Article published online: 2026-07-08

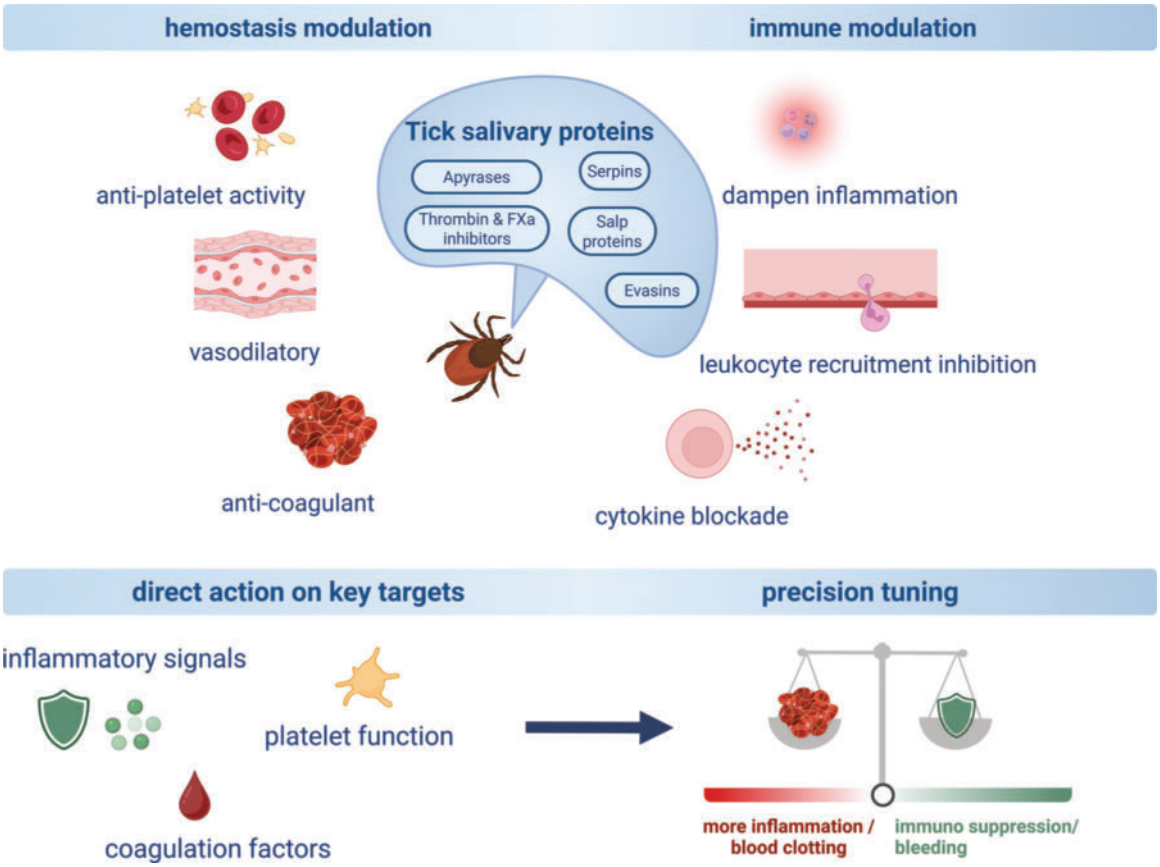
Review Article

Beyond the Bite: Tick Salivary Proteins Targeting Hemostasis and Inflammation; Implications for Cardiovascular Disease

Mohamed Amine Jmel[1,2], Emilia Laura Bialek[3,4], Marie Sels[3,5], Michalis Kotsyfakis[6], Ingrid Dijkgraaf[3,7]

Affiliation addresses are listed at the end of the article.

GRAPHICAL ABSTRACT



ABSTRACT

Ticks have evolved a diverse repertoire of salivary proteins that enable prolonged blood feeding by finely modulating host hemostatic, vascular, and immune responses, providing an unexpected source of candidates for cardiovascular and anti-inflammatory therapy. Tick saliva contains molecules that interfere with vasoconstriction, platelet activation, coagulation and fibrinolysis, while at the same time shaping leukocyte recruitment and cytokine release, placing these proteins at the crossroads of hemostasis, inflammation and cardiovascular disease. In this review, the main families of tick-derived effectors are discussed, including thrombin and factor Xa inhibitors, apyrases, serpins, and multispecific proteins that act on both coagulation and inflammatory pathways, with an emphasis on how their mechanisms could be harnessed for anti-thrombotic and anti-inflammatory therapies. Particular attention is given to salp proteins and the chemokine-binding evasins, which remodel chemokine networks and immune cell trafficking in models of atherosclerosis, ischemia–reperfusion injury and stroke, where they can dampen leukocyte infiltration, matrix degradation and plaque destabilization. Taken together, these insights show how millions of years of tick–host coevolution have produced a molecular toolkit that not only clarifies fundamental aspects of thromboinflammation, but also provides a basis for next-generation biologics targeting cardiovascular and inflammatory disorders.

Keywords tick saliva, protein function, haemostasis, inflammation, cardiovascular disease therapeutics

received January 06, 2026 | **accepted after revision** June 18, 2026 | **article published online** 2026

Bibliography Thromb Haemost **DOI** 10.1055/a-2899-3775 **Art ID** TH-25-12-0707

Correspondence Ingrid Dijkgraaf, PhD, MSc, Department of Biochemistry, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, LI, the Netherlands, Email: i.dijkgraaf@maastrichtuniversity.nl

Introduction

Blood feeding is a critical step for the development and reproduction of soft and hard ticks. To successfully obtain a blood meal, these hematophagous ectoparasites have to overcome the host's defense mechanisms, which are activated upon insertion of the hypostome into the skin.[1] Hard ticks (family *Ixodidae*) remain attached to their vertebrate hosts for several days, continuously facing immune and inflammatory responses. In contrast, soft ticks (family *Argasidae*) feed rapidly, typically completing their meal within a few hours and thus experiencing shorter exposure to host defenses.[2] Because of their feeding habits, ticks are vectors for several pathogens that cause important human diseases, including tick-borne encephalitis, Crimean–Congo hemorrhagic fever, and Lyme borreliosis. The transmission of diseases to the host is facilitated by tick saliva released at the site of the bite, and the saliva exploitation by pathogens to promote their invasion and establishment in the host was originally termed "saliva-assisted transmission."[3]

During blood feeding, ticks anchor themselves to the host with their mouthparts, damaging capillaries and other tissues to create a feeding cavity. This tissue disruption triggers a multifaceted host response, including platelet aggregation, vasoconstriction, blood clotting, activation of the complement system, inflammation, and antigen-specific acquired immunity.[4] To counteract these defense mechanisms, ticks secrete a wide variety of bioactive molecules such as proteins, lipids, nucleic acids, and other molecules through their saliva. These bioactive compounds work synergistically to maintain blood fluidity and to suppress the host's immune responses, thereby facilitating prolonged feeding and enhancing the likelihood of pathogen transmission.[5]

The secreted compounds act by targeting different stages and components of the host hemostatic response at both the primary and secondary hemostasis level. Upon vascular injury, primary hemostasis is initiated by platelet adhesion to exposed subendothelial matrix components such as collagen and von Willebrand factor,[6] followed by platelet activation and aggregation to form a temporary platelet plug. A central mediator of platelet aggregation is the integrin GPIIb/IIIa (αIIbβ3), which undergoes conformational activation, enabling high-affinity binding to fibrinogen and other ligands. These ligands often contain an Arg-Gly-Asp (RGD) or related motif (e.g., RGDS), which is recognized by GPIIb/IIIa and facilitates platelet crosslinking. In addition to this ligand-binding role, GPIIb/IIIa also transduces signals that further stabilize platelet adhesion, promote cytoskeletal rearrangement, and support thrombus consolidation. Consequently, many natural and pharmacological inhibitors, including several tick-derived peptides, target this integrin by mimicking or blocking RGD-dependent interactions.[7–9]

In parallel, secondary hemostasis reinforces the platelet plug through activation of the coagulation cascade, culminating in thrombin generation and fibrin formation. A key central axis of this process involves the conversion of factor X to factor Xa, which, together with factor Va,[10] forms the prothrombinase complex that catalyzes the conversion of prothrombin into thrombin. Thrombin then cleaves fibrinogen into fibrin, leading to the formation of a stable fibrin mesh that consolidates the formed clot. Thrombin also amplifies coagulation through positive feedback activation of upstream coagulation factors and platelets. Given this central FXa–thrombin–fibrin axis, it is not surprising that many tick salivary proteins and clinically used anticoagulants target factor Xa or thrombin to effectively disrupt clot formation.[10]

Moreover, among the various families of inhibitors present in tick saliva, some serine proteases, for example, can act as anticoagulants, specifically by modulating the activity of different molecules including thrombin, factor Xa and other proteases that play a central role in the intrinsic and extrinsic pathways of the enzymatic cascade leading to blood coagulation.[11] Other molecules directly target the host's inflammatory response simultaneously. Protease inhibitors secreted in saliva can act specifically on different key cells in this process, modulating the production of inflammatory cytokines produced, neutrophil recruitment, and antigen-specific CD4+ T cell proliferation induced by dendritic cells (DCs).[11]

Given the highly specific roles these molecules play in modulating hemostasis and inflammatory processes during tick–host interactions, their potential translational applications in treating related human disorders warrants thorough investigation.

Thrombosis is the result of a dysfunction in the hemostatic response that leads to the formation of clots inside blood vessels, interrupting normal blood flow, and the activation of an inflammatory response that likewise reinforces thrombus formation.[12] Once formed, the inflammatory process associated with thrombosis can be defined as immunothrombosis (physiological immune-driven clot formation) or thromboinflammation (pathological interplay between inflammation and thrombosis),[13] which is characterized by a loss of the antithrombotic and anti-inflammatory functions of endothelial cells and contributes not only to cardiovascular diseases, but autoimmune diseases as well.[12,14] Given the complex array of bioactive molecules present in saliva that modulate the tick–host interface, and considering the growing interest in their potential therapeutic applications, this review aims to summarize

the current literature in the context of cardiovascular diseases and inflammation.

It summarizes the multifaceted effects of tick salivary proteins toward the regulation of hemostatic and inflammatory pathways with a focus on the therapeutic effects for cardiovascular and inflammatory disorders, especially for the Evasin and Salp protein families. Ultimately, we aim to bridge fundamental tick research and translational medicine by showing how tick proteins may be the base of future therapeutics for thrombotic, inflammatory, and cardiovascular diseases.

Tick Feeding versus Hemostasis

Among hematophagous parasites, ticks are regarded as some of the most successful arthropods in securing their blood meal, largely due to their well-coordinated mechanisms for overcoming host hemostatic defenses.[1,15] For instance, hard ticks remain attached to their host for days to weeks, whereas other blood-feeding arthropods require only a few minutes. This long-lasting attachment requires a continuous suppression of host hemostatic and immune responses to ensure constant blood flow and avoid occlusion at the feeding site.[5,16] At the host level, the hemostatic system consists of a complex and essential network of interconnected pathways with the sole objective of preventing blood loss after a vascular injury.[17] This system is formed by a well-orchestrated response involving three components: vasoconstriction, primary hemostasis (consisting of the platelet plug formation), and secondary hemostasis (coagulation and fibrin clot formation). In addition, the fibrinolytic system intervenes after the vascular repair to ensure the dissolution of the clot.[10]

All the hemostatic cascades mentioned present an obstacle for the successful feeding of the ticks and therefore require efficient countermeasures. Here comes the role of tick saliva with its diversified arsenal of bioactive compounds that targets every axis of the hemostatic system.[18] These bioactive molecules are constantly delivered throughout the tick feeding to ensure and maintain a constant suppression of host defenses. It reflects millions of years of co-evolution between ticks and their vertebrate hosts, yielding highly specific and efficient molecular effectors.[5,18,19]

The tick feeding process starts mechanically through the insertion of the tick hypostome into the host tissue, generating a feeding cavity that triggers host hemostatic responses. Vasodilators from tick saliva counteract vasoconstriction and maintain constant blood flow to the feeding site. At the same time, antiplatelet compounds prevent the formation of a platelet plug that may cause the occlusion of the feeding cavity.[20,21] Simultaneously, multiple anticoagulant proteins block the coagulation cascade, preventing fibrin production and clot formation during feeding.[5,16,18,22]

One of the most remarkable features of tick saliva is the multifunctionality of its salivary effectors. Rather than targeting individual components of the host's hemostatic system, ticks have evolved to produce compounds with broad-spectrum inhibitory activities that simultaneously disrupt multiple pathways (coagulation proteases, platelet receptors, etc.). This strategy allows, on one hand, an efficient inhibition with a low metabolic cost of protein production, and on the other hand, a protection against host adaptation, as one inhibitory compound can compensate for the failure of others.[5,23,24] From a biomedical perspective, these properties of tick salivary proteins gave important insights into the regulation of hemostatic components and gave several therapeutic candidates.[18,22,25,26] The potency and specificity of these nature-derived compounds provide an unprecedented foundation for drug development targeting thrombotic, inflammatory, and cardiovascular diseases.[21,27–29]

Molecular Mechanisms of Tick Salivary Proteins in Modulating Hemostasis

Hemostasis represents a tightly regulated process that involves vascular constriction, platelet activation and aggregation, and fibrin production.[30] In the following paragraphs, we list tick salivary proteins that were reported for their effects on blood coagulation, platelets, vascular modulation, or a combined action on several processes such as the interplay between inflammation and hemostasis.

Inhibitors of Platelet Activation and Aggregation

Platelets play a central role in the hemostatic response to vascular injury as they are the first to adhere to the injured endothelium, forming a temporary plug and simultaneously secreting procoagulant compounds to propagate clot formation.[14] Here, we provide a few examples of salivary proteins secreted by ticks that target platelet activation and/or aggregation.

GPIIb/IIIa Antagonists

The GPIIb/IIIa receptor, also called αIIbβ3 or fibrinogen receptor, is the most abundant platelet cell-surface protein; moreover, it cannot be found on other cell types than platelets.[30] Activation of this receptor induces platelet activation and facilitates binding of the receptor to fibrinogen, fibrin, von Willebrand Factor, fibronectin, vitronectin, and thrombospondin. This further promotes platelet aggregation.[31] Aggregation inhibitors form a complex with the IIb and IIIa glycoproteins of the fibrinogen receptor on platelets, inhibiting platelet activation and subsequent aggregation.[32,33] (**Tables 1** and **2**)

Collagen-Mediated Platelet Aggregation

Platelets bind collagen through GPIa/IIa and GPVI glycoprotein receptors. Both receptors play an important role in collagen-mediated platelet activation, but utilize a different mode of action. GPVI plays an important role in early phases of platelet–collagen interactions and enhances GPIa/IIa activation.[34,35]

Thrombin-Mediated Coagulation and Platelet Aggregation

Thrombin is a serine protease and an essential tool in the coagulation cascade, functioning at the convergence of the extrinsic and intrinsic coagulation pathway (**Fig. 1**).[36] Besides, thrombin contributes to a positive feedback loop in the coagulation cascade, which stimulates the cleavage of prothrombin into thrombin.[37] Thrombin activates platelets specifically by binding

Table 1 Inhibitors of fibrinogen receptors

Protein	Species	Molecular weight	Structure	Mode of action	Reference
Monogrins	*Argas monolakensis*, soft tick	10 kDa	Canonical Arg-Gly-Asp (RGD) motif	• Block the fibrinogen receptor	33
Variabilin	*Dermacentor variabilis*, hard tick	5 kDa	RGD motif, no flanking cysteines	• Block the fibrinogen receptor	8
Disagregin	*Ornithodoros moubata*, soft tick	6 kDa	Arg-Glu-Asp (RED) sequence	• Block the fibrinogen receptor	20
Savignygrin	*Ornithodoros savignyi*, soft tick	6 kDa	RGD motif	• Suppresses aggregation triggered by ADP, collagen, thrombin receptor–activating peptide, and epinephrine	9
Ixodegrin	*Ixodes scapularis and Ixodes pacificus*, hard tick	8 kDa	RGD motif with flanking cysteine residues	• Blocks fibrinogen receptor	34

Table 2 Inhibitors of collagen receptors

Protein	Species	Molecular weight	Mode of action	Reference
Longicomin	*Haemaphysalis longicornis*, hard tick	16 kDa	• Interacts with the platelet–collagen receptor (GPVI).	35
Moubatin	*Ornithodoros moubata*, soft tick	17 kDa	• Platelet-specific: prevents platelet aggregation triggered by collagen • At higher concentrations, it acts as a thromboxane A_2 receptor antagonist,	37,38
Tick adhesion in*hibitor (TAI)*	*Ornithodoros moubata*, soft tick	15 kDa	• TAI competes directly with collagen for binding to the platelet $\alpha_2\beta1$ (Ia-IIa) integrin complex–> blocking platelet adhesion • Inhibits the adhesion of endothelial cells to collagen	38

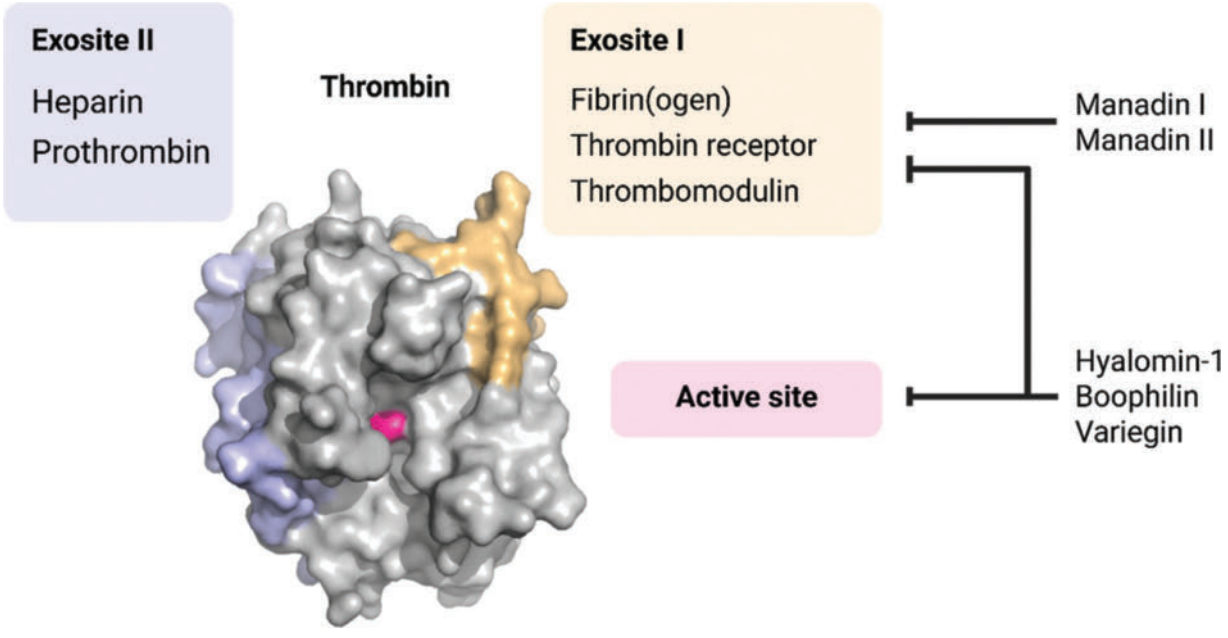


Fig. 1 Thrombin structure (PDB: 1ppb) with ligand-binding domains exosite I (orange), exosite II (blue) and the active site (pink). Source: Thrombin domains were adopted from Troisi et al.[36] Licensed under CC BY 4.0. [rerif]. Source: Created in BioRender. Proost, P. (2026) https://BioRender.com/630hpj0.

Table 3 Thrombin inhibitors

Protein	Species	Molecular weight	Structure	Mode of action	Reference
Sculptin	*Amblyomma cajen nense*, hard tick	17 kDa		• Specific and reversible inhibitor of thrombin	40
Savignin	*Ornithodoros savignyi*, soft tick	12 kDa		• Competitive, slow, and tight-binding inhibitor of α-thrombin.	33,41,42
Ornithodorin	*Ornithodoros moubata*, soft tick	Approximately 12 kDa		• Highly selective thrombin inhibitor	43
Monobin	*Argas monolakensis*, soft tick	14 kDa		• Thrombin inhibitor	33
Madanin 1 and 2	*Haemaphysalis longicornis*, hard tick	Approximately 7 kDa		• Competitive thrombin inhibitor	36,44
Hyalomin-1	*Hyalomma margina tum rufipes*, hard tick	6 kDa	Pro-Arg-Leu motif is critical for activity	• Selective thrombin inhibitor, binding noncompetitively to boththe enzyme's active site and exosite I → Thereby delaying fibrin clot formation and further suppressing thrombin-mediated activation of coagulation factors XI and V	45
Boophilin	*Boophilus microplus*, hard tick	14 kDa	Two Kunitz-type domains	• Classic, noncompetitive inhibitor of thrombin • Interferes with the activity of trypsin, plasmin, neutrophil elastase, kallikrein, cathepsin G and FXIa	46,47
Amblin	*Amblyomma hebraeum*, hard tick	18 kDa	Sequence homology with both tissue factor pathway inhibitor and Boophilin	• Thrombin inhibitor	48
Chimadanin	*Haemaphysalis longi cornis*, hard tick	10 kDa	No kunitz domains	• Competitive thrombin inhibitor that interacts with the active site and exosite II of thrombin	44
Variegin	*Amblyomma variegatum*, hard tick			• Disrupts thrombin's catalytic triad • Competitive inhibitor before cleavage, after cleavage a noncompetitive inhibitor	49–51

and cleaving protease-activated receptor molecules on platelets, and in return, activated platelets expose phosphatidylserine, which interacts with the tenase complex and Prothrombinase complex, promoting the conversion of circulating prothrombin into thrombin, thus enhancing thrombin generation indirectly. (**Table 3**) [36,38–51]

Table 4 Inhibitors of the coagulation pathway other than thrombin

Protein	Species	Molecular weight	Structure	Mode of action	Reference
Ixolaris	*Ixodes scapularis*, hard tick	16 kDa	Two Kunitz-like domains	• Serine protease inhibitor • Binds to factor X and factor Xa. • Inhibits the FX(a)/tissue factor/FVIIa complex formation, preventing the initiation of the extrinsic coagulation pathway.	25,46,47,52
Tick anticoagulant peptide *(TAP)*	*Ornithodoros moubata*, soft tick	7 kDa		• Highly selective inhibitor of FXa	43,48
Amblyomin-X	*Amblyomma cajennense*, hard tick	12 kDa		• Noncompetitive serine protease inhibitor that targets FXa	27,29
Penthalaris	*Ixodes scapularis*, hard tick	Approximately 35 kDa	Five Kunitz domains	• Binds both factor X and factor Xa–> inhibits factor X activation via the extrinsic coagulation pathway	49

Table 5 Modulators of the vascular function

Protein	Species	Molecular weight	Structure	Mode of action	Reference
Tick histamine release factor (tHRF)	*Ixodes scapularis*, hard tick			• Binds to basophils and triggers release of histamine	50
Histamine release factor homolog (DVHRF)	*Dermacentor variabilis*, hard tick	20 kDa		• Induces histamine secretion by basophils	51
Prostacyclin/prostaglandin I_2 (PGI_2)				• Inhibits platelet aggregation	53,54
Nitrophorins	*Ornithodoros moubata* and *Rhipicephalus appendiculatus*, soft and hard tick		Conserved β-barrel fold that forms a hydrophobic pocket for ligand binding	• Histamine binding properties • Increasing the NO levels	41,42

Inhibitors of the Coagulation Pathway Other Than Thrombin

To ensure uninterrupted feeding, ticks secrete salivary protease inhibitors with anticoagulant properties that specifically target proteases involved in the coagulation cascade.[20,22] Below, we present several reported examples of anticoagulant molecules in tick saliva (**Table 4**).[52]

Vascular Modulation

Beyond anticoagulant proteins, ticks modulate host vascular responses to facilitate prolonged blood feeding by inducing vasodilation and dampening inflammatory cascades.[1] Tick saliva contains several proteins and lipid mediators that modulate vascular function (**Table 5**).[53,54]

Proteins Inhibiting Inflammatory Responses

Tick saliva contains numerous proteins that possess immunomodulatory properties, serving to suppress both inflammatory and immune responses in the host. These salivary proteins act through multiple mechanisms: Evasins bind and neutralize chemokines,[20] cystatins inhibit host cysteine proteases,[55,56] Prostaglandins are lipid mediators that reduce T cell activation and the secretion of pro-inflammatory cytokines.[57,58] Through these coordinated activities, tick salivary components reduce local inflammation, limit immune cell recruitment and activation, and prevent effective host immune recognition at the feeding site. (**Table 6**)[53,59–62]

Proteins Acting at the Interplay between Hemostasis and Inflammation

The interplay between inflammation and hemostasis is well established as a key component of tissue repair and host defense mechanisms. Studies on tick salivary proteins have demonstrated the effectiveness of targeting the interplay between inflammation and hemostasis by simultaneously inhibiting key components of both processes.[16,20,23,44,45] This ability provides key insights into therapeutic approaches that target at the same time inflammatory and cardiovascular disorders. Below, we enumerate some examples of multi-specific tick salivary proteins. Some of these regulate critical biological processes, including coagulation and inflammation, by precisely controlling protease activity. These serine protease inhibitors (serpins) consist of a typical core fold with three β-sheets (A, B, and C) and eight or nine α-helices. They are characterized by a flexible, exposed reactive center loop (RCL),

Table 6 Inhibitors of inflammatory responses

Protein	Species	Mode of action	Reference
Sialostatin L	*Ixodes scapularis*, hard tick	• Inhibitor of cysteine protease: inhibits cathepsin L • Reduces the production of inflammatory cytokines (like IL-9 from Th9 cells) by immune cells	59
Sialostatin L2		• Inhibits cathepsins C, L, S, and V and suppresses the secretion of IL-1β and IL-18 by macrophages • Inhibits the activity of caspase-1 and the NLRC4 inflammasome	60
Hyalomin A and B	*Hyalomma asiaticum*, hard tick	• Directly inhibiting host secretion of inflammatory factors such as TNF-α, MCP-1, and IFN-γ • Indirectly increasing the secretion of immunosuppressant cytokine IL10 • Neutralizes free radicals	61
Evasins		• Binds and inhibits proinflammatory chemokines • Prevents leukocyte recruitment	20,43
Prostaglandin E2 (lipid mediator)	*Ixodes scapularis*, hard tick	• Inhibits the production of pro-inflammatory cytokines (such as TNF-α) by macrophages and dendritic cells • Inhibits the proliferation of T lymphocytes by reducing interleukin 2 (IL-2) expression • Blocks the dendritic cell (DC) function	53,62

Table 7 Modulators linking coagulation and inflammation

Protein	Species	Molecular weight	Structure	Mode of action	Reference
Apyrases	*Ornithodoros savignyi* (soft tick) and *Ixodes scapularis* and *Hya lomma dromedarii* (hard ticks)	67 kDa		• Hydrolyzes the phosphodiester bonds of extra cellular ATP and ADP leading to inhibition of inflammatory pathways activated by ATP/ADP via purinergic P1 and P2 receptors. • Disaggregates platelets	31,56,63–67
Ixodes Ricinus serpin-2 (IRS-2)	*Ixodes ricinus*, hard tick	42 kDa	A conical serpin fold composed of 3 large β-sheets and 9 α-helices.	• Targets specifically the chymotrypsin-like proteases, cathepsin G and chymase • Inhibits platelet aggregation induced by both thrombin and cathepsin G	32,68
Iripin-3	*Ixodes ricinus*, hard tick	42 kDa	Serpin fold, consisting of three β-sheets, ten α-helices, and a cleaved RCL	• Inhibits trypsin-like serine proteases (kallikrein and matriptase), thereby inhibiting blood coagulation and reducing inflammation, itch and pain • Reduces the production of pro-inflammatory cytokines by LPS-activated macrophages	69
Longistatin	*Haemaphysalis longicornis*, hard tick	17.8 kDa	Contains two EF-hand domains	• RAGE antagonist that inhibits NF-κB nuclear translocation and downregulation of adhesion molecule expression, thereby mitigating the inflammatory responses • Can directly hydrolyze fibrinogen, the precursor of fibrin. • Can bind to fibrin and specifically converts inactive plasminogen into its active form, plasmin.	70
q-2	*Ixodes ricinus*, hard tick	43 kDa		• Inhibitor of human leukocyte elastase, thereby modulating inflammation • Suppresses T cell and splenocyte proliferation and modulates cytokine production from peripheral blood mononuclear cells (PBMCs) • Interferes with both coagulation and fibrinolysis	71

which serves as their defining structural feature. Serpins trap target proteases by using the RCL to form a stable covalent complex with the enzyme. (**Table 7**)[63–71]

Chemokine Inhibition in Cardiovascular Diseases: The Example of Evasins

Inflammation has a crucial role in cardiovascular diseases such as atherosclerosis or myocardial infarction, and targeted anti-inflammatory treatment can have beneficial effects.[72] Leukocyte migration is a hallmark of inflammation and is orchestrated by chemokines, small chemotactic cytokines (8–14 kDa) classified into four groups (CC, CXC, CX3C, and XC) based on the arrangement of two conserved cysteine residues and a nonconserved amino acid (X) in their NH_2-terminal region.[73,74] The CXC-chemokine family is subdivided depending on the presence of a glutamate-leucine-arginine (ELR) motif between the N-terminus and the first conserved cysteine.[75] Chemokine activity is established on three levels: the formation of a chemokine gradient by binding glycosaminoglycans (GAGs), activating one of the four classes of chemokine receptors (CXCR, CCR, CX3CR, and XCR), and post-translational modifications that affect chemokine activity.[76–78] Due to the fine-tuned character and redundancy of the chemokine network, therapeutic targeting remains challenging, with only three anti-chemokine receptor drugs approved to date (Maraviroc, Plerixafor, and Mogamulizumab), none of which are for strictly inflammatory or cardiovascular pathologies.[79] Nevertheless, chemokine inhibition remains under investigation as a potential target for cardiovascular therapies.[80] Tick saliva contains chemokine-binding proteins named Evasins, as prevention of leukocyte recruitment is a necessary strategy for any hematophagous organism. First discovered in tick salivary gland extracts of *Rhipicephalus sanguineus*, to date, this family counts 51 validated proteins, divided into two structurally distinct groups—class A and B, binding CC and CXC chemokines, respectively.[81–84] Interestingly, Evasins overcome the redundant character of the chemokine network by binding and inhibiting multiple chemokines. As this may provide benefit to anti-chemokine strategies targeting a single protein, Evasins were investigated as therapeutic agents, including cardiovascular in vivo models, where they presented varied outcomes (**Table 8**).[55–58,66,85–87]

Chronic Ischemia

Myocardial ischemia can result in persistent sterile cardiac inflammation with excessive leukocyte infiltration, linked to maladaptive cardiac remodeling with increased risk for further complications such as ventricular dysfunction or malignant arrhythmias.[88] Many chemokines, among which CXCL1, CXCL2, CCL2, and CCL5, are elevated in in vivo models of ischemic myocardial injury.[78] The CXCR2-CXCL1-axis was found responsible for neutrophil, monocyte, and macrophage infiltration into the arterial wall of the injured heart. Monocyte infiltration, managed largely by CXCR2-CXCL1 in this model, was linked to adverse cardiac remodeling

Table 8 Therapeutic effects of Evasins in cardiovascular diseases

Myocardial ischemia

Procedure	Evasin	Interacting chemokines	EVA-treatment	Effect	Reference
Chronic ischemia induced by total coronary occlusion by surgical ligation of the left anterior coronary artery at the inferior edge of the left atrium	EVA-3	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8	Intraperitoneal after ischemia onset Dose: 10 µg/mouse	Early effects (day 1) ↓ infarct size = ejection fraction, end-systolic volume, end-diastolic volume, septum-to-lateral end-systolic wall thickness ratio, ↑ end-systolic lateral wall thickness, septum end-systolic thickness Late effects (day 21) = survival, infarct size, collagen deposition, ejection fraction, end-systolic volume, end-diastolic volume, septum-to-lateral end-systolic wall thickness ratio, end-systolic lateral wall thickness, septum end-systolic thickness	55,85,86
	EVA-4	CCL1, CCL3, CCL7, CCL8, CCL11, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26	Intraperitoneal after ischemia onset Dose: 1 µg/mouse	Early effects (day 1) ↓ infarct size, septum-to-lateral end-systolic wall thickness ratio = ejection fraction, end-systolic volume, end-diastolic volume, septum end-systolic thickness ↑ end-systolic lateral wall thickness Late effects (day 21) ↑ survival = infarct size and collagen deposition = ejection fraction, end-systolic volume, end-diastolic volume, septum-to-lateral end-systolic wall thickness ratio, end-systolic lateral wall thickness, septum end-systolic thickness	56,85

Ischemia reperfusion injury

Myocardial

Procedure	Evasin	Interacting chemokines	EVA-treatment	Effect	Reference
Surgical ligation of the left anterior coronary artery at the inferior edge of the left atrium (30 min) followed by reperfusion	EVA-3	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8	Intraperitoneal during ischemia Dose: 0.1–10 µg/mouse	0.1 µg and 1 µg No effect 10 µg ↓ infarct size, neutrophil infiltration, serum cTnI levels = macrophage infiltration	55,66,86
Surgical ligation of the left anterior coronary artery at the inferior edge of the left atrium (30 min) followed by reperfusion for 2 h	EVA-3	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8	Into Langendorff system during ischemia 5 µg/mL	= infarct size	55,66,86

Intestinal

Procedure	Evasin	Interacting chemokines	EVA-treatment	Effect	Reference
60 min occlusion of superior mesenteric artery followed by reperfusion	EVA-3	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8	Subcutaneous 30 min before reperfusion Dose: 0.01–1 µg/mouse	0.01 µg = survival 0.1–1 µg ↑ survival	55,66,86
60 min occlusion of superior mesenteric artery followed by reperfusion	EVA-1	CCL3, CCL4, CCL14, CCL18, CCL3L1, CCL4L1	Subcutaneous 30 min before reperfusion Dose: 10–30 µg/mouse	10 µg = survival 30 µg ↑ survival	55,57,58
Cerebral					

Table 8 (*Continued*)

Cerebral

Procedure	Evasin	Interacting chemokines	EVA-treatment	Effect	Reference
Occlusion of middle cerebral artery (45 min) followed by 24 h eperfusion	EVA-3	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8	Intraperitoneal 5 min after ischemia onset Dose: 1–10 µg/mouse	↓ neutrophil cerebral infiltration = macrophage infiltration, neurological outcomes, cerebral infarct size, poststroke brain edema, BBB permeability	55,66,86

Atherosclerosis

Procedure	Evasin	Interacting chemokines	EVA-treatment	Effect	Reference
ApoE$^{-/-}$ mice with a cast placed on right common carotid artery following a Western diet (chronic cardiovascular stress) f or 9 wk	EVA-3	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8	Intraperitoneal 1 µg/d/mouse 5 d a week for 3 wk	Carotid low shear stress region ↓ intraplaque neutrophils = intraplaque lipids, macrophages, collagen Carotid oscillating shear stress region ↓ intraplaque neutrophils, lipids = intraplaque macrophages, collagen Aortic root plaques ↓ intraplaque neutrophils ↑ collagen = intraplaque macrophages, lipids	55,66,86

Viral myocarditis

Procedure	Evasin	Interacting chemokines	EVA-treatment	Effect	Reference
Intraperitoneal injection of 10^5 PFU of CVB3-H3	P672	CCL1, CCL2, CCL3, CCL7, CCL8, CCL11, CCL13, CCL14, CCL15, CCL16, CCL18, CCL23, CCL3L1	Intraperitoneal 5 mg/kg every 12 h after infection	Early effects (day 3) = body weight, hypothermia Heart = virus load, myocarditis score, left ventricular enddiastolic volume, left ventricular ejection fraction, cardiac output, S' velocity	57
	BK1.3	CCL2, CCL3, CCL7, and CCL8	Intraperitoneal 5 mg/kg every 12 h after infection	Early effects (day 3) = body weight ↓ hypothermia Heart = virus load, myocarditis score, eft ventricular enddiastolic volume, left ventricular ejection fraction, cardiac output, S' velocity Late effects (day 8) = body weight, survival, hypothermia Heart ↓ virus load, monocytes and macrophages, longitudinal strain = myocarditis score, T cells, natural killer cells, B cells, heart rate, left ventricular enddiastolic volume, left ventricular ejection fraction ↑ cardiac output, S' velocity	87

after injury.[67] As EVA-3 inhibits ELR+ chemokines (CXCL1–3 and CXCL5–8), Braunersreuther et al investigated its effects as an anti-chemokine strategy in a model of ischemic myocardial injury.[79] The therapeutic effect of EVA-3 was limited, with reduced early infarct size, but no improvement of adverse cardiac remodeling, infarct size, or long-term survival.

As CCL5 is upregulated and inhibition of CCL5 in a similar model of chronic ischemia improved outcome by reducing infarct size and postinfarction heart failure, broader CC-chemokine inhibition by EVA-4 administration was investigated.[89,90] Despite decreased inflammation and improved survival with EVA-4 treatment, only marginal differences for cardiac remodeling and inflammatory markers were observed. The differences in clinical outcomes between specific anti-CCL5 and Evasin-4 treatment remain unclear, similar to the reason for the difference between survival of EVA-3 and EVA-4 treated

mice, but authors speculate that cardiac arrhythmias might be involved.[90]

Ischemia Reperfusion Injury

Restoration of blood supply after an ischemic event is crucial to prevent ischemic tissue injury; however, a common side effect of this process is the development of ischemia-reperfusion injury, with leukocytes as important mediators.[68]

Following myocardial ischemia, neutrophils can aggravate injury during reperfusion by releasing oxygen-derived free radicals, proteolytic enzymes, and other proinflammatory mediators.[68] EVA-3 was used to inhibit neutrophil recruitment to the reperfused myocardium, and decreased infarct size and serum levels of cardiac troponin I, a sensitive biomarker for myocardial damage.[91] This was supported by the EVA-3 treatment in the Langendorff model, an ex vivo system where the heart is perfused without circulating leukocytes. Following the same procedure and treatment regimen, EVA-3 did not attenuate the infarct size in this model, suggesting that its beneficial effect derives from prevention of leukocyte recruitment to the infarcted heart during reperfusion.[91]

In a mouse model of intestinal ischemia-reperfusion injury, both EVA-3 and EVA-1 treatment improved survival. However, the provided data are limited, as only survival was measured; therefore, a mechanistic explanation for improved survival remains unspecified.[55]

During cerebral ischemia-reperfusion, neutrophils can have a deteriorating effect and promote brain injury, disruption of the blood–brain barrier, and cerebral edema.[92] Therefore, EVA-3 was used as a means to prevent neutrophil migration to the ischemic brain, but did not improve any of the measured clinical outcomes.[92]

Atherosclerosis

Cerebral ischemic stroke is a common result of carotid atherosclerotic plaque rupture, where its development is considered a progressive and inflammatory process.[90] Neutrophil infiltration is associated with unstable, rupture-prone atherosclerotic plaques, characterized by a large lipid core and low collagen amount.[73] As a stroke prevention strategy, EVA-3 treatment was used to inhibit neutrophil-attracting chemokines, and three individual regions were investigated: low shear stress, oscillating shear stress, and aortic root plaques. Neutrophils and MMP-9 were decreased in all regions; however, the effects remained limited. Lipid contents were only decreased in the oscillatory shear stress region, and collagen in aortic root plaques.[90]

Viral Myocarditis

Viral myocarditis induces an immune response to counteract infection but may cause abundant inflammatory tissue injury during the process, aggravating cardiac cell death and initiating fibrosis. In a preclinical model of viral myocarditis due to coxsackievirus B3 (CVB3) infection, various CC-chemokines are upregulated, and mainly myeloid immune cells infiltrate into the cardiac tissue. Therefore, EVA-P672, a broad-spectrum CC-chemokine inhibitor, and BK1.3, an EVA-P672-derived peptide with a more restricted chemokine binding range, were compared, and various cardiac parameters were investigated. EVA-P672 did not have any effect on disease outcome or cardiac parameters. The therapeutic effects of BK1.3 were similarly limited, but a smaller decrease in cardiac output and S' velocity, a marker for right ventricular systolic function, was measured, together with improved global longitudinal strain.[74]

Altogether, evidence for therapeutic potential of Evasins in cardiovascular disorders is limited. This may derive from a lack of conceptual understanding of adverse or beneficial effects of specific chemokine and leukocyte populations in these diseases, or the fact that in vitro chemokine binding does not necessarily translate to inhibition of migration by Evasins, which allows to question the effective scope of administered treatment. Moreover, it is understudied how posttranslational modifications of chemokines affect the affinity of these chemokines to Evasins.

Salivary Proteins (Salp) and their Implications in Cardiovascular Research

The Salp family, first described by Das et al,[75] comprises 14 immunodominant salivary gland proteins from I. scapularis, with molecular weights ranging from 9 to 26 kDa. The Salp proteins have several mechanisms of action and targets; some Salps have a suppressive effect on the host's immune system, while others target hemostasis by inhibiting blood coagulation. Salp14 was initially characterized as an FXa inhibitor[76]; however, chromogenic assays indicate that it does not directly affect FXa amidolytic activity.[77] Instead, Salp14 has a polylysine motif in its basic tail region, which is like the C-terminus of tissue factor pathway inhibitor α and functions in the same manner, namely by inhibiting the activity of the prothrombinase complex. Salp14 is proposed to bind to the acidic region of factor V and, as such, targets the initiation phase of coagulation and reduces thrombin generation.[77] This indirect mode of action distinguishes Salp14 from conventional FXa inhibitors and positions it as a potential template for the development of novel anticoagulants aimed at preventing arterial and venous thrombotic events, including stroke, deep vein thrombosis, and pulmonary embolism.[28] Notably, Salp14 also revealed anti-complement activity by inhibiting initiation of the lectin complement pathway (**Fig. 2**). This happens via interaction with mannan-binding lectin–associated serine proteases, which, in normal circumstances, are needed to bind to carbohydrate groups on the surface of bacterial cells.[77] Given the close interplay between complement activation and coagulation in thromboinflammation, this dual activity may be particularly relevant in cardiovascular settings.[81,82]

Anticoagulants are frequently used in case of a thrombotic event, and mostly they are highly effective; however, there is an increased risk of hemorrhagic complications. This limitation highlights the need for complementary or alternative strategies, including approaches that target inflammatory pathways. In this context, other Salp proteins that modulate inflammatory pathways and the innate immune system are of interest.[13] Salp20 inhibits activation of the alternative complement pathway by preventing the cleavage of C3 into C3a and C3b, thereby reducing C3b deposition on target surfaces.[83] As complement activation is increasingly recognized as a driver of thrombosis and vascular inflammation, modulation of this pathway may attenuate thrombus formation and vascular injury.[82]

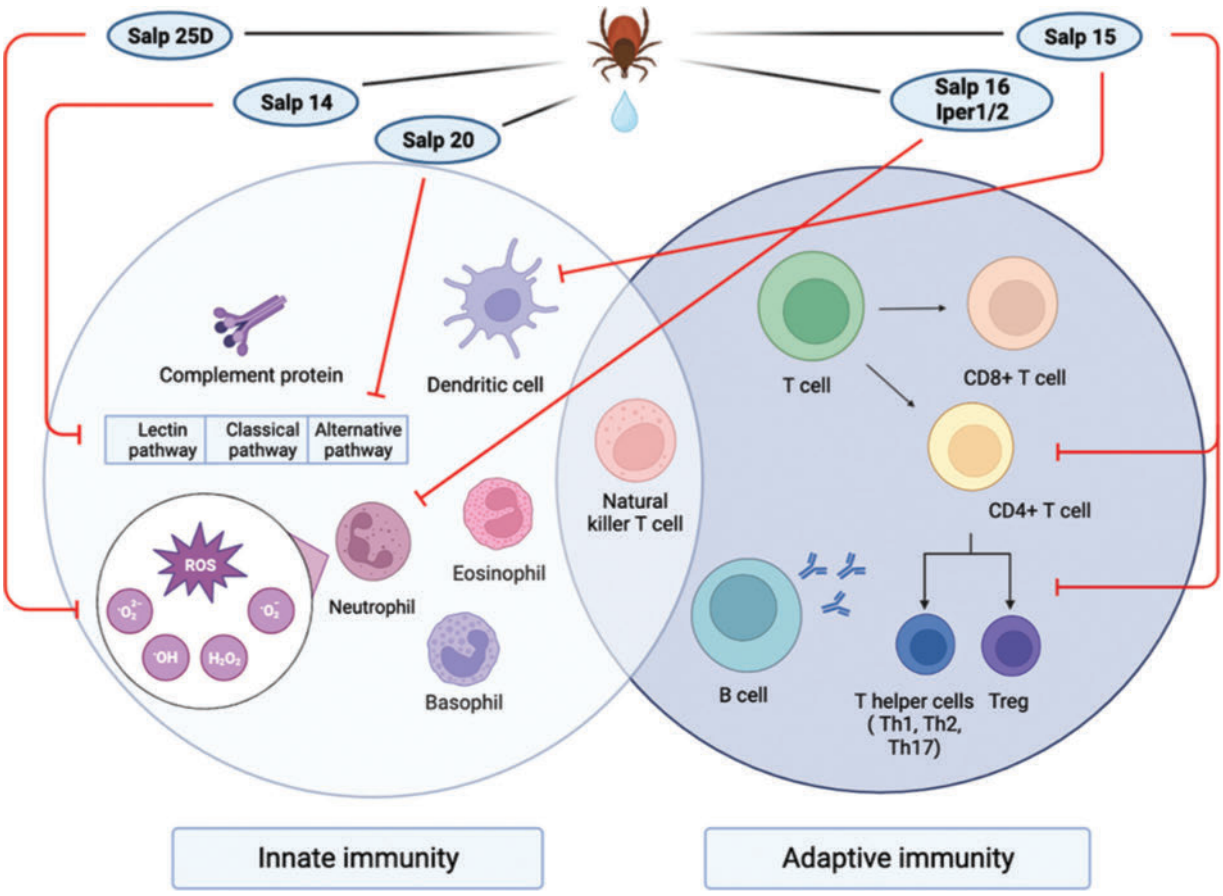


Fig. 2 Overview of the tick salivary proteins and their functions. Salp14 and Salp20 exhibit anti-complement activity by inhibiting the lectin pathway or alternative pathway, respectively. Salp16, Iper1, and Iper2 inhibit neutrophil function and migration. Salp16, Iper1, Iper2, and Salp25d lead to reduced formation of reactive oxygen species (ROS). Salp15 inhibits the activation of CD4+ T cells and T cell proliferation and leads to a reduced production of IL2. In addition, Salp15 suppresses dendritic cell functions, which are essential for initiating adaptive immune responses in naive hosts. [rerif]. Source: Created in BioRender. Sels, M. (2026) https://BioRender.com/p4gj9bs.

Additional Salp proteins may influence cardiovascular disease through effects on oxidative stress and leukocyte function, which both contribute to atherothrombosis. Salp16 homologs identified in Ixodes persulcatus impair neutrophil function by reducing reactive oxygen species (ROS) production and inhibiting their migration induced by the chemoattractant interleukin-8 (CXCL8).[75,84] Salp25D, shown to have glutathione peroxidase activity, also reduces the formation of ROS (**Fig. 2**) by catalyzing the reduction of hydrogen peroxide in the presence of reduced glutathione and glutathione reductase.[93] Hence, these antioxidative and immunomodulatory effects suggest a potential role in modulating vascular inflammation and plaque progression.

Salp15, a 15-kDa protein from tick salivary glands, exerts immunosuppressive effects via various mechanisms by[94] inhibiting CD4+ T cell activation and proliferation.[94,95] Salp15 also affects the innate immune system by interacting with Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Nonintegrin (DC-SIGN) on DCs, thereby suppressing their functions (**Fig. 2**). The mechanism involves a novel Raf-1/MEK-dependent signaling pathway and leads to a decrease in IL-6 and TNF-α mRNA stability and impaired nucleosome remodeling at the IL-12p35 promoter 132. By acting on both cytokine transcriptional and posttranscriptional levels, Salp15 is modulating Toll-like receptor–induced DC activation. From a cardiovascular perspective, Salp15-mediated immune suppression may reduce vascular inflammation, modulate adaptive immune contributions to plaque progression, or provide insight into T cell–targeted therapies in atherosclerosis.

Emerging Therapeutic Insights of Tick Salivary Proteins

The unprecedented ability of tick salivary proteins in targeting several pathways such as inflammation, immunity, or coagulation, in addition to their high specificity, has positioned these compounds as promising molecules for therapeutic development. Several tick-derived molecules progressed to the preclinical and clinical stages, and we expect an increase in this number in the next few years across multiple medical fields.[96]

Despite their numerous advantages, several challenges need to be addressed before considering the application of tick salivary proteins in biomedical research.

A first and major concern is the immunogenicity of tick salivary proteins. Although tick saliva is considered a source of low immunogenic compounds, some epitopes can induce an immune response in humans. These concerns can be addressed using

structure-guided engineering of these immunogenic compounds with the objective of masking the concerned epitopes.[97–99]

A further concern of tick salivary proteins is related to their production and bioavailability. Increased structural complexity of tick proteins raises significant concerns regarding their expression and proper folding (serpins, e.g.). Additionally, posttranslational modifications can be important in certain cases, necessitating the use of appropriate expression systems. Furthermore, efficient delivery of the studied salivary peptides and proteins to the target tissue requires careful optimization. Various strategies such as the use of nanoparticles or conjugation to scaffolds are currently being explored to maximize bioavailability.[96]

The repertoire of tick-derived therapeutics related to cardiovascular, inflammatory, and immune disorders is expected to expand with the unprecedented advances in transcriptomics and proteomics. Therefore, the continued identification of novel salivary effectors and the study of their molecular and structural mechanisms will be of great importance in the coming years.

Tick saliva contains a rich set of bioactive proteins that are emerging as exciting candidates for treating cardiovascular disease. By acting directly on coagulation factors, platelet function, and key inflammatory signals, these molecules can very precisely tune thrombotic and thrombo-inflammatory responses rather than shutting down the system broadly. Their evolution as stealth tools that allow ticks to feed without triggering strong immune reactions gives them an intrinsic advantage as templates for new drugs. Important hurdles remain, including improving stability in vivo, optimizing delivery, and scaling up production, but work on recombinant formats and shorter peptide derivatives is rapidly moving the field forward. Together, these efforts position tick-derived salivary proteins as promising next-generation anticoagulant and anti-inflammatory agents in cardiovascular medicine.

What is known about this topic?

- Tick saliva contains proteins that modulate coagulation and inflammation.
- Various tick-derived salivary proteins target coagulation, platelet activation, and inflammatory responses through highly specific molecular mechanisms.
- Some of these polypeptides have shown therapeutic potential in preclinical models of thrombotic, inflammatory, and cardiovascular diseases.

What does this paper add?

- This review provides an integrated overview of tick salivary proteins that regulate both hemostasis and inflammation, emphasizing their interconnected roles in thrombo-inflammation.
- It highlights evasins and salp proteins as modulators of vascular inflammation and cardiovascular diseases.
- Tick saliva is presented as a source of novel antithrombotic and anti-inflammatory therapeutics, addressing both opportunities and challenges for translation.

Author Affiliations

1 Czech Academy of Sciences, Institute of Parasitology, Biology Centre, České Budějovice, Czech Republic

2 Université de Lorraine, CNRS, IMoPA, Nancy, Lorraine, France

3 Department of Biochemistry, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, LI, the Netherlands

4 Department of Microbiology, Immunology and Transplantation, Laboratory of Molecular Immunology, Rega Institute, KU Leuven, Leuven, Belgium

5 UHasselt, BIOMED, Agoralaan, Diepenbeek, Belgium

6 Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Heraklion, Greece

7 Department of Radiology and Nuclear Medicine, Maastricht University Medical Center (MUMC), Maastricht, the Netherlands

Statements and Additional Information

Conflict of Interest The authors declare that they have no conflict of interest.

References

1 Nuttall PA. Wonders of tick saliva. Ticks Tick Borne Dis 2019;10(02):470–481

2 Anderson JF. The natural history of ticks. Med Clin North Am 2002;86 (02):205–218

3 Jongejan F, Uilenberg G. The global importance of ticks. Parasitology 2004;129 (suppl):S3–S14

4 Mans BJ, Neitz AW. Adaptation of ticks to a blood-feeding environment: evolution from a functional perspective. Insect Biochem Mol Biol 2004;34(01):1–17

5 Francischetti IM, Sa-Nunes A, Mans BJ, Santos IM, Ribeiro JM. The role of saliva in tick feeding. Front Biosci (Landmark Ed) 2009;14(06):2051–2088

6 Haberichter SL, O'Donnell JS. Structure and multiple functions of von Willebrand factor. Haematologica 2026;111(01):15–25

7 Sepúlveda C, Palomo I, Fuentes E. Primary and secondary haemostasis changes related to aging. Mech Ageing Dev 2015;150:46–54

8 Wang X, Coons LB, Taylor DB, Stevens SE Jr, Gartner TK. Variabilin, a novel RGD-containing antagonist of glycoprotein IIb-IIIa and platelet aggregation inhibitor from the hard tick Dermacentor variabilis. J Biol Chem 1996;271 (30):17785–17790

9 Mans BJ, Louw AI, Neitz AW. Savignygrin, a platelet aggregation inhibitor from the soft tick Ornithodoros savignyi, presents the RGD integrin recognition motif on the Kunitz-BPTI fold. J Biol Chem 2002;277(24):21371–21378

10 Kuijpers MJE, Heemskerk JWM, Jurk K. Molecular mechanisms of hemostasis, thrombosis and thrombo-inflammation. Int J Mol Sci 2022;23(10):5825

11 Chmelař J, Kotál J, Langhansová H, Kotsyfakis M. Protease inhibitors in tick saliva: the role of serpins and cystatins in tick-host-pathogen interaction. Front Cell Infect Microbiol 2017;7:216

12 Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood 2019;133(09):906–918

13 Marcos-Jubilar M, Lecumberri R, Páramo JA. Immunothrombosis: molecular aspects and new therapeutic perspectives. J Clin Med 2023;12(04):1399

14 Wagner DD, Heger LA. Thromboinflammation: from atherosclerosis to COVID-19. Arterioscler Thromb Vasc Biol 2022;42(09):1103–1112

15 Chmelař J, Kotál J, Karim S, et al. Sialomes and Mialomes: a systems-biology view of tick tissues and tick-host interactions. Trends Parasitol 2016;32(03):242–254

16 Champagne DE. Antihemostatic strategies of blood-feeding arthropods. Curr Drug Targets Cardiovasc Haematol Disord 2004;4(04):375–396

17 Clemetson KJ. Platelets and primary haemostasis. Thromb Res 2012;129 (03):220–224

18 Chmelar J, Calvo E, Pedra JHF, Francischetti IMB, Kotsyfakis M. Tick salivary secretion as a source of antihemostatics. J Proteomics 2012;75(13):3842–3854

19 Kotál J, Langhansová H, Lieskovská J, et al. Modulation of host immunity by tick saliva. J Proteomics 2015;128:58–68

20 van den Kerkhof DL, Nagy M, Wichapong K, et al. Inhibition of platelet adhesion, thrombus formation, and fibrin formation by a potent αIIbβ3 integrin inhibitor from ticks. Res Pract Thromb Haemost 2020;5(01):231–242

21 Francischetti IM. Platelet aggregation inhibitors from hematophagous animals. Toxicon 2010;56(07):1130–1144

22 Jmel MA, Voet H, Araújo RN, Tirloni L, Sá-Nunes A, Kotsyfakis M. Tick salivary Kunitz-type inhibitors: targeting host hemostasis and immunity to mediate successful blood feeding. Int J Mol Sci 2023;24(02):1556

23 Karasuyama H, Miyake K, Yoshikawa S. Immunobiology of acquired resistance to ticks. Front Immunol 2020;11:601504

24 Jmel MA, Aounallah H, Bensaoud C, et al. Insights into the role of tick salivary protease inhibitors during ectoparasite-host crosstalk. Int J Mol Sci 2021;22 (02):892

25 Francischetti IM, Valenzuela JG, Andersen JF, Mather TN, Ribeiro JM. Ixolaris, a novel recombinant tissue factor pathway inhibitor (TFPI) from the salivary gland of the tick, Ixodes scapularis: identification of factor X and factor Xa as scaffolds for the inhibition of factor VIIa/tissue factor complex. Blood 2002;99(10):3602–3612

26 Martins LA, Kotál J, Bensaoud C, Chmelař J, Kotsyfakis M. Small protease inhibitors in tick saliva and salivary glands and their role in tick-host-pathogen interactions. Biochim Biophys Acta Proteins Proteom 2020;1868(02):140336

27 Branco VG, Iqbal A, Alvarez-Flores MP, et al. Amblyomin-X having a Kunitz-type homologous domain, is a noncompetitive inhibitor of FXa and induces anti-coagulation in vitro and in vivo. Biochim Biophys Acta 2016;1864(10):1428–1435

28 De Caterina R. The current role of anticoagulants in cardiovascular medicine. J Cardiovasc Med (Hagerstown) 2009;10(08):595–604

29 Chudzinski-Tavassi AM, De-Sá-Júnior PL, Simons SM, et al. A new tick Kunitz type inhibitor, Amblyomin-X, induces tumor cell death by modulating genes related to the cell cycle and targeting the ubiquitin-proteasome system. Toxicon 2010;56 (07):1145–1154

30 Saboor M, Ayub Q, Ilyas S, Moinuddin. Platelet receptors; an instrumental of platelet physiology. Pak J Med Sci 2013;29(03):891–896

31 Bennett JS. The molecular biology of platelet membrane proteins. Semin Hematol 1990;27(02):186–204

32 Desidério CS, Flávio-Reis VHP, Pessoa-Gonçalves YM, et al. Binding molecules in tick saliva for targeting host cytokines, chemokines, and beyond. Biomolecules 2024;14(12):1647

33 Mans BJ, Andersen JF, Schwan TG, Ribeiro JM. Characterization of anti-hemostatic factors in the argasid, Argas monolakensis: implications for the evolution of blood-feeding in the soft tick family. Insect Biochem Mol Biol 2008;38(01):22–41

34 Francischetti IM, My Pham V, Mans BJ, et al. The transcriptome of the salivary glands of the female western black-legged tick Ixodes pacificus (Acari: Ixodidae). Insect Biochem Mol Biol 2005;35(10):1142–1161

35 Zhang P, Solari FA, Heemskerk JWM, et al. Differential regulation of GPVI-induced Btk and Syk activation by PKC, PKA and PP2A in human platelets. Int J Mol Sci 2023;24(09):7776

36 Troisi R, Balasco N, Autiero I, Vitagliano L, Sica F. Exosite binding in thrombin: a global structural/dynamic overview of complexes with aptamers and other ligands. Int J Mol Sci 2021;22(19):10803

37 Crawley JT, Zanardelli S, Chion CK, Lane DA. The central role of thrombin in hemostasis. J Thromb Haemost 2007;5 (Suppl 1):95–101

38 Coughlin SR. Protease-activated receptors in hemostasis, thrombosis and vascular biology. J Thromb Haemost 2005;3(08):1800–1814

39 Zwaal RF, Comfurius P, Bevers EM. Lipid-protein interactions in blood coagulation. Biochim Biophys Acta 1998;1376(03):433–453

40 Iqbal A, Goldfeder MB, Marques-Porto R, et al. Revisiting antithrombotic therapeutics; Sculptin, a novel specific, competitive, reversible, scissile and tight binding inhibitor of thrombin. Sci Rep 2017;7(01):1431

41 Mans BJ, Louw AI, Neitz AW. Amino acid sequence and structure modeling of Savignin, a thrombin inhibitor from the tick, Ornithodoros savignyi. Insect Biochem Mol Biol 2002;32(07):821–828

42 Nienaber J, Gaspar AR, Neitz AW. Savignin, a potent thrombin inhibitor isolated from the salivary glands of the tick Ornithodoros savignyi (Acari: Argasidae). Exp Parasitol 1999;93(02):82–91

43 van de Locht A, Stubbs MT, Bode W, et al. The Ornithodorin-thrombin crystal structure, a key to the TAP enigma? EMBO J 1996;15(22):6011–6017

44 Li Q, Liu Y, Ren B, et al. Recombinant neorudin and its active metabolite hirudin: the fate in vivo of a novel anticoagulant drug. Front Pharmacol 2024;15:1443475

45 Jablonka W, Kotsyfakis M, Mizurini DM, et al. Identification and mechanistic analysis of a novel tick-derived inhibitor of thrombin. PLoS One 2015;10(08): e0133991

46 Monteiro RQ, Rezaie AR, Bae JS, Calvo E, Andersen JF, Francischetti IMB. Ixolaris binding to factor X reveals a precursor state of factor Xa heparin-binding exosite. Protein Sci 2008;17(01):146–153

47 Carneiro-Lobo TC, Konig S, Machado DE, et al. Ixolaris, a tissue factor inhibitor, blocks primary tumor growth and angiogenesis in a glioblastoma model. J Thromb Haemost 2009;7(11):1855–1864

48 Waxman L, Smith DE, Arcuri KE, Vlasuk GP. Tick Anticoagulant Peptide (TAP) is a novel inhibitor of blood coagulation factor Xa. Science 1990;248(4955):593–596

49 Francischetti IM, Mather TN, Ribeiro JM. Penthalaris, a novel recombinant five-Kunitz tissue factor pathway inhibitor (TFPI) from the salivary gland of the tick vector of Lyme disease, Ixodes scapularis. Thromb Haemost 2004;91 (05):886–898

50 Dai J, Narasimhan S, Zhang L, Liu L, Wang P, Fikrig E. Tick Histamine Release Factor is critical for Ixodes scapularis engorgement and transmission of the Lyme disease agent. PLoS Pathog 2010;6(11):e1001205

51 Mulenga A, Macaluso KR, Simser JA, Azad AF. The American dog tick, Dermacentor variabilis, encodes a functional histamine release factor homolog. Insect Biochem Mol Biol 2003;33(09):911–919

52 Nazareth RA, Tomaz LS, Ortiz-Costa S, et al. Antithrombotic properties of Ixolaris, a potent inhibitor of the extrinsic pathway of the coagulation cascade. Thromb Haemost 2006;96(01):7–13

53 Ali A, Zeb I, Alouffi A, et al. Host immune responses to salivary components - a critical facet of tick-host interactions. Front Cell Infect Microbiol 2022;12:809052

54 Ribeiro JM, Makoul GT, Robinson DR. Ixodes dammini: evidence for salivary prostacyclin secretion. J Parasitol 1988;74(06):1068–1069

55 Déruaz M, Frauenschuh A, Alessandri AL, et al. Ticks produce highly selective chemokine binding proteins with antiinflammatory activity. J Exp Med 2008;205 (09):2019–2031

56 Déruaz M, Bonvin P, Severin IC, et al. Evasin-4, a tick-derived chemokine-binding protein with broad selectivity can be modified for use in preclinical disease models. FEBS J 2013;280(19):4876–4887

57 Eaton JRO, Alenazi Y, Singh K, et al. The N-terminal domain of a tick Evasin is critical for chemokine binding and neutralization and confers specific binding activity to other Evasins. J Biol Chem 2018;293(16):6134–6146

58 Dias JM, Losberger C, Déruaz M, Power CA, Proudfoot AE, Shaw JP. Structural basis of chemokine sequestration by a tick chemokine binding protein: the crystal structure of the complex between Evasin-1 and CCL3. PLoS One 2009;4(12): e8514

59 Sá-Nunes A, Bafica A, Antonelli LR, et al. The immunomodulatory action of Sialostatin L on dendritic cells reveals its potential to interfere with autoimmunity. J Immunol 2009;182(12):7422–7429

60 Wang X, Shaw DK, Sakhon OS, et al. The tick protein Sialostatin L2 binds to annexin A2 and inhibits NLRC4-mediated inflammasome activation. Infect Immun 2016;84(06):1796–1805

61 Wu J, Wang Y, Liu H, et al. Two immunoregulatory peptides with antioxidant activity from tick salivary glands. J Biol Chem 2010;285(22):16606–16613

62 Sá-Nunes A, Bafica A, Lucas DA, et al. Prostaglandin E2 is a major inhibitor of dendritic cell maturation and function in Ixodes scapularis saliva. J Immunol 2007;179(03):1497–1505

63 Mans BJ, Gaspar AR, Louw AI, Neitz AW. Apyrase activity and platelet aggregation inhibitors in the tick Ornithodoros savignyi (Acari: Argasidae). Exp Appl Acarol 1998;22(06):353–366

64 Mans BJ, Gasper AR, Louw AI, Neitz AW. Purification and characterization of apyrase from the tick, Ornithodoros savignyi. Comp Biochem Physiol B Biochem Mol Biol 1998;120(03):617–624

65 Mans BJ, Coetzee J, Louw AI, Gaspar AR, Neitz AW. Disaggregation of aggregated platelets by apyrase from the tick, Ornithodoros savignyi (Acari: Argasidae). Exp Appl Acarol 2000;24(04):271–282

66 Katayama H, Nagata K. Application of 2,2′-dipyridyl disulfide-mediated thiazolidine ring-opening reaction to glycoprotein synthesis: total chemical synthesis of Evasin-3. J Pept Sci 2021;27(02):e3290

67 Wang L, Zhang YL, Lin QY, et al. CXCL1-CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy and remodelling through regulation of monocyte infiltration. Eur Heart J 2018;39(20):1818–1831

68 Hansen PR. Role of neutrophils in myocardial ischemia and reperfusion. Circulation 1995;91(06):1872–1885

69 Chlastáková A, Kotál J, Beránková Z, et al. Iripin-3, a new salivary protein isolated from *Ixodes ricinus* ticks, displays immunomodulatory and anti-hemostatic properties in vitro. Front Immunol 2021;12:626200

70 Anisuzzaman HT, Hatta T, Miyoshi T, et al. Longistatin in tick saliva blocks advanced glycation end-product receptor activation. J Clin Invest 2014;124 (10):4429–4444

71 Chmelar J, Oliveira CJ, Rezacova P, et al. A tick salivary protein targets cathepsin G and chymase and inhibits host inflammation and platelet aggregation. Blood 2011;117(02):736–744

72 Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377 (12):1119–1131

73 Ionita MG, van den Borne P, Catanzariti LM, et al. High neutrophil numbers in human carotid atherosclerotic plaques are associated with characteristics of rupture-prone lesions. Arterioscler Thromb Vasc Biol 2010;30(09):1842–1848

74 Saxena N, Rajagopalan N, Edelman K, López-Candales A. Tricuspid annular systolic velocity: a useful measurement in determining right ventricular systolic function regardless of pulmonary artery pressures. Echocardiography 2006;23 (09):750–755

75 Das S, Marcantonio N, Deponte K, et al. SALP16, a gene induced in Ixodes scapularis salivary glands during tick feeding. Am J Trop Med Hyg 2000;62 (01):99–105

76 Narasimhan S, Koski RA, Beaulieu B, et al. A novel family of anticoagulants from the saliva of Ixodes scapularis. Insect Mol Biol 2002;11(06):641–650

77 Denisov SS, Ippel JH, Castoldi E, Mans BJ, Hackeng TM, Dijkgraaf I. Molecular basis of anticoagulant and anticomplement activity of the tick salivary protein Salp14 and its homologs. J Biol Chem 2021;297(01):100865

78 Vanheule V, Metzemaekers M, Janssens R, Struyf S, Proost P. How post-translational modifications influence the biological activity of chemokines. Cytokine 2018;109:29–51

79 Miao M, De Clercq E, Li G. Clinical significance of chemokine receptor antagonists. Expert Opin Drug Metab Toxicol 2020;16(01):11–30

80 Noels H, Weber C, Koenen RR. Chemokines as therapeutic targets in cardiovascular disease. Arterioscler Thromb Vasc Biol 2019;39(04):583–592

81 Nording H, Giesser A, Patzelt J, et al. Platelet bound oxLDL shows an inverse correlation with plasma anaphylatoxin C5a in patients with coronary artery disease. Platelets 2016;27(06):593–597

82 Nørgaard I, Nielsen SF, Nordestgaard BG. Complement C3 and high risk of venous thromboembolism: 80517 individuals from the Copenhagen General Population Study. Clin Chem 2016;62(03):525–534

83 Tyson K, Elkins C, Patterson H, Fikrig E, de Silva A. Biochemical and functional characterization of Salp20, an Ixodes scapularis tick salivary protein that inhibits the complement pathway. Insect Mol Biol 2007;16(04):469–479

84 Hidano A, Konnai S, Yamada S, et al. Suppressive effects of neutrophil by Salp16-like salivary gland proteins from Ixodes persulcatus Schulze tick. Insect Mol Biol 2014;23(04):466–474

85 Braunersreuther V, Montecucco F, Pelli G, et al. Treatment with the CC chemokine-binding protein Evasin-4 improves post-infarction myocardial injury and survival in mice. Thromb Haemost 2013;110(04):807–825

86 Lee AW, Deruaz M, Lynch C, et al. A knottin scaffold directs the CXC-chemokine-binding specificity of tick Evasins. J Biol Chem 2019;294(29):11199–11212

87 Kelm N, Kespohl M, Smagurauskaite G, et al. Assessing customized multivalent chemokine-binding peptide treatment in a murine model of coxsackievirus B3 myocarditis. Basic Res Cardiol 2025;120(02):393–422

88 Wang Y, Shou X, Wu Y, Li D. Immuno-inflammatory pathogenesis in ischemic heart disease: perception and knowledge for neutrophil recruitment. Front Immunol 2024;15:1411301

89 Montecucco F, Braunersreuther V, Lenglet S, et al. CC chemokine CCL5 plays a central role impacting infarct size and post-infarction heart failure in mice. Eur Heart J 2012;33(15):1964–1974

90 Copin J-C, da Silva RF, Fraga-Silva RA, et al. Treatment with Evasin-3 reduces atherosclerotic vulnerability for ischemic stroke, but not brain injury in mice. J Cereb Blood Flow Metab 2013;33(04):490–498

91 Montecucco F, Lenglet S, Braunersreuther V, et al. Single administration of the CXC chemokine-binding protein Evasin-3 during ischemia prevents myocardial reperfusion injury in mice. Arterioscler Thromb Vasc Biol 2010;30(07):1371–1377

92 Jickling GC, Liu D, Ander BP, Stamova B, Zhan X, Sharp FR. Targeting neutrophils in ischemic stroke: translational insights from experimental studies. J Cereb Blood Flow Metab 2015;35(06):888–901

93 Narasimhan S, Sukumaran B, Bozdogan U, et al. A tick antioxidant facilitates the Lyme disease agent's successful migration from the mammalian host to the arthropod vector. Cell Host Microbe 2007;2(01):7–18

94 Das S, Banerjee G, DePonte K, Marcantonio N, Kantor FS, Fikrig E. Salp25D, an Ixodes scapularis antioxidant, is 1 of 14 immunodominant antigens in engorged tick salivary glands. J Infect Dis 2001;184(08):1056–1064

95 Anguita J, Ramamoorthi N, Hovius JW, et al. Salp15, an Ixodes scapularis salivary protein, inhibits CD4(+) T cell activation. Immunity 2002;16(06):849–859

96 Aounallah H, Bensaoud C, M'ghirbi Y, Faria F, Chmelar JI, Kotsyfakis M. Tick salivary compounds for targeted immunomodulatory therapy. Front Immunol 2020;11:583845

97 Darlot B, Eaton JRO, Geis-Asteggiante L, et al. Engineered anti-inflammatory peptides inspired by mapping an Evasin-chemokine interaction. J Biol Chem 2020;295(32):10926–10939

98 Denisov SS, Dijkgraaf I. Immunomodulatory proteins in tick saliva from a structural perspective. Front Cell Infect Microbiol 2021;11:769574

99 Déruaz M, Frauenschuh A, Alessandri AL, et al. Ticks produce highly selective chemokine binding proteins with antiinflammatory activity. J Exp Med 2008;205 (09):2019–2031