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Tick host immunity: Vector Immunomodulation and Acquired Tick Resistance

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Abstract

Ticks have adapted an unparalleled ability to parasitize diverse land vertebrates. Their natural persistence and vector competence are supported by the evolution of sophisticated hematophagy and remarkable host immune evasion activities. Herein, we analyze the immunomodulatory roles of tick saliva, which facilitates the acquisition of the vector's blood meal from natural hosts and allows for pathogen transmission. We also discuss the contrasting immunological events of tick-host associations in non-reservoir or incidental hosts, in which the development of acquired tick resistance can deter tick attachment. A critical appraisal of the intricate immunobiology of tick-host associations can plant new seeds of innovative research and contribute to the development of novel preventive strategies against ticks and tick-transmitted infections.

Evolution of Sophisticated Hematophagy in Ticks and Perplexing Immunobiology of Tick-Host Associations:

Ticks comprise a diverse group of highly adapted and obligate blood-feeding ectoparasites classified into the *Ixodidae* (**hard tick**) and *Argasidae* (**soft tick**) families, encompassing 692 and 186 species, respectively [1]. A third ancestral family called *Nuttalliellidae* is represented by a single surviving species that exists only in South Africa [2]. While there is uncertainty about the precise location or timeline of the origin of ticks, it is likely that they evolved and diversified over a wide geological time period in the early Mesozoic era (~225 million years ago, MYA) [3], including the Jurassic age, with a major dispersal beginning in the Tertiary period (65 – 5 MYA) [4] and continuing throughout recent years and across the globe (Figure 1). According to their phylogenetic tree, ticks underwent a monophyletic evolution and are likely a sister group to Holothyrida, a clade of free-living mites that

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scavenge on the body fluids of dead arthropods [5]. It is believed that tick **hematophagy** originated with primeval reptile or amphibian hosts and evolved to include modern birds, reptiles, and placental mammals. How did ticks become such resilient ectoparasites of a diverse set of land vertebrates? Based on the distinctions between the remarkable biology and lifestyles of hard and soft ticks, it is probable that various blood-feeding adaptations occurred independently in the major tick families. Notably, the rapid divergence of major tick families coincided with the early divergence of modern birds and placental mammals in the late Cretaceous period (120 – 92 MYA), implying that the latter event could have been a driving force in the evolution of distinct hematophagy processes in ticks. In fact, studies show that tick anti-hemostatic components evolved separately in the major families, as suggested by the analysis of blood coagulation and platelet aggregation inhibitors from soft ticks of the genus *Ornithodoros* [6], in addition to dramatic adaptive changes in their respective organs (such as the salivary gland), feeding behaviors, and reproductive strategies [7]. Taken together, it seems that hematophagy diversified over millions of years through the co-option of tick physiology, while also undergoing dramatic expansion in host selectivity.

Along with the geographic expansion of ticks [8], there has been a parallel and alarming increase in the global occurrence of tick-transmitted infections [3,9]. During the last two decades, at least thirteen novel tick-borne pathogens have been identified in the Western Hemisphere alone [9]. The highly evolved hematophagy of ticks, which is integral to their ability to engorge on diverse hosts, has also adapted to evade host detection and modulate host immune responses, ensuring prolonged and direct contact with the vertebrate throughout the feeding process [2,3]. This contributes to the extraordinary vector competence of ticks, which allows for the entry, persistence, and transmission of a wide range of viral, bacterial, and protozoan pathogens [10]. Whereas about 90% of tick species prefer a particular host [11], or are constrained by specific host-ectoparasite associations, some tick species have adapted a much broader host range, such as *Ixodes* spp., whose range is distributed across multiple continents [12]. Ixodid ticks pursue three feeding events during their entire life span of a few years, with each engorgement lasting for 3–15 days, and can ingest a huge blood meal that is up to 100 times greater than their body weight [13]. In comparison, the other two families (argasid or *Nuttalliella* ticks) are rapid and frequent feeders, achieving engorgement in seconds to hours [2,3]. Therefore, unlike rapidly-feeding hematophagous vectors, the immunobiology of host associations with hard ticks is likely unique and warrants further empirical research; indeed, a series of recent studies have led to major scientific discoveries, including a deeper understanding of tick interactions with pathogens [14,15]. As evidenced by the tick-transmitted infections that have emerged in the last few decades [9], hard ticks pose a higher threat to human health, as they transmit a greater number and more diverse set of pathogens than other species of ticks; therefore, this review article discusses our most current state of knowledge on the immunological basis of Ixodid tick-host interactions [16]. Primarily using *Ixodes* spp. or other hard ticks as a model vector, we highlight the intricate cellular and molecular bases of immunomodulation by ticks via their dynamic suite of salivary gland proteins, which collectively support tick hematophagy, dictating the success of blood meal acquisition and the subsequent **saliva-assisted transmission** of pathogens.

Acquired tick resistance (ATR) is an astounding phenomenon of tick-host associations involving **incidental hosts**, such as guinea pigs, when they are repeatedly exposed to ticks [17], wherein a rapid inflammatory reaction at the tick bite site results in the detachment or even death of ticks [18]. In some experimental cases of ATR in guinea pigs, rapid tick detachment in tick-immune incidental hosts prevented the transmission of tick-borne infections, such as *Borrelia burgdorferi* (**Lyme disease**) [19–21]. The phenomenon of ATR also potentially exists in humans, as suggested by the development of **cutaneous basophilic hypersensitivity** against tick bites and the decreased occurrence of Lyme disease in the residents of a disease-endemic site who had prior exposure to vector ticks [22]. Similarly to **natural hosts** such as wild mice, such incidental hosts are usually permissive to an initial tick infestation; however, they quickly acquire transient yet robust resistance to secondary infestations, often reflected by an intense and histolytic erythema in the skin [23,24]. Further research is needed to decipher the immunological basis of acquired immunity and the prevention of tick engorgement in incidental hosts, as it can not only enrich this unexplored field of mammalian immunology but might also provide opportunities for future tick preventive strategies. In fact, in the past few decades, we have witnessed significant advancements in our understanding of the immunobiology of tick-host associations [16], which likely involve multifactorial immunological cascades. We highlight these exciting theories and experimental evidence, which attempt to explain both the lack of acquired tick immunity in natural hosts and the development of ATR in incidental hosts [25]. It is possible that the arsenal of tick activities against host immune responses may target a small, defined number of natural vertebrate species that are required to maintain the vector population. However, due to limited opportunities to parasitize these natural hosts, or in chance encounters with other species, ticks can also feed on more incidental hosts, where the development of an immune response might not be evolutionarily relevant. In fact, tick immunomodulatory activities (via their saliva) are well-defined in natural hosts (such as the mouse), but it is unclear whether these are maintained when feeding on incidental hosts that display tick immunity. Herein, we compare the most salient immunological aspects of tick engorgement in natural **reservoir hosts** versus nonnatural incidental hosts, in addition to the perplexing host responses that dictate the outcome of tick feeding, including the immunomodulatory roles of the tick salivary gland and saliva-assisted transmission of pathogens. We speculate that this information is paramount to our knowledge of the unique immunobiology of vector-host associations, while also fueling the development of novel preventions against ticks and the infections they transmit.

Tick Immunomodulation of Natural Hosts:

Because ticks (particularly hard tick species) engorge for a prolonged time on permissive vertebrates, including natural or reservoir hosts, they must counteract or circumvent a variety of the host's complex defense mechanisms that have evolved to prevent blood loss and infection. Here, we focus on the cytological events at the tick bite site and the multidimensional roles of tick saliva proteins, especially their influences on major host defenses, which allow the vectors to successfully secure a blood meal. Tick saliva and certain saliva constituents from various tick species have been found to specifically

target different aspects of host physiology and immune responses [26–29], favoring the transmission of tick-borne pathogens, as highlighted below.

Histological parameters and cellular infiltrates at the bite site:

A hallmark of tick engorgement in vertebrates is the infiltration of host immune cells on or around the tick bite site (Figure 2), which does not interfere with the blood feeding process [23]. Although the timing of cellular recruitment and the composition of the infiltrates can vary to some degree from species to species, all hosts exhibit intense cellular infiltration at the bite site within the first 6 hours of tick attachment [23]. These inflammatory responses generally escalate over the course of tick engorgement, and become even more dramatic in repeat feedings (i.e., after the first tick exposure) [30]. Indeed, studies of laboratory mice show that the cellular infiltrates in the skin contain a mixed population of inflammatory cells, mostly neutrophils, lymphocytes, eosinophils, and basophils, with the occasional presence of tissue macrophages (histocytes) [24,30]. Mice typically display mild to moderate ulcerations at the tick bite site of the skin where the **tick hypostome** is inserted, in addition to central invagination of the epidermis, necrosis, and a clear sign of vascular injury in the adjacent dermis, including vascular dilation and extravasation of erythrocytes [30]. Like laboratory mice, the white-footed mouse (*Peromyscus leucopus*), which is the natural host for *Ixodes* ticks, also demonstrates a similar inflammatory response, characterized by focal granulomas with leukocytic dermatitis, surrounded by signs of hemorrhage with extravasated erythrocytes [23]. During repeated tick infestations, more extensive **epidermal hyperplasia** and **serocellular crusting**, marked by **broad sessile lesions**, are observed at the bite sites, despite the dermal architecture remaining intact [23]. In humans, comparable numbers of inflammatory cellular infiltrates are also noted at tick bite sites, with a predominant recruitment of immune cells, such as macrophages and dendritic cells, and an occasional presence of lymphocytes [30,31]. Notably, reduced numbers of cellular infiltrates (other than lymphocytes) have been reported at the bite sites on human skin and at later time points (beyond 24 hours of tick attachment), and might be due to the putative suppressive effects of saliva and/or its constituents acting as immunomodulators, as assessed by the expression of cytokines and leukocyte markers, in addition to dermal histopathological changes in human skin biopsies [31]. However, this possibility remains to be rigorously tested. We now briefly highlight representative examples of these presumed immunomodulatory activities and their potential to counteract various host responses (Figure 3) via tick saliva or salivary gland (SG) proteins, and which may enable the acquisition of a blood meal.

Tick immunomodulation of host responses:

Tick feeding triggers a series of counteractive measures within the host to prevent blood loss. Such host hemostatic responses orchestrate a quick restoration of damaged blood vessels, primarily via controlled vasoconstriction, platelet aggregation, and clot formation using the coagulation cascade [27]. Ticks have evolved to produce an array of anti-hemostatic SG proteins [32] that can target (and impair) specific stages or molecules associated with key steps of **hemostasis**, in order to promote blood flow from punctured vasculature or to delay wound healing [27,28]. To interfere with vasoconstriction, ticks produce bioactive molecules, such as prostacyclin and other prostaglandins, such as PGE_2

and $PGF_{2\alpha}$, which act as vasodilators by promoting local blood flow at the tick bite site [33,34]. The RNA-interference mediated knockdown of the *Ixodes scapularis* tick histamine release factor (tHRF) results in lower engorgement weights of nymphal ticks relative to wildtype controls, while recombinant tHRF can mediate histamine release from host basophils [35]. *In vitro* studies demonstrate that IRS-2, a serine proteinase inhibitor in *Ixodes ricinus* ticks, affects the cleavage of big endothelins (ETs), the precursors of potent vasoconstrictors, by inhibiting the enzymes cathepsin G and chymase [36]. Together, these studies show that tHRF and IRS-2 can influence vascular permeability, thus facilitating host blood meal acquisition in ticks [35,36]. Primary hemostasis (involving the function of platelets) is inhibited by many hard and soft ticks, such as *Ixodes* or *Ornithodoros* spp., respectively, via the production of **apyrase**, **Tick Adhesion Inhibitor (TAI)**, or the **αIIbβ3 integrin inhibitor**, which prevent various steps of platelet activation, aggregation, and adhesion [37–39]. Specific steps in host secondary hemostasis, characterized by the coagulation cascade, can be directly blocked by an arsenal of SG proteases [40–43]; for example, *I. scapularis* metalloprotease, exerts gelatinase and fibrinolytic activities in *in vitro* assays [40], and protease inhibitors such as *I. scapularis* Salp14 (an anticoagulant), display specific inhibitory effects on the enzymatic activities of factor Xa in *in vitro* chromogenic assays [41]. Additionally, the factor Ixolaris inhibits the initiation of coagulation by binding to the TF/FVIIa complex *in vitro* using human umbilical vein endothelial cells (HUVECs) [42], and Penthalaris displays an Ixolaris-like mechanism of coagulation inhibition [43]. Finally, hard ticks such as *Ixodes*, *Dermacentor*, and *Rhipicephalus* spp. produce disintegrin- or thrombospondin-like molecules, which can bind growth factors, including transforming growth factor-β1, platelet-derived growth factor (PDGF), fibroblast growth factor-2, and hepatocyte growth factor [44]; these impede cell-extracellular matrix interactions as well as angiogenesis, ultimately affecting the host's wound healing activities [45–49]. In addition, the saliva and salivary gland extracts collected from *Dermacentor variabilis* ticks can impair PDGF-stimulated fibroblast movement *in vitro*, although the identity of the inhibitory tick molecule remains unknown [49]. Studies using the saliva of *I. scapularis* or the cattle tick *Rhipicephalus microplus* indicate the presence of proteins with metalloprotease activity, inhibiting angiogenesis as well as the proliferation of microvascular endothelial cells [46]. Similarly, a troponin I-like molecule has been identified in the saliva of *Haemaphysalis longicornis*, inhibiting the capillary formation of human vascular endothelial cells *in vitro* [47]. A novel Kunitz inhibitor, termed Haemangin, has also been identified from the same tick species, and can disrupt angiogenesis and wound healing by blocking the proliferation of vascular endothelial cells and the induction of apoptosis [48]. In addition, many *Ixodes* SG proteins, such as *I. scapularis* salivary anticomplement (Isac) [50] and Salp20 [51], or *I. ricinus* anticomplement (IRAC) protein I and II [52], and tick salivary lectin pathway inhibitor (TSLPI) protein [53], can impair the host **complement system**; they can do so by inhibiting the substrate binding of C3b, blocking the function of C3 convertase, or by binding the mannose-binding lectin [50–53].

A key immunomodulatory activity of ticks is their ability to block inflammation by binding tick molecules to specific host chemokines, cytokines, or growth factors. Some ticks, such as *Rhipicephalus sanguineus*, *Rhipicephalus appendiculatus*, *Dermacentor reticulatus*, and *Amblyomma variegatum*, produce SG proteins, including a series of chemokine binding

proteins called **evasins**, which function as chemoattractants for immune cells [54,55]. For example, Evasin-1, binding CCL3, CCL4, and CCL18, and Evasin-3, binding CXCL8 and CXCL1, both affect leukocyte recruitment and host inflammation, as demonstrated via *in vitro* assays and in studies using the administration of recombinant Evasin proteins in BALB/c and C57BL/6 mice [54]. The activity of Evasin-3 and its selective binding to neutrophil chemoattractants, such as CXCL8 and CXCL1, as indicated by ELISA analyses, have also been detected in salivary gland extracts from *A. variegatum*, *R. appendiculatus*, and *D. reticulatus* ticks [55].

The anti-inflammatory activities elicited by tick saliva are also mediated by serine protease inhibitors, such as the AAS27 and AAS41 serpins of *A. americanum* ticks, which block various enzymes, such as plasmin, trypsin, chymase, and α-chymotrypsin, whose functions are required for inflammation [56,57]. Moreover, the **kininase** activity in *I. scapularis* saliva has been implicated in the hydrolysis of bradykinin, as evidenced from *in vitro* analysis of tick saliva and salivary gland homogenates, and when using purified salivary kininase and bradykinin [58]. A number of *Ixodes* salivary proteins have also been reported to influence the functions of dendritic cells or T lymphocytes [59–61]. Prostaglandin E_2 (PGE_2), a protein from *I. scapularis* saliva, inhibited the production of IL-12 and TNF-α in bone marrow-derived dendritic cells (BMDC) isolated from C57BL/6 mice [59]. Similarly, a secreted cysteine protease inhibitor, Sialostatin L, inhibited lipopolysaccharide (LPS)-induced maturation of dendritic cells from C57BL/6 mice, in addition to impairing early T cell expansion and proliferation *in vivo* [60]. In *I. ricinus* ticks, the immunomodulatory activity of a novel cystatin, Iristatin, was described, based on the crystal structure of the recombinant protein; Iristatin blocked the proteolytic activity of cathepsins L and C, in addition to impairing $CD4^+$ T cell proliferation and leukocyte recruitment *in vivo* in mice, and *in vitro* [61]. Likewise, DsCystatin, a *Dermacentor silvarum* salivary inhibitor of cathepsins L and B, can diminish the expression of specific cytokines in mouse macrophages and inhibit the activation of murine macrophages and dendritic cells [62]. Ticks also produce additional proteins that target specific host neurotransmitters, increase local blood flow, and promote itching and allergic responses associated with inflammation in the host. Indeed, histamine- and/or serotonin-binding proteins, as well as antioxidant proteins, have been characterized in various tick species [63–66]. For example, a histamine-binding protein was studied in *R. appendiculatus* using crystal structure analysis [63], while another protein from *D. reticulatus* binding both histamine and serotonin was also identified [64]. An *I. scapularis* antioxidant, Salp25D, was reported as a major immunodominant antigen in engorged tick salivary glands, and has catalyzed the reduction of hydrogen peroxide in the presence of reduced glutathione and glutathione reductase [65].

As a final example, ticks produce SG proteins that have been implicated in the regulatory activities of T and B lymphocytes, thereby modulating host adaptive immune responses. Specifically, several SG proteins in *Dermacentor andersoni*, *I. scapularis*, and *I. ricinus* ticks, such as Da-p36, Salp15, or Iris, can suppress T cell activities and generate helper T cell type 2 (**Th2) immune responses** [67–69]. The Da-p36 protein, isolated from *D. andersoni* salivary glands, has suppressed cytokine production from macrophages and helper T cell type 1 (Th1) lymphocytes derived from naïve sheep (i.e. not previously exposed to ticks), in

addition to blocking the proliferation of murine $CD4^+$ T cells *in vitro* [67]. The *I. scapularis* salivary protein Salp15 has inhibited $CD4^+$ T cell activation *in vitro* and in BALB/c mice [68]. Similarly, the *I. ricinus* SG protein Iris has been implicated in the regulation of T cell and splenocyte proliferation, in addition to inducing a Th2 type immune response associated with immunosuppression activities, as evidenced from *in vitro* studies using BALB/c mice naïve spleen, as well as isolated human peripheral blood mononuclear cells (PBMC) [69]. Along with its influence on T cells, tick saliva can also affect B cell function in vitro (e.g. LPS-induced proliferation), as demonstrated for *I. ricinus* and *Hyalomma asiaticum* [70–72]. Indeed, *I. ricinus* salivary protein, Bcell inhibitory protein (BIP), impaired the in vitro proliferation of murine B cells when induced by bacterial LPS or by purified recombinant *B. burgdorferi* outer surface proteins (Osp)[71]. The *H. asiaticum* SG protein B-cell inhibitory factor (BIF) also impaired LPS-induced B cell proliferation *in vitro* [72]. Moreover, although a specific protein was not identified, BALB/c mouse infestation by *Ixodes* ticks has resulted in impaired local mature B cell differentiation into plasma cells and downregulation of specific antibody responses [73].

In summary, various studies have addressed possible mechanisms by which ticks might modulate host responses via tick saliva or SG proteins, and these include the induction of immunosuppressive outcomes in hosts that might allow the vector's successful acquisition of a blood meal (Table 1). As discussed above, the profound influences exerted by tick SG proteins on host immune responses can contribute to vector competence, ultimately supporting the transmission and establishment of tick-transmitted infections in the host.

Saliva-Assisted Pathogen Transmission:

Except for a defined set of **transovarially-transmitted pathogens**, most tick-borne diseases are passively transmitted to the host dermis via tick saliva [26,74]. Ticks, such as *I. scapularis*, produce multiple SG proteins with anti-hemostatic, anti-inflammatory, and (as shown in many experimental studies) immunosuppressive properties, which can support the transmission of tick-borne pathogens (Table 1) [15,29]. For example, as highlighted in Table 1, transmission of *B. burgdorferi*, *Anaplasma phagocytophilum*, or other pathogens, is promoted by specific tick SG proteins, such as TSLPI, [75], Isac [76], Salp25D [77], Salp15 [78], Salp12 [79], and Salp16 [80], that interfere with specific aspects of host immunity, including the inhibition of the complement system, neutrophil functions, detoxification of reactive oxygen radicals, local blood flow, and the proliferation and function of B and T cells, or which facilitate spirochete chemotaxis towards ticks [21,35,51,75–79,81]. Studies using cultured tick cells have also highlighted important roles of tick saliva or specific proteins; for example, silencing the gene encoding subolesin significantly reduced infection with *Anaplasma marginale* in cultured BME26 cells derived from *R. microplus* ticks [82]. In another instance, the treatment of cultured murine BMDC with tick saliva inhibited the maturation and function of these cells [83], raising the possibility that such immunomodulatory activities might support the survival of tick-borne pathogens. As host immune dysregulation favors *Anaplasma* infection [84], the immunomodulatory activities of *I. scapularis* or *D. variabilis* SG proteins might aid in the transmission of additional pathogens (*Anaplasma phagocytophilum* and *A. marginale*, respectively) [80,85]. Along with the initial observation of saliva-assisted transmission of the Thogoto virus [86], a

number of other tick-borne viruses also appear to greatly benefit from tick saliva-mediated transmission, including the tick-borne encephalitis virus (TBEV) [87] and Powassan virus (POWV) [88]. Such viral transmission can occur between co-feeding ticks, as shown for TBEV transmission between *I. ricinus* and *R. appendiculatus* ticks parasitizing guinea pigs [87], or for the transmission of POWV from *I. scapularis* ticks in BALB/c mice, either in the presence or absence of exogenous SG extracts (footpad inoculation) [88]. However, in most cases, the identities of the SG molecules involved in saliva-assisted pathogen transmission, or the precise mechanisms underlying their contributions to microbial transmission remain unknown, yet represent highly warranted areas of future investigation.

Acquired Tick Resistance:

While some tick species such as *I. scapularis* can feed repeatedly without apparent resistance on their natural or reservoir hosts, e.g. the white-footed mouse (*P. leucopus*), certain non-natural or incidental hosts can quickly develop strong resistance against tick bites [25]. William Trager first reported this spectacular immunological event in 1939, when guinea pigs were shown to develop robust resistance against multiple infestations by the American dog tick, *D. variabilis* [17]. This phenomenon, called acquired tick resistance (ATR), can lead to a weight reduction in fed ticks, complete blockade of blood meal ingestion, or even death of attached ticks [18]. ATR has been demonstrated in a variety of tick-mammal associations involving non-natural hosts for a given tick species, such as mice [89,90], rabbits [91,92], guinea pigs [17,23,24,93–95], goats [96], dogs [97], cattle [98–101], and potentially humans [22] (Table 2).

Proposed mechanisms of ATR:

A series of studies in which guinea pigs and mice were experimentally challenged with ticks has provided novel insights into the cellular and molecular bases of ATR development. ATR likely involves a multifactorial mechanistic process, as various factors have been shown to contribute to this process, such as cellular, inflammatory, and adaptive events, in addition to dermal structural changes at the tick bite site [25]. Of note, substantial differences exist in the immunological responses to a specific tick species between various mammalian hosts [25]; however, in all hosts tested, ATR is marked by a rapid accumulation of immune cells at or around the tick bite site, as well as erythema formation, and this process increases in intensity during repeated tick infestations [23,24,102] (Figure 4).

Cellular infiltrates:

The precise cellular infiltrates vary according to the host-vector combination and experimental parameters [23,24]. For example, in guinea pigs, neutrophils and macrophages populate the bite site, with an occasional presence of mast cells, basophils, and eosinophils, within the first several hours to days of tick attachment [23]. By two to three days of attachment, the initial accumulation of cells can be accompanied by an intense infiltration of leukocytes, including T cells, basophils, and eosinophils [23]. Intense localized granulomas and dermatitis, along with signs of substantial hemorrhage, are formed at the tick bite site in guinea pigs [23]. Those that are fully immune (usually after two successive infestations) demonstrate profound histolytic lesions in the skin, characterized by epidermal hyperplasia

and **hyperkeratosis** around the bite site, as evidenced by dry scab-like areas on the skin [23]. Many studies of tick-immune guinea pigs have identified a heavy infiltration of basophils and/or eosinophils at the tick bite site, including when the animals have been challenged with *I. scapularis* or *D. andersoni* ticks [93,94]. While mice are generally permissive to repeated infestations from many tick species, they can develop ATR against certain species, such as *H. longicornis* ticks [89]. Mice are considered a non-natural host for *H. longicornis*, which typically feeds on birds or larger mammals such as cattle or deer. Subsequently, a mouse model of ATR was reported in which C57BL/6 mice, upon exposure to larval *H. longicornis* ticks, developed robust resistance against subsequent tick bites, even after a single infestation [89]. In such ATR mice, heavy infiltration of basophils and eosinophils together with neutrophils has been noted, and may include the occasional presence of lymphocytes and macrophages [18]. In another study, released histamine by skin-infiltrating basophils, but not by skin-resident mast cells, was crucial to the resistance of C57BL/6 mice against *H. longicornis* infestation [103]. Overall, these studies suggest that despite considerable heterogeneity in immune responses during specific tick-host associations, cellular infiltrates relevant to allergic inflammation, namely basophils and eosinophils, are important for ATR development in various rodent and tick species.

Cellular, inflammatory, and adaptive events:

The exact inflammatory pathways or molecular mechanisms of ATR remain to be elucidated. ATR is likely triggered by tick saliva or its components, as suggested by recent studies using guinea pigs immunized with fractionated tick saliva, which identified a set of proteins associated with the development of acquired resistance to *I. scapularis* nymphs [102,104]. It is likely that host responses associated with ATR are initiated by keratinocytes, endothelial cells, and resident leukocytes, which make immediate contact with tick saliva or the tick hypostome; once activated, these cell types release pro-inflammatory cytokines, attracting additional immune cells [28,105,106]. Infiltrating cells such as neutrophils can degranulate and release enzymes, such as serine proteases [107] and myeloperoxidase [108] -- thought to influence the expansion of the tick bite lesion [23]. Studies in mammals, including an examination of murine cutaneous responses to *D. andersoni* ticks, have suggested that immune cells such as macrophages or neutrophils, can secrete nitric oxide and reactive oxygen species (ROS) [109,110], although it remains unknown if or how these molecules might impact the genesis of ATR. A number of studies have pursued the experimental manipulation of ATR animals, such as the genetic depletion of mast cells in W/Wv mice [111,112], T cell deficiency in C57BL/6J mice [90], or the targeted depletion of basophils in C57BL/6 mice [89], in addition to the transfer of immune serum in guinea pigs [113,114]. These experiments identified several key drivers that were essential to ATR development in W/Wv or C57BL/6J mice against *H. longicornis* infestation, such as mast cell infiltration and the production of IgE antibodies [112], basophil infiltration and IgFc receptor expression (using basophil depletion transgenic mouse models) [89], and skin memory $CD4^+$ T cell-derived interleukin-3 (IL-3) production and basophil recruitment to infected sites [90]. The importance of adaptive immunity and humoral factors was also demonstrated for guinea pig resistance against *Amblyomma americanum* [113] or *D. andersoni* ticks [114]. The passive transfer of **peritoneal exudate cells** [115] or serum [115,116] from donor guinea pigs (immunized by prior infestations with either larval *A.*

americanum, *D. andersoni*, or *R. sanguineus* ticks) reflected robust ATR in recipient guinea pigs when challenged with homologous tick larvae. In addition, studies using complement C4-deficient guinea pigs that were repeatedly infested with *D. andersoni* suggested that the alternative pathway of complement activation played an important role in tick rejection [95]. Furthermore, guinea pigs [93] and cattle [98], repeatedly exposed to *D. andersoni* or *A. americanum* ticks, respectively, exhibited cutaneous basophilic hypersensitivity (mediated by basophils) -- a well-known mechanism of ATR [25,93,98]. Similarly, studies using C57BL/6 mice, either treated with histamine H1 receptor antagonist or genetically deficient in histamine production due to the lack of histidine decarboxylase, suggested that histamine played a key role in the development of ATR against *H. longicornis* [103]. Recent work reported that, contrary to reservoir hosts such as mice (*Mus musculus* or *P. leucopus*), ATR hosts such as guinea pigs, induce specific pathways that control local blood flow at the bite sites of nymphal *I. scapularis* ticks [24] and reflect more severe histolysis at these bite sites, as well as unique dermal architectural changes and apparent signs of pain and itching [23]; this ultimately favored the prompt detachment of ticks [23,24]. Unlike wildtype mice, humanized mice engineered to express human HLA DR3 (HLA class II) displayed partial ATR to repeated *I. scapularis* infestations, including reduced infection with *B. burgdorferi* [117]; however, how such resistance may have developed in these mice remains unknown. Despite these initial results, future studies are warranted to determine whether humanized mice such as these might serve as reliable ATR models. Such approaches may help decipher the complex ATR mechanisms against *I. scapularis* infestation, as seen in incidental hosts (e.g. guinea pigs).

Dermal structural changes:

Organizational and structural changes in the host's skin can also impact the development of ATR [23]. Because the tick mouthpart (particularly the hypostome, which varies in length from 50 to 500 μm) [118] penetrates the host epidermis to access the dermal vasculature, inflammation of the host dermis is likely impacted by the overall organization of the mammal's skin, including the architecture of the feeding lesion, which ultimately influences the outcome of feeding in ATR hosts. In many immune animals, such as guinea pigs that are re-exposed to *I. scapularis* ticks, a significant series of inflammatory changes in the skin can result in a large cavitary lesion that weakens tick attachment and induces irritation, scratching, and itching behavior, resulting in tick detachment and removal, as studied by tick feeding parameters and histopathological evaluation of the dermal tick bite sites. Of note, the thickness of the host's skin varies greatly by species (e.g., up to 662, 2040, 2174, and 2906 μm in mice, rats, rabbits, and humans, respectively) [119], implying that skin anatomy might be an important influence on the genesis of ATR. Additional organizational differences include a subcutaneous muscle layer called the **panniculus carnosus** [120], which contributes to wound healing via muscular contraction, as shown in guinea pigs using panniculectomy [121]; it is present in rodents but absent in humans [25].

Furthermore, some animals display **hereditary resistance** to ticks, as seen in *Bos taurus indicus* cattle when infested with *R. microplus* or other ticks, as evidenced from tick counts on naturally exposed animals, serum complement amounts, and delayed skin hypersensitivity [122]; however, the precise genetic or immunological basis for such

resistance remains unknown [99–101,123,124]. Moreover, the differential infiltration of immune cells, such as eosinophils, mast cells, macrophages, and plasma cells, has been reported in the skin of sensitive versus resistant cattle [100], including inflammatory episodes such as cutaneous basophil hypersensitivity [98], skin degradation, and cytokine signaling [99]; in addition, major events of skin remodeling, particularly involving components of the dermal extracellular matrix have also been noted [100]. However, research has yet to identify the specific tick proteins that can trigger the inflammatory reactions associated with ATR in incidental hosts or genetically-resistant cows; nevertheless, it is reasonable to speculate that these antigens might include saliva components, as highlighted by recent studies showing that immunization of guinea pigs with isolated *I. scapularis* saliva [102], or even one of its fractions containing 24 identified proteins, induced partial ATR against subsequent challenges with nymphal ticks [102,104].

ATR as a putative anti-tick strategy:

Humans are likely to develop ATR, due to their status as non-natural tick hosts. Many people experience mild to severe erythema after a single tick bite; some, such as forest or outdoor workers, even develop tick antigen-specific antibodies [125,126]. In fact, an erythema called **Jones-Mote hypersensitivity**, which occurs in humans, is comparable to the cutaneous basophilic hypersensitivity observed in ATR animals, as both hypersensitivity reactions are characterized by visible erythemas due to the rapid recruitment of immune cells, including allergic inflammatory cells such as basophils and eosinophils [127]. Experimental results also suggest that ATR -- as evidenced from severe skin inflammation -- prevented tick-borne infections in immune guinea pigs or mice by blocking the transmission of pathogens such as *B. burgdorferi* [19,20] -- transmitted from a feeding tick to the host 24 hours after attachment (or later) [128]. Moreover, ATR can prevent the transmission of other tick-borne pathogens such as *Francisella tularensis* from infected *D. variabilis* ticks to tick-sensitized rabbits [92]. Similarly, cattle breeds that are genetically resistant to tick bites, e.g. *Bovis indicus* cows, also reflect resistance to *R. microplus* tick-transmitted infections with *Babesia bovis* and *Babesia bigemina* pathogens [129]. In fact, there is evidence supporting the hypothesis that itching and previous tick exposures might protect individuals living in areas endemic for Lyme disease, from *B. burgdorferi* infection [22]. In such areas, the frequency of itching increases with the number of reported tick bites, and the incidence of *B. burgdorferi* infection and Lyme disease, decreases when tick-associated itching is reported more than three times in an individual; these findings suggest that repeated exposure to vector ticks might prevent the establishment of human Lyme disease in disease-endemic areas [22]. Therefore, future studies are needed to address the molecular basis of ATR, perhaps via the identification of vector and host antigens that can trigger tick rejection. As explored in recent studies [104], such antigens, derived from *I. scapularis* saliva, might be leveraged as new putative targeting strategies, including a potential for anti-tick vaccines, and ideally might inform preventive strategies against vector-transmitted infections such as Lyme disease and other pathologies. However, it remains unknown is ATR can influence additional human infections, such as Powassan virus or *Babesia sp.* Infections; these can transmit rapidly (in less than 24 hours) from infected *Ixodes* ticks [130], although specific cattle breeds that are genetically resistant to tick bites are also protected from babesiosis [129].

Contrasting and Overlapping Immune Responses: The Possible Outcomes of Tick-Host Associations:

Here, we discuss the major hypothesis that the immune responses of natural reservoir hosts versus non-natural incidental hosts might dictate differing outcomes of tick feeding events. We also present a comparison of these types of host responses.

Immune tolerance:

There is a lack of direct experimental evidence addressing the potential for repeated tick infestations in inducing transient **immune tolerance** in natural or reservoir hosts [131,132]. Studies suggest that T cells collected from BALB/c mice previously infested with *I. ricinus*, exhibit a suppressed response to *in vitro* concanavalin A stimulation, compared to cells from non-infested mice [133]. This indirect evidence suggests the possibility that re-exposure to antigenic tick saliva might prime the host immune system to trigger a de facto immune memory response termed **trained immunity** [134,135], an adaptation to the host's innate defense mechanisms. A contrasting outcome to trained immunity is innate immune tolerance, in which a host that is re-exposed to tick saliva is unable to activate certain specific immune responses, such as those resulting in **LPS tolerance** [136]; this can prevent the overactivation of host inflammatory responses. However, whether immune tolerance is operative at the tick bite sites on natural or reservoir hosts, but is absent in non-natural or incidental hosts, remains an enigmatic question that merits further attention.

Immune evasion:

A more widely accepted hypothesis is the **immune evasion theory** [137], which states that ticks can evade the anti-parasitic immune offenses of the host, as highlighted in recent studies showing that *I. scapularis* ticks could engorge repeatedly on their natural host, *P. leucopus*, despite an increasingly intense dermal inflammation in the mammal [23]. As discussed earlier, SG proteins, bearing hundreds of secreted bioactive compounds, can modulate or even disable host immune responses [28,29]. Thus, the co-evolution of pharmacological mediators in tick saliva along with the pharmacological mediators of inflammation and edema in reservoir hosts has allowed the tick **sialome** to efficiently engage and disable murine adaptive immune responses [137], such that repeated and successful parasitism can occur if the tick can counteract the immune mediators of edema in natural reservoir hosts. However, this "lock and key" hypothesis, which involves efficient interactions between tick salivary antagonists and the repertoire of immunopharmacological agonists in natural hosts, might not occur in non-natural or incidental hosts, such as guinea pigs, as vertebrates can differ in their inflammatory responses [137]. Therefore, the inability of ticks to engage and evade the immunopharmacological responses of incidental hosts might facilitate the genesis of immune memory responses, along with more rapid erythema formation, followed by the infiltration of host immune cells [24] and intense histolytic inflammation, compared to the diffuse and sessile edema displayed in natural hosts [23]. Ultimately, these events might lead to rapid dermal changes, such as scarring and the disintegration of dermal tissues, in addition to the induction of itchiness and apparent pain, which altogether favor tick detachment and rejection, as observed for the *I. scapularis* bite

site on immune guinea pigs [23]. However, as discussed in recent studies, the tick sialome is dynamic and varies both by the duration of feeding [21] and by the host species [138,139]. Therefore, the host-specific differential expression of tick saliva immunomodulators might also contribute to the tick's disparate evasion of host defense responses [25]. Indeed, a better understanding of the dynamic nature of the sialome [28,29,45], particularly its differential expression of immunomodulators when ticks repeatedly engorge on natural hosts versus certain non-natural ATR hosts, may have important implications for our understanding of tick hematophagy. It is evident that future empirical studies are required to more fully understand the molecular basis of the tick's hypothesized immune evasion strategy against host responses, which might involve tick salivary components, as well as the permissiveness of the host.

Immune incompetence or specificity:

Host immune incompetence might also influence resistance to tick bites, such as when the host is unable to mount an effective anti-parasitic inflammatory response. However, as highlighted in earlier studies using repeated *I. scapularis* infestations on natural hosts such as *P. leucopus* versus incidental hosts such as guinea pigs [23,24,30], both natural and ATR hosts can exhibit an increasingly strong dermal inflammatory response to repeated tick infestations, suggesting that inflammatory responses are not the only determinants of tick resistance. Alternatively, host immune incompetence might still play a possible role: the specific "type" of inflammatory or host response driving tick rejection might be absent in natural or reservoir hosts but be present in non-natural or incidental hosts. For example, histamine-rich basophils are abundant at tick bite sites on guinea pigs [140], yet the cell type is rarely detected in *P. leucopus* [23]. Research has identified that the immune pathways, particularly the cellular or molecular composition of such responses, differ in a host-specific manner, as illustrated in studies examining the repeated infestation of *I. scapularis* ticks on natural versus incidental hosts: specifically, allergic inflammatory cells such as eosinophils, might be the most predominant infiltrates in the tick bite site of immune guinea pigs [24], compared to mononuclear cells or mixed leukocytic infiltrates in laboratory or white-footed mice [23]. Finally, as there are variations in the anatomical, sensory, and neurological aspects of dermal architecture in different mammals [119,141,142], it stands to reason that tick-host associations might also be determined by host-specific factors or behaviors, their suppression by tick saliva, or the possible incompetency in natural hosts. Therefore, host immune incompetence or specificity for the anti-edema components of tick saliva might potentially contribute to the successful outcome of tick parasitism.

Concluding Remarks:

Gaps, Challenges, and Future Directions:

Ticks, which originated before the first dinosaurs, evolved a remarkable hematophagy through millions of years of parasitism. Given the monophyletic nature of tick evolution and the unique hematophagy of hard ticks, their vector-host associations are likely to be fundamentally different from other blood-feeding arthropods [143,144]. Recent studies involving repeated engorgements of *Ixodes* tick on mice and guinea pigs have unearthed new paradigms for the concepts of tick immune evasion via saliva proteins and tick

immunity in ATR hosts [24,25]. A rigorous elucidation of these putative ATR mechanisms might be potentially applied to the development of novel anti-tick vaccines, although there are many barriers to success, including the limited availability of reagents and tools for non-conventional models. The host's response to a tick bite is dictated by a complex series of factors, including the host species, duration of feeding, and pathogen-induced changes in the tick saliva proteome [23–25,29,138]. As various tick stages (subadult and adult) can effectively parasitize and transmit pathogens, a comparison of their sialomes and immunomodulation warrants further investigation, which is important for the rational design of candidate anti-tick vaccine strategies. Moreover, the identities of tick saliva components or host effector molecules that might trigger tick rejection remain highly warranted research propositions (see Outstanding Questions). Our existing knowledge of arthropod and mammalian immunity, coupled with recent biotechnological developments, could propel future scientific discoveries, and foster new paradigms in the biology of tick-host associations. These efforts can enrich our understanding of mammalian immunology and contribute to novel potential interventions, such as anti-tick measures, to ideally combat the transmission of tick-borne diseases.

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Glossary

Acquired Tick Resistance (ATR)
immunological mechanism allowing certain hosts to develop immunity against repeated infestations by ticks. It develops after multiple successive tick infestations in a non-natural host, leading to tick detachment or death

Apyrase
ATP-diphosphohydrolase catalyzing the sequential hydrolysis of ATP to ADP and ADP to AMP, releasing inorganic phosphate. In ticks, apyrase can impair platelet aggregation by breaking down ADP released by activated platelets and damaged cells

αIIbβ3 integrin inhibitor
interacts with αIIbβ3 integrin, a major transmembrane protein on the surface of platelets. The αIIbβ3 integrin inhibitor can impair platelet function, subsequently impacting the processes of hemostasis and thrombosis

Broad sessile lesions
area of tissue with different characteristics from the surrounding tissue; in skin, it is characterized by a broad and flat cellular mass with little dermal disruption

Complement system
system of more than 30 proteins in the plasma and on cell surfaces, constituting an appreciable portion (up to 15%) of the globular fraction of plasma. Evolutionarily, the

system represents an ancient component of host defense responses. It can be activated through three major pathways: classical, lectin, and alternative. Complement activation results in a proteolytic cascade that can end with opsonization and lysis of the pathogen, in addition to the genesis of inflammatory responses

Cutaneous basophilic hypersensitivity
cellular immune response characterized by the infiltration of large numbers of basophilic granulocytes

Epidermal hyperplasia
increased number of cells in the epidermis

Evasins
family of chemokine binding proteins present in tick saliva

Jones-Mote hypersensitivity
distinct form of an immunologic dermal response typically reflected by a flat, well-circumscribed erythema, bearing similarities to delayed hypersensitivity and classic antibody-mediated reactions such as anaphylaxis

Hard ticks
About 700 species of ticks belonging to the family *Ixodidae*, some of which can transmit distinct viral, bacterial, and protozoan diseases; characterized by a hard shell just behind their mouthparts; they feed on two or three hosts during their life cycle, which lasts a few years

Hemostasis
physiological process that directs the prevention of blood loss and the restoration of damaged blood vessels through the well-regulated processes of vasoconstriction, platelet aggregation, and clot formation

Hematophagy
Feeding behavior characterized by blood consumption; only form of feeding for ticks and many small animals

Hereditary resistance
here, inherent ability of a previously unexposed organism to resist tick feeding

Hyperkeratosis
condition where the stratum corneum (the outermost layer of the skin), containing keratin, becomes thickened

Immune evasion theory
here, strategy used by parasitic organisms to evade or suppress the host immune response

Immune tolerance
state of unresponsiveness of the immune system against biological stimuli or substances that normally elicit an immune response in a given organism

Incidental host
A non-natural or accidental host for a parasite, often exhibiting immunity or other forms of resistance towards the parasite, especially in repeated infestations. For example, domestic guinea pigs (*Cavia porcellus*) serve as incidental hosts for *Ixodes* ticks

Kininase
carboxypeptidase-type enzyme involved in the breakdown of polypeptide hormones termed kinins, (e.g. bradykinin); promotes blood vasodilation and the lowering of blood pressure

LPS tolerance
a cell exhibits a reduced capacity to respond to bacterial lipopolysaccharide (LPS) after prior exposure to this stimulus. This is a transient response and is considered a type of innate immune memory, which can prevent the over-activation of the inflammatory response

Lyme disease
multi-organ infection that can manifest as a distinct skin lesion, carditis, arthritis, and a variety of neurological symptoms; caused by the bacterium *Borrelia burgdorferi* and, rarely, by *Borrelia mayonii*; transmitted to humans through the bite of infected *Ixodes* ticks prevalent in the United States and Eurasia

Natural host
organism in a specific environment, upon which a parasite primarily depends for its survival and reproduction

Panniculus carnosus
thin sheet of striated muscle, intimately attached to the skin and fascia of many lower mammals, including rodents; provides skin twitching and contraction functions

Reservoir host
wild host in a specific environment where a parasite primarily depends for its survival. Like natural hosts, these animals serve as natural hosts during the life cycle of a parasite, without exhibiting apparent resistance

Peritoneal exudate cells
A vascular fluid (which can sometimes be collected from the peritoneal cavity) that accumulates in lesions or areas of inflammation and contains leukocytes, such as neutrophils, macrophages, and lymphocytes

Serocellular crusting
accumulation of serum and cells, forming a crust on the skin surface

Sialome
Transcriptomic and proteomic composition of the salivary glands

Soft ticks
Nearly 200 species of ticks belonging to the *Argasidae* family, some of which can transmit viral and bacterial diseases. Instead of a hard shell, they are characterized by a leathery integument with an oval-shaped body, where the head and mouthparts are hidden

underneath. They feed multiple times, with each event lasting minutes to hours, on many mammalian and avian hosts, and usually live within burrows

Saliva-assisted transmission
immunomodulatory properties of arthropod saliva that modulate host defense mechanisms, thereby facilitating the transmission of pathogens

Th2 immune response
mediated by the helper $CD4^+$ T cell subset; express Th2-type cytokines e.g. interleukin 4 (IL-4), IL-5, IL-6, IL-9, IL-13, and IL-17E (IL-25). These responses can upregulate antibody production and target parasitic organisms; also responsible for eosinophil activation and the inhibition of several macrophage functions, providing phagocyte-independent protective responses

Tick Adhesion Inhibitor (TAI)
15-kDa protein identified in the soft tick *Ornithodoros moubata*; shown to impair platelet aggregation by blocking the adhesion of platelets to collagen through its interaction with specific integrins

Tick hypostome
chitinous sword- or spear-like structure of the tick mouth; armed on each side with numerous barbs designed to anchor the tick in the host dermis

Trained immunity
altered, adaptive innate immune response to a secondary challenge; an epigenetic reprogramming adaption to (here) repeated tick infestations

Transovarially-transmitted pathogens
Infectious agents transmitted from a female to the next generation (i.e., mother to offspring), through the infection of the reproductive organs and developing egg

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Outstanding Questions

What specific “types” of inflammatory or host pathways/responses drive tick rejection in incidental/resistant hosts, yet are absent in natural/non-resistant hosts? Are these multifactorial? Do they differ in tick-host specific contexts? Addressing these questions might help elucidate novel evolutionary aspects of tick hematophagy and host selectivity, particularly addressing whether and how tick anti-immune activities selectively target natural hosts, or if they are also operative across resistant hosts.

Both subadult and adult ticks can effectively parasitize mammals and transmit pathogens. What are the similarities and differences in their sialomes and immunomodulatory activities? Future studies addressing these questions might potentially identify key tick immunomodulators or mechanisms required for effective parasitism.

The generation of acquired tick resistance (ATR) against one tick species can confer resistance against additional distinct tick species. Are there conserved elements or pathways dictating such cross-protections? If so, can these elements and cross-resistance be experimentally transferred to a naïve, natural, or incidental host? Such inquiries are relevant to achieve a greater understanding of the molecular mechanisms of ATR.

What are the identities of the tick saliva components triggering tick rejection in ATR hosts? What host molecules, as effectors, drive such tick rejection? Do these molecules exist (and exert their effects) at the tick bite site of the host, or as ingested factors inside the body of the attached tick? The exploration of these questions might not only enrich our knowledge of unique tick hematophagy processes and ATR mechanisms, but might also contribute to the development of potential anti-tick measures.

Tick-immune hosts (ATR) can avoid infection against tick-borne pathogens, such as Lyme disease agents, reflecting slow transmission (more than 24 hours) from the vector to the host. Can ATR provide protection against other tick-borne diseases that are transmitted more quickly, often within 24 hours (or earlier) of tick attachment? This inquiry might support the future development of novel preventive strategies against some widespread tick-borne diseases.

Can the concept of ATR be leveraged for the development of novel anti-tick preventive strategies in humans? What aspects of ATR are needed for a translational human vaccine? Anti-tick vaccines might potentially be developed to alert immunized individuals of the presence of ticks by promoting heightened tactile sensations or itchiness at the beginning of tick attachment. Could quick removal of the vector be sufficient to protect individuals from tick-borne infections? These concerns are relatively difficult to address, yet represent highly warranted future directions; they might lead to a better understanding of the neurological and sensory aspects of ATR, and potentially inform new candidate anti-tick measures in humans.

Highlights

Ticks can repeatedly parasitize their permissive reservoir hosts. Recent studies suggest that the tick bite sites reflect a broad sessile lesion without signs of pain or itchiness, despite intense inflammation. These observations reinforce the “immune evasion theory”, where the tick sialome can efficiently engage and evade immune responses in permissive hosts.

Many non-natural or incidental hosts, potentially including humans, can develop acquired tick resistance against repeated tick bites. New research has uncovered key factors that drive these tick rejections in resistant hosts, suggesting involvement and variations in the architectural, sensory, and neurological aspects of tick bite lesions and the types of host responses.

Although research has yet to identify the precise tick proteins that trigger the host responses associated with tick rejection in incidental hosts, new studies suggest that repeated host exposure to tick saliva, specifically its glycoproteins or particular saliva fractions can independently drive partial immunity against tick bites.

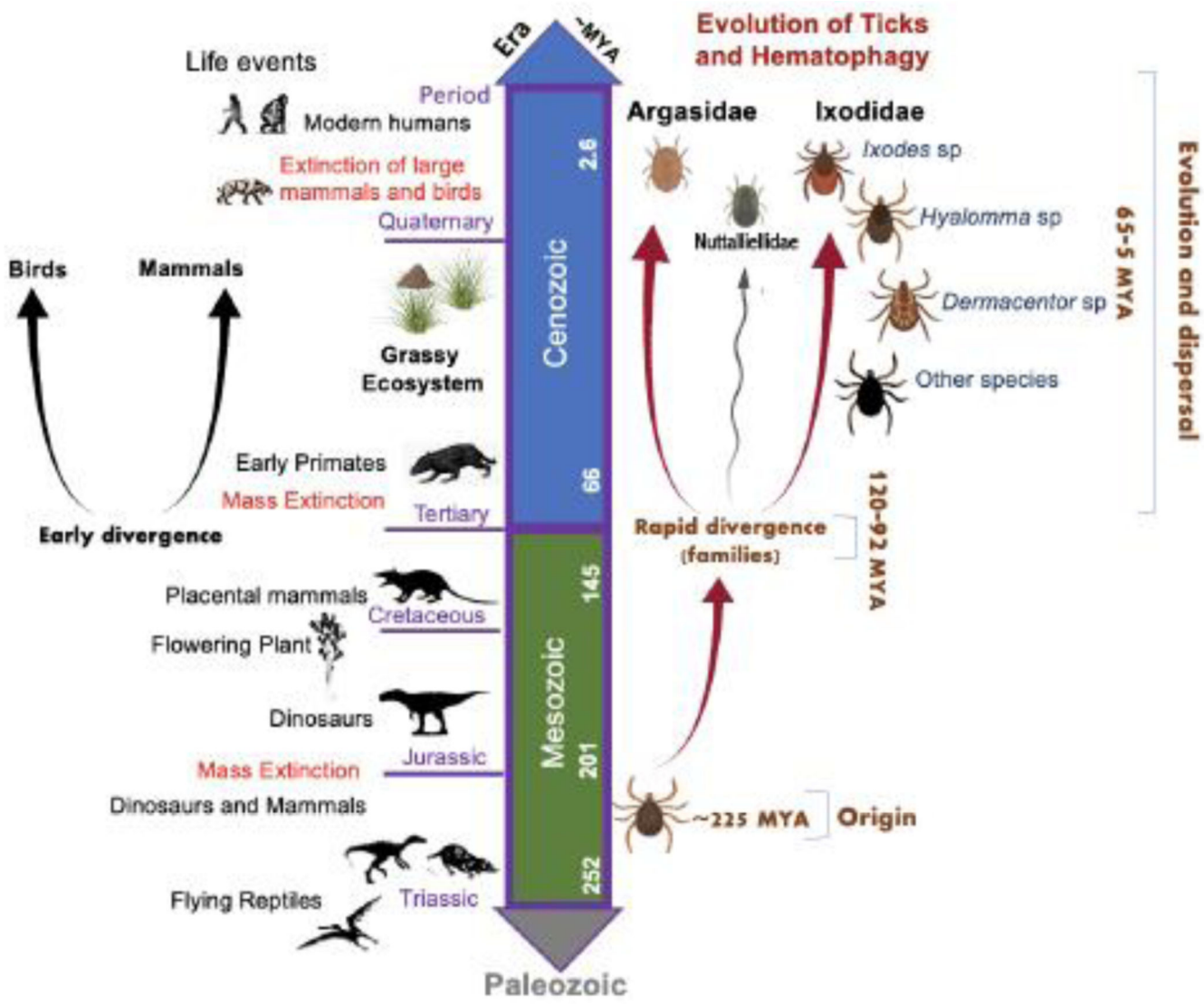

Figure 1: Schematic representation of the geological time-scale, highlighting major life events, the origin of ticks, and evolution of hematophagy.

Ticks originated and diversified over a wide geological time period in the early Mesozoic era, with a major dispersal in the Tertiary period [1,3,4]. The rapid divergence of major tick families coincided with the divergence of modern birds and placental mammals in the late Cretaceous period (120 – 92 MYA*)[6], suggesting that the latter event might be a driving force in the evolution of distinct hematophagy processes in ticks. *MYA: million years ago.

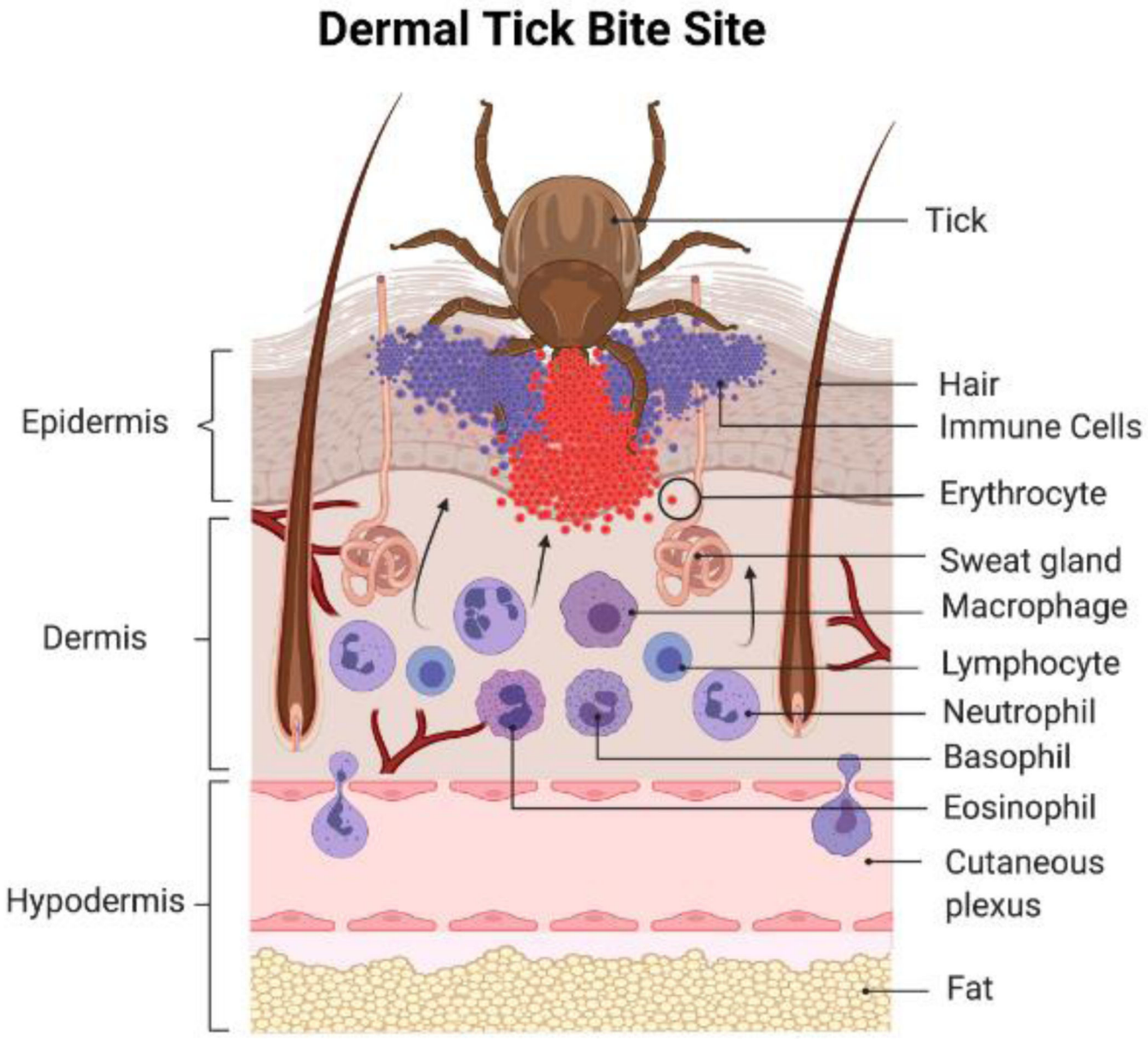

Figure 2: Schematic structure of mammalian skin, highlighting major cellular infiltrates at the bite site of a natural host.

Tick (e.g. *Ixodes scapularis)* engorgement in reservoir [23] or non-resistant [24] hosts results in the infiltration of host immune cells on or around the tick bite site. The variable cellular infiltrates are mostly a mixed population of inflammatory cells, such as neutrophils, lymphocytes, eosinophils, and basophils, with the occasional presence of tissue macrophages (histocytes). Depicted are mild to moderate ulcerations at the tick bite site, along with central invagination and vascular injury, including vascular dilation and extravasation of erythrocytes. This figure was created using BioRender (https://biorender.com/).

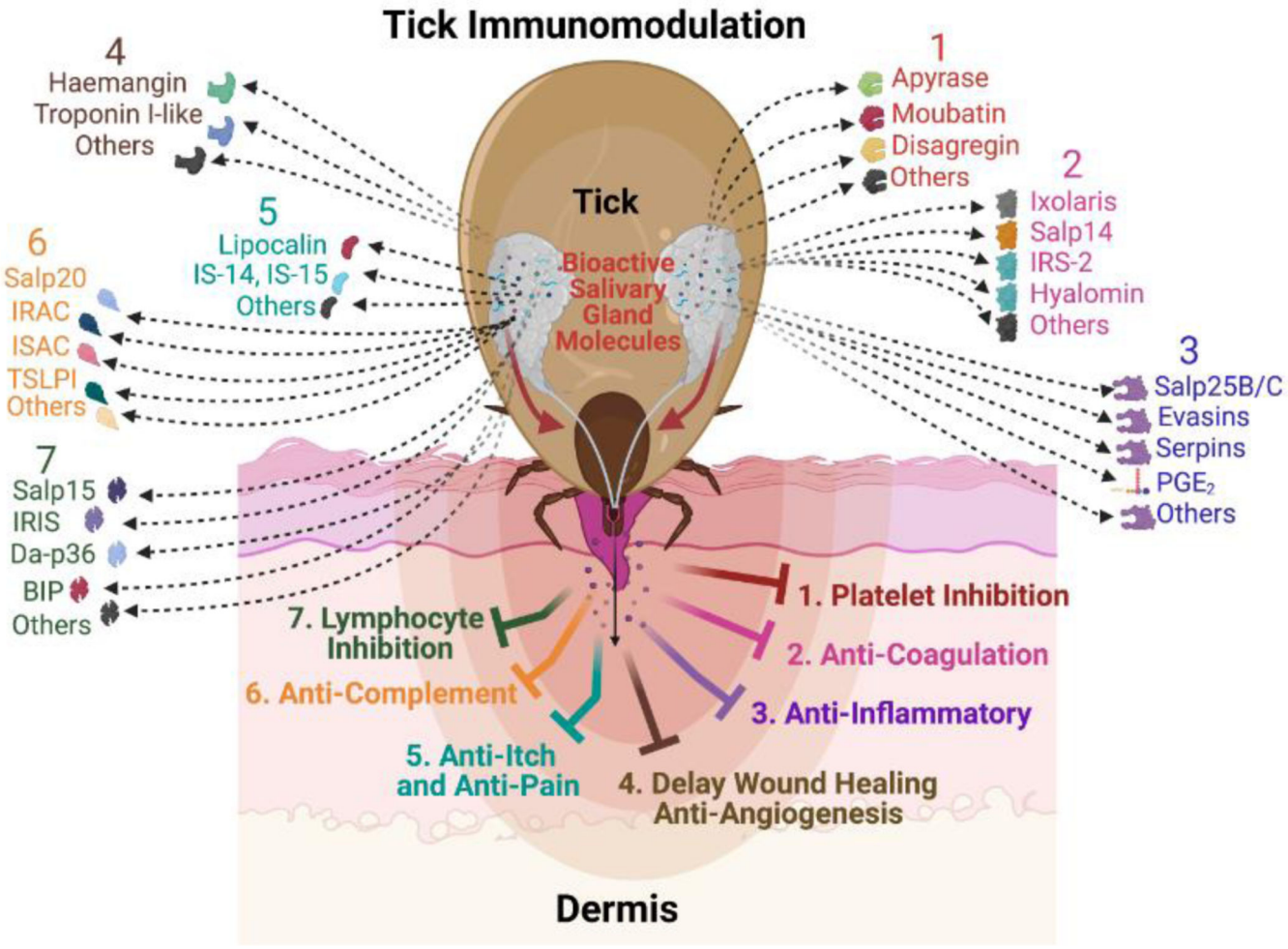

Figure 3: Tick immunomodulation of major mammalian host responses by tick saliva components.

The tick salivary gland contains a large panel of bioactive molecules that are secreted into the host dermis, targeting host cells and molecules, thereby modulating various host responses that ultimately favor the successful acquisition of a blood meal. Representative examples of identified tick saliva molecules and their effects on selected host responses are shown [26,28,29,170]. For details, please refer to the text and Table 1. This figure was created using BioRender (https://biorender.com/).

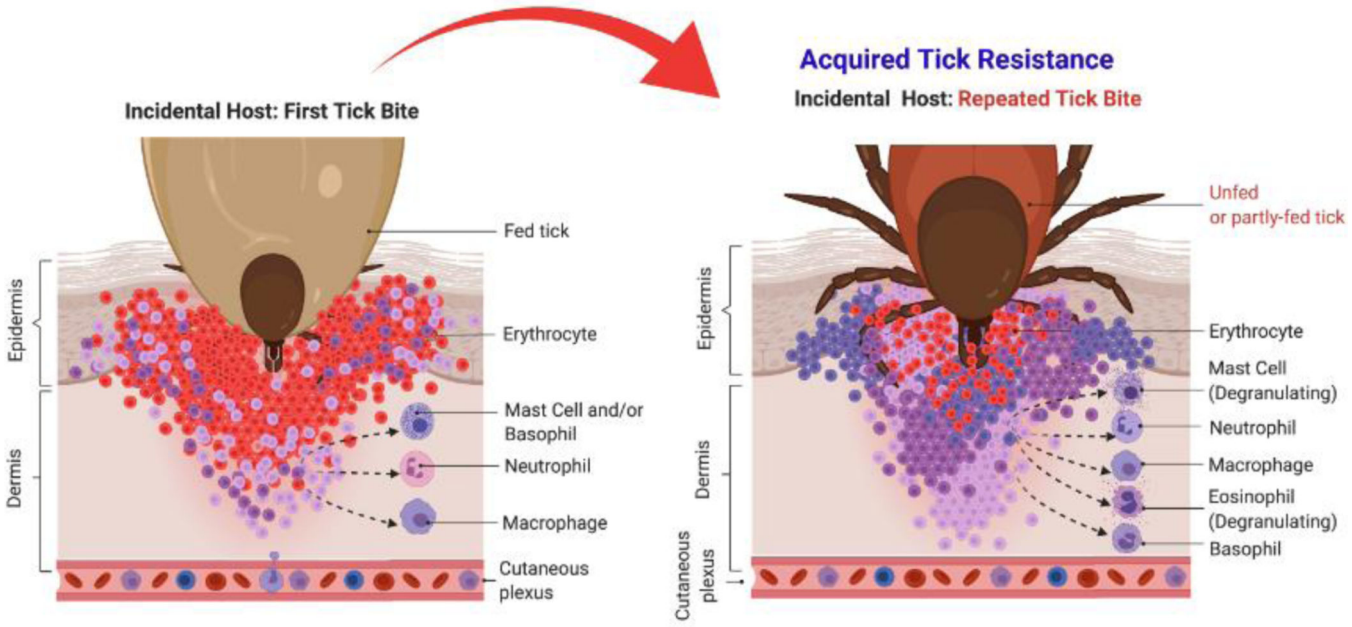

Figure 4: Acquired tick resistance in a mammalian incidental host.

The image shows the major histological changes at the tick bite sites of an incidental host, such as in guinea pigs, during the genesis of acquired tick resistance via repeated tick bites. The left panel shows the histological parameters at the first tick bite, characterized by the relatively decreased infiltration of immune cells relative to immune, tick-exposed incidental hosts (right panel), which is (depending on the species) mostly comprised of leukocytes and localized granulomas, as well as dermatitis with substantial hemorrhage at the tick bite site [23,24]. As shown in the right panel, during repeated tick exposure, the same host reflects acquired resistance to tick infestation, resulting in the detachment of the vector as an unfed or partially-fed tick. The tick bite site can show histolytic lesions with epidermal hyperplasia and hyperkeratosis, in addition to more intense leukocytic infiltrations with the predominant presence of eosinophils, basophils, and mast cells [23,24]. This figure was created using BioRender (https://biorender.com/).

Table 1:

Tick salivary gland proteins modulating mammalian host responses

Tick species	Tick molecules	Function/Mechanism	Ref
	Anti-platelet aggregation and anticoagulant activity		
Ornithodoros savignyi	Apyrase	Inhibition of platelet aggregation; stimulated by ATP and ADP	[145]
	Tick anticoagulant peptide (TAP)	Inhibition of blood coagulation factor Xa	[146]
Ornithodoros moubata	Moubatin	Inhibition of platelet aggregation; stimulated by collagen	[147]
	Tick Adhesion Inhibitor (TAI)	Inhibition of platelets and adhesion to collagen	[38]
	Disagregin (as αIIbβ3 integrin inhibitor)	Inhibition of collagen and ADP; induction of platelet aggregation	[39]
	Disagregin	Inhibition of platelet aggregation; stimulated by ADP, collagen, thrombin or other agonists by binding to the platelet fibrinogen receptor	[148]
	Enolase	Plasminogen receptor; stimulation of fibrinolysis	[149]
Argas monolakensis	Monobin	Anti-thrombin and anti-platelet activity	[150]
Ixodes scapularis	Ixolaris	Anti-coagulation activity by interaction with complex TF/FVIIa	[42]
	Penthalaris	Anti-coagulation activity by binding to the complex TF/FVIIa	[43]
	Salp14	Inhibition of coagulation factor Xa	[41]
	Metalloprotease	Gelatinase and fibrinolytic activity	[40]
	HSP-70 like protein	Fibrinolytic activity	[151]
	Ixonnexin	Fibrinolytic and antithrombotic activity	[152]
Ixodes ricinus	Iris	Fibrinolytic and anti-coagulation activity	[153]
	IRS-2	Inhibition of cathepsin G- and thrombin-induced platelet aggregation	[36]
	Ir-CPI	Coagulation contact phase inhibitor	[154]
Amblyomma americanum	Serine protease inhibitor (Serpin19)	Inhibition of blood clotting factors Xa and Xia, trypsin, and plasmin	[155]
	AamAV422	Anti-platelet aggregation; anti-blood clotting; anticomplement activity	[156]
	A. americanum serine protease inhibitor 6-AamS6	Inhibition of serine- and papain-like cysteine proteases; anti-platelet aggregation; anti-blood clotting	[157]
Rhipicephalus haemaphysaloides	Rhipilin-1	Anticoagulant activity	[158]
	Rhipilin-2	Inhibition of serine protease trypsin and elastase; anticoagulant activity	[159]
Rhipicephalus microplus	Serine protease inhibitor (Serpin) & RmS-15	Thrombin inhibitor; anti-blood clotting activity	[160]
	Microphilin	Inhibition of fibrinocoagulation and thrombin-induced platelet aggregation	[161]
Hyalomma marginatum Hyalomma rufipes	Hyalomin-1	Thrombin inhibitor; anti-platelet aggregation; anticoagulant activity	[162]
Amblyomma variegatum	Avathrin	Thrombin inhibitor	[163]
	Anti-inflammatory activity		

Tick species	Tick molecules	Function/Mechanism	Ref
Dermacentor reticulatus	Serotonin- and histamine-binding lipocalin	Itch and pain modulator; anti-inflammatory activity	[64]
I. scapularis	Salivary proteins Salp25B & Salp25C	Histamine-binding proteins	[65]
	IS-14; IS-15	Histamine- and serotonin-binding proteins	[66]
Rhipicephalus appendiculatus	Histamine-binding proteins (HBPs) & lipocalins	Histamine-binding molecules; itch and pain modulators; anti-inflammatory activity	[63]
Rhipicephalus sanguineus	Chemokine binding proteins (CHPBs) & evasin-1 and −3	Anti-chemokine activity; leukocyte recruitment inhibition; anti-inflammatory activity	[54]
A. variegatum *R. appendiculatus* *D. reticulatus*	Evasin-3	Anti-chemokine activity	[55]
Amblyomma cajennense	Evasin ACA-01	Anti-chemokine activity	[164]
I. ricinus	Lipocalin from *I. ricinus* (LIR6)	Binds to neutrophils and chemoattractant leukotriene B_4	[165]
Dermacentor variabilis	Histamine release factor homolog (DVHRF)	Vasodilator	[166]
I. scapularis	Tick histamine release factor (tHRF)	Facilitates *B. burgdorferi* transmission via vascular permeability modulation and increased blood flow	[35]
Amblyomma americanum	Serine protease inhibitor (Serpin 27 / AAS27)	Anti-inflammatory activity; plasmin and trypsin inhibitor	[56]
	Serine protease inhibitor (Serpin 41 / AAS41)	Anti-inflammatory activity; chymase and α-chymotrypsin inhibitor	[57]
	Macrophage Migration Inhibitory Factor (MIF)	Inhibition of macrophage migration	[167]
I. scapularis	Prostaglandin E_2 (PGE_2)	Blocks DC function and T cell proliferation	[59]
	Cysteine protease inhibitor Sialostatin L (SialoL)	Inhibition of DC function and T cell proliferation	[60]
I. ricinus	Cysteine protease inhibitor Iristatin	Suppression of cytokine production and T cell proliferation; inhibition of leukocyte recruitment	[61]
Dermacentor silvarum	DsCystatin	Suppression of cytokine production; inhibition of DCs and macrophage function	[62]
Haemaphysalis longicornis	Troponin I-like molecule	Angiogenesis inhibitor	[47]
	Serine proteinase inhibitor Haemangin	Inhibition of angiogenesis, cell proliferation, and wound healing	[48]
I. scapularis	*I. scapularis* salivary anticomplement (Isac)	Complement pathway regulator	[50]
	Salivary protein 20 (Salp20)	Facilitates *B. burgdorferi* transmission by regulating the complement pathway	[51]
I. ricinus	*Ixodes ricinus* anticomplement (IRAC) proteins I and II	Inhibition of the complement alternative pathway	[52]
	Serine protease inhibitor Iripin-3	Anticoagulant activity; suppression of cytokine production, T cell proliferation, and Th1 responses	[168]
	T and B cell immunomodulatory molecules		
Dermacentor andersoni	Da-p36	Inhibition of T cell proliferation	[67]
I. scapularis	Salivary protein Salp15	Inhibition of $CD4^+$ T cell activation	[68]
I. ricinus	*Ixodes ricinus* immunosuppressor (Iris)	Regulator of T cell proliferation; inducer of Th2 type immune responses	[69]
	B cell inhibitory protein (BIP)	Inhibition of B cell proliferation	[71]

Tick species	Tick molecules	Function/Mechanism	Ref
Tick species; pathogen species	**Tick mediators of pathogen transmission**	**Blockade of host responses favoring pathogen transmission**	**Ref**
I. scapularis *Borrelia burgdorferi*	Lectin complement pathway inhibitor (TSLPI)	Inhibition of lectin complement cascade and neutrophil function	[75]
	Tick salivary protein Salp15	Binds to *B. burgdorferi* outer surface protein (Osp) C; protects the spirochete from antibody-mediated killing	[78]
	Anticomplement gene (*isac*)	Reduced spirochete load in *isac*-silenced infected nymphs (as indicated by FlaB protein)	[76]
	Salivary protein Salp25D	Antioxidant; scavenges ROS at the vector-pathogen-host interface	[77]
	Salivary protein Salp12	Spirochete chemoattractant	[79]
I. scapularis *Anaplasma phagocytophilum*	Salivary protein Salp16	Facilitates pathogen migration to salivary glands	[80]
I. ricinus *Borrelia afzelii*	Lipocalins	Serotonin- and histamine-binding molecules	[81]
D. variabilis *Anaplasma arginale*	Glutathione S-transferase (GST); Salivary selenoprotein M (SelM); (vATPase); subolesin	Modulate pathogen development in ticks	[85]

DC, dendritic cells; ROS, reactive oxygen species; Ref, references.

Table 2:

Representative Examples of Acquired Tick Resistance (ATR)

Re-exposed tick species	Hosts	Cellular Infiltrates / Mechanisms	Pathogens affected	Ref
Ixodes scapularis	Guinea pig	Eosinophils; FcεRI signaling; complement and coagulation pathways	ND	[24]
		Mixed cells with leukocytes; architecture of skin lesions	ND	[23]
I. scapularis (saliva)	Guinea pig	Saliva proteins and/or glycoproteins	ND	[102]
I. scapularis (saliva fractions)	Guinea pig	Immunization with a chromatographic fraction of tick saliva can induce partial ATR. The fraction contains a set of identified 24 saliva proteins	ND	[104]
Dermacentor andersoni	Guinea pig	Cutaneous basophil hypersensitivity	ND	[93]
Amblyomma americanum	Guinea pig	Basophil-derived eosinophil-chemotactic factors	ND	[94]
D. andersoni	Guinea pig	Basophils; alternative pathway of complement	ND	[95]
		Passive transfer of high-titer antibodies confers partial ATR	ND	[114]
A. americanum	Cattle	Cutaneous basophil hypersensitivity	ND	[98]
Rhipicephalus microplus	Cattle	Cytokines; skin degradation and remodeling pathways; Wingless (WNT)-signaling pathway	ND	[99]
R. microplus	Cattle	Decreased cellular infiltrates; induction of extracellular matrix genes	ND	[100]
R. microplus	Cattle	γδ T cells; granulocytes; and MHC class II-expressing cells	ND	[101]
R. microplus	Cattle	Hereditary, breed-specific resistance	ND	[123]
R. microplus	Cattle	Stabilized T-cell-mediated response, including high expression of specific cytokines.	ND	[124]
A. cajennense	Goat	Cutaneous basophils	ND	[96]
Haemaphysalis longicornis	Basophil-deficient C57BL/6 mice	Basophils (IgFc receptors)	ND	[89]
H. longicornis	C57BL/6 mice	$CD4^+$ memory T cells; Interleukin-3-mediated basophil recruitment	ND	[90]
H. longicornis	W/Wv mice	Mast cells and IgE	ND	[112]
D. variabilis	Mast cell- deficient W/Wv and +/+ mice	Basophils; neutrophils; eosinophils	ND	[111]
H. longicornis	Various C57BL/6 knockout mice	Histamine; skin-infiltrating basophils	ND	[103]
I. scapularis	Dog	Tick immunity	ND	[97]
R. sanguineus	Guinea pig	Basophils; eosinophils	ND	[169]
R. appendiculatus, A. variegatum, A. hebraeum	Rabbit	Variable homospecific or heterospecific immunity	ND	[91]
R. microplus	Cattle	Breed-specific tick immunity	*Babesia bovis*; *Babesia bigemina*	[129]
D. variabilis	Rabbit	Allergic klendusity	*Francisella tularensis*	[92]
I. scapularis	Guinea pig	Tick immunity	*B. burgdorferi*	[19]
I. scapularis	BALB/c mice	Tick immunity	*B. burgdorferi*	[20]

Re-exposed tick species	**Hosts**	**Cellular Infiltrates / Mechanisms**	**Pathogens affected**	**Ref**
I. scapularis	DRBI*0301 (DR3) transgenic mice: HLA DR3 transgenic “humanized” mice	Th2 cytokines	*B. burgdorferi*	[117]
Tick bite (various species)	Humans	Tick immunity	*B. burgdorferi*	[22]

N.D. Not Determined