# Mechanism of Immunity to Tick infestation in Livestock

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## Abstract

Immunological interaction at the tick host interface involves both innate and acquired host defenses against infestation and Immunomodulatory countermeasures by thetick. Acquired resistance to tick infestation involves humoral and cellular immlmoregulatory effector pathways. Tick-borne disease-causing agentspr exploit tick suppression of host defenses during transmission and initiation of infection. Because of the public health importance of ticks and tick-borne diseases, it is crucial that we understand these interactions and exploit them in novel immunological control.
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## Introduction

The tick-host-pathogen interface is characterized by complex immunological interactions. Immunological interaction at the tick host interface involve both innate and acquired host defenses against infestation and Immunomodulatory countermeasures by the tick. The cellular and molecular immunological bases of these host-parasite relationships are being defined. Acquired resistance to tick infestation involves humoral and cellular immlmoregulatory effector pathways. It impairs tick engorgement, ova production, and viability Ticks responds by suppressing antibody production, complement and cytokine elaboration by both antigen-presenting cells and specific T cell subset . Tick countermeasures to host defenses reduce T-lymphocyte proliferation, elaboration of the Th1 cytokines interleukin-2 and interferon-y, production of macrophage cytokines interleukin-1 and tumor necrosis factor, and antibody responses. Tick-borne disease-causing agentspr exploit tick suppression of host defenses during transmission and initiation of infection. Because of the public health importance of ticks and tick-borne diseases, it is crucial that we understand these interactions and exploit them in novel immunological control.The dynamic balance between acquired resistance and tick modulation of host immunity affects engorgement and pathogen transmission. So a thorough understanding of mechanism of host immunity to ticks is essential for rational devlopement of antitick vaccine.

## Perspectives and Overview

* Disease-causing agents transmitted by blood-feeding arthropods are significant public health concerns. In addition to the emergence of new diseases, many well-recognised vector-borne diseases are occurring more frequently and are increasing the range over which they occur. Many factors contribute to the emergence and re-emergence of arthropod-borne diseases: insecticide/acaricide resistance; drug resistance; economic and social factors; environmental change; and genetic changes in the vector-borne pathogens.
* On a global basis, ticks are second only to mosquitoes as vectors of disease-causing agents to humans, and they are the most important arthropod transmitting pathogens to other animal species.The public health importance of ticks is not diminishing. Furthermore, new tick-borne disease causing agents are being discovered. Lyme borreliosis, caused by Borrelia burgdorferi, occurs in regions with temperate climates, and it is the most frequently reported vector-borne disease in the United States. In the United States, the vectors of *B. burgdorferi* are Ixodes scapularis in the east and midwest and Ixodes pacificus in the west. In addition to *B. burgdorferi, I. scapularis* is a vector of the human pathogens: *Babesia microti*; the causative agent of human granulocytic ehrlichiosis and a recently described encephalitis-like virus, In addition, *Ehrlichia chaffeensis*, transmitted by *Amblyomma americanum*, causes human monocytic ehrlichiosis, which was

described as a new species in 1991.Furthermore, E. chaffeensis infections have been reported from Europe and Africa. Throughout the world, it would be surprising if new emerging and re-emerging tick-borne diseases are not encountered in the coming years.

* The tick is clearly not just a crawling hypodermic needle and syringe with regard to the transmission of tick-borne pathogens. Tick-transmitted infectious agents undergo developmental cycles within the vector. The microorganisms can express molecules during the vector phase that are not evident during infection of the mammalian host. Additional factors of great importance in tick feeding and pathogen transmission are the number and diversity of pharmacologically active molecules in tick saliva. Those activities include anti-coagulants; inhibitors of platelet aggregation; vasodilators; and suppressants of host immune defenses. Ticks, as well as blood-feeding arthropods in general, are indeed 'smart pharmacologists. This report focusses on the ability of ticks to modulate host immune responses and the potential consequences of that immuno-suppression for pathogen transmission. Furthermore, the inhibition of the action of tick-derived host immunosuppressants might provide a powerful, novel, strategy for the control of tick-transmitted pathogens. Rather than targeting each individual tick-borne pathogen for vaccine development, develop a vector-blocking vaccine to those tick factors essential for successful transmission and establishment of disease-causing agents.

## Acquired Resistance

Tick feeding induces host immune regulatory and effector pathways involving antibodies, complement, cytokines, antigen-presenting cells, and T lymphocytes. Immunologically acquired host resistance to tickfeeding can result in reduced blood-meal volume, decreased engorgement weight, prolonged duration of feeding, diminished production of ova, reduced viability of ova, inhibition of molting, and death of engorging ticks. Acquired resistance has been most often observed after infestation by female ticks. However, feeding male ixodids also induce acquired resistance, but to a lesser degree than that caused by females alone or together with males.

Host grooming is an important factor in reducing tick burden .Immunological mediators induced by tick antigens introduced into host skin contribute to the itch sensation, which stimulates grooming.

The genetic background of an experimental host must be considered in any study of acquired immunological resistance. For example, bovine breeds differ in their resistance to ticks, a factor recognized and extensively used by cattle breeders .

The alternative pathway of complement activation contributes to expression of acquired resistance. Levels of complement component C3 increase during tick infestations. In addition, development of tick-specific IgG has been reported for many ixodid host associations.

Continuous introduction of saliva during feeding would allow complexes of circulating antibody and antigen to form and be deposited at feeding sites. Subsequent fixation of complement could enhance lesion formation and potentially have an impact on the engorging tick.

Complement activated by either the alternative or classical pathways could contribute to feeding-lesion formation through anaphylatoxin generation and chemotactic activities. C3a and C5a cause degranulation of mast cells and basophils and a concomitant release of eosinophil chemotactic factors (histamine, eosinophil chemotactic factor of anaphylaxis) and vasoactive substances. Digestive tracts of ticks that obtained blood meals from resistant hosts contained intact basophils, intact eosinophils, and granules of both cell types. Basophil and eosinophil granules were observed within tick gut cells that displayed membrane damage and other signs of injury. Bioreactive molecules released by basophils, eosinophils, and mast cells may influence tick physiological responses, thus causing cellular injury and behavioral changes. Histamine, leuko-trienes, prostaglandins, eosinophil major basic protein, enzymes, and other mediators of inflammatory and immune responses likely contribute to formation of the lesion at the bite site and affect the engorging tick. Ultrastructural analysis of tick-attachment sites on resistant mice revealed the accumulation of large numbers of basophils.

Cutaneous immune responses at tick-bite sites during acquisition and expression of acquired resistance require the participation of antigen-presenting cells, antigen-specific T and B lymphocytes, Langerhans cells and cytokines.

Bovine resistance to tick infestation consists of innate and acquired components. *Bos indicus* cattle exhibit the strongest innate resistance. Natural and acquired resistance of Hereford calves to *B. microplus* seem unrelated, and individual animals differ in natural susceptibility to infestation .Innate resistance,

which partly reflects the ability to mount a more intense immune response to infestation, appears to be linked to breed differences in immune response capabilities .As for acquired resistance, upon exposure to tick salivary-gland immunogens, *B. indicus* had heightened immune responsiveness compared with Bos taurus, as measured by macrophage elaboration of interleukin-l (IL-1) and in vitro proliferation of B and T lymphocytes to mitogens. The tropics and subtropics have placed strong selection pressures on B. indicus cattle to enable them to withstand harsh environmental factors in addition to parasites and other disease-causing agents .Selection of animals with the ability to limit tick infestation by heightened immune responsiveness results in a survival advantage.

By the third or fourth infestation, *B. taurus* cows and calves repeatedly infested with *D. andersoni* adults developed peripheral blood lymphocytes reactive in vitro with salivary-gland extracts of the same ixodid species. Purebred *B. indicus* calves infested with *A. americanum* developed in vitro lymphocyte responsiveness to this tick's salivary-gland extract after the first, second, and third infestations, whereas the reactivity of cells from crossbred animals was considerably less .

Changes in tick salivary-gland proteins during the course of feeding point to an array of tick immunogens and responses to host factors. In addition to other components in saliva, immunogens unique to attachment cement could contribute to host reactivity. Attachment cement likely serves to expose saliva immunogens to host skin and allow them to be adsorbed during feeding and, possibly, be a site of continued exposure after detachment. Similar antigenic determinants were detected in attachment cement and salivary glands of several ixodid species .

## Pharmacological Properties of Tick Saliva

Salivary gland-derived molecules have antihemostatic, vasodilatory, antiinflammatory, and immunosuppressive properties. Several tick salivary-gland factors appear to have more than one biological activity. For example, molecules inhibiting coagulation and enhancing vasodilation contribute to formation of the feeding site. Antiinflammatory and immunosuppressive molecules reduce host defenses that impair tick engorgement. Tick-mediated host immunosuppression appears to achieve a balance between reduction of immune defenses that limit engorgement and maintenance of sufficient immunocompetence for host survival. In addition, tick-induced host immunosuppression likely contributes to successful establishment of infection by tick-borne pathogens. Tick salivary glands contain apyrase, which inhibits platelet aggregation by hydrolyzing adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to adenosine monophosphate (AMP) and orthophosphate. Prostaglandin E2 (PGE2), which is produced by tick salivary glands, inhibits platelet aggregation and causes vasodilation .Salivary apyrase may prevent aggregation of neutrophils and mast cell degranulation. *A. americanum* saliva contains very high concentrations of PGE2 and *I. dammini* saliva contains prostacyclin, which blocks platelet aggregation, inhibits mast cell degranulation, and induces vasodilation. Intrinsic and extrinsic pathways of coagulation are inhibited by elements of *D. andersoni* saliva that act upon factors V and VI1 .Salivary-gland extracts of *R. appendiculatus* contain a 65-kDa anticoagulant that inhibits the activity of factor Xa or other components of the prothrombinase complex.

## Tick Modulation of Host Immune Function

Vector-mediated immunosuppression of the host helps in both blood-meal acquisition as well as in effective transmission of pathogens. In addition, the responses to both arthropods and pathogens involve common elements of the immune system.

Tick feeding also suppressed the generation of a primary IgM response to a thymic-dependent immunogen. Immunosuppression was attributed to lymphocytotoxic factors in tick salivary glands. Reduced lymphocyte proliferative responses and cytokine elaboration resulting from salivary-gland extracts of other tick species were not caused by cytotoxicity. Tick salivary gland-derived molecules reduce host T-lymphocyte function, which could suppress regulatory and effector pathways involved in acquired resistance. *Boophilus microplus* infestation of purebred *B. taurus* caused a marginal decrease in numbers of T lymphocytes, beginning with the second infestation and lasting until the end of a fourth exposure .

Tick modulation of host immunity inhibits regulatory and effector pathways involved in acquisition and expression of acquired resistance. Inhibition of the alternative pathway of complement activation, antianaphylatoxin activity, and reduction of natural killer cell function suppresses the innate response pathways of the host immune system. Reduced antibody responses facilitate feeding by reducing host immunoglobulins reactive with tick salivary-gland molecules. Analysis of host cytokine

networks reveals that macrophage and THl-lymphocyte function are suppressed by tick salivary-gland extracts. Tick countermeasures appear to target the major pathways involved in acquired host immunuity.

Tick modulation of host immunity appears to be mediated by salivary gland-derived proteins and possibly by PGE2. PGE, inhibits TH1, but not TH2, production of cytokines. Efforts to identify, isolate, and characterize tick salivary gland-derived molecules that suppress host immune responses are under way. A vaccine would allow more complete development and expression of host immunity to the vector and any introduced pathogens.

## Resistance

The following model accounts for recognized host defenses and tick countermeasures to these responses. Obviously, the responses of different tick and host species will vary.

The introduction of tick saliva into the skin of an unsensitized host causes degranulation of mast cells, possibly via enzymatic breakdown of plasma membranes. Chemoattractants and vasoactive factors released in this manner could contribute to formation of the modest leukocytic influx observed at tick-attachment sites during primary exposure. Generation of C5a by activation of the alternative complement pathway would contribute to cellular influx at the bite site. Ticks can modulate both innate and primary immune responses of hosts. Tick saliva contains inhibitors of the alternative pathway of complement activation, anaphylatoxins, and natural killer cells, which are all innate defenses. Tick saliva also reduces macrophage cytokine elaboration, which impairs the earliest steps in development of antitick immunity by altering signals to T and B lymphocytes. T-lymphocyte proliferative capacity is impaired, as shown by Con A responses. Furthermore, THl-lymphocyte production of IL-2 and IFN-y is reduced, while TH2-lymphocyte cytokine elaboration of IL-4 is normal. Reduced TH1 lymphocyte function would diminish delayed type hypersensitivity to tick immunogens, which contributes to the cellular influx at attachment sites on resistant hosts. Reduced IFN-y would impair macrophage activation.

In resistant animals, basophils appear to be attracted to attachment sites by soluble mediators and T lymphocytes. Tick salivary antigens introduced over the course of engorgement could result in an equally long-term release of bioactive molecules from mast cells already present as well as from infiltrating mast cells.

Repeated, or continuous, exposure brings feeding ticks into contact with the immune effector elements induced by primary infestation. Primary introduction of tick saliva stimulates generation of memory T and B lymphocytes, which assure a more vigorous immune response upon reinfestation.

Eosinophils act as feedback regulators of basophil and mast cell-derived bioactive molecules. Basophil and mast cell-derived histamine, leukotriene B4, and the eosinophil chemotactic factor of anaphylaxis attract eosinophils to the bite site. Macrophages observed in feeding lesions are probably involved in the elimination of antigen, as well as in antigen processing and presentation to any influx of immunocompetent cells.

Very little is known about the specific mechanisms that disrupt tick feeding, impair egg production, and reduce viability. Histamine, eosinophil basic protein, prostaglandins, leukotrienes, enzymes, and other biologically active molecules released might all be contributing factors. Although antibodies, lymphocytes, complement, and other elements of the immune and inflammatory responses participate in acquired resistance, their specific roles must still be established. For example, how do tick-reactive immunoglobulins affect the feeding ixodid? What is the importance, if any, of prostaglandins, leukotrienes, eosinophil basic protein, and other constituents of cells attracted to bite sites on resistant hosts? Do cytokines and acute-phase proteins have a direct role in expression of acquired resistance? Cytotoxic T lymphocytes and natural killer cells have not been implicated in antitick resistance. However, this topic remains to be fully investigated. The immunogens involved in acquisition and expression of acquired resistance must be identified and characterized. Certainly, a considerable body of interesting work awaits us.

## Anti-Tick Vaccine

Acaricide resistance is a significant threat to effective control of ticks and tick-borne diseases. The development of antitick vaccines represents one of the most promising alternatives to chemical control and has the advantages of target-species specificity, environmental safety, lack of human health risk, ease of administration, and cost. Numerous investigators have used whole-tick extracts and salivary-glandhomogenates as vaccine immunogens, which induced variable levels of protection. Particular attention has focused on concealed or novel immunogens not normally introduced into the host

during feeding, and tick gut immunogens have received the most attention. An elegant series of studies resulted in development of a recombinant vaccine to limit *B. microplus* infestation. A recombinant protein, derived from a well-characterized membrane glycoprotein of digest cells, Bm86, was expressed in various systems, with a eukaryotic expression system thought to be optimal. Antibodies to Bm86 inhibit digest-cell endocytosis. An additional *B. microplus* immunogen, Bm91, was identified and purified for use as an antitick vaccine immunogen. Multiple immunogens may produce an even more effective vaccine.

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