2002) inhibit coagulation factor Xa (FXa), a serine proteinase catalyzing formation of thrombin in both coagulation pathways, while ornithodorin (van de Locht et al. 1996), americanin (Zhu et al. 1997), ixin (Hoffmann et al. 1991) and an unnamed 60-kDa-protein fraction (Horn et al. 2000) are specific thrombin inhibitors. The function of some tick anticoagulants is yet unclear (Mulenga et al. 2001).

Activated platelets express surface adhesion receptor proteins, collectively known as integrins that enable cell–cell and cell–matrix interactions. Tick-derived disintegrin-like peptides savignygrin in argasid (Mans et al. 2002) and variabilin in ixodid ticks (Wang et al. 1996) contain the integrin recognition motif RGD used for binding to integrins and can inhibit platelet aggregation by preventing the binding of other ligands to a platelet receptor. There is no amino-acid sequence similarity between variabilin and savignygrin, and the position of the RGD motif is completely different. This suggests that platelet aggregation inhibitors with RGD-like motifs have evolved after the divergence of hard and soft ticks. This implies that the main tick families have adapted to their blood feeding environments independently (Mans et al. 2002). Disagregin (Karczewski et al. 1994; Karczewski and Connolly 1997) and TAI (Karczewski et al. 1995) both