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Impact of insect salivary proteins in blood feeding, host immunity, disease, and in the development of biomarkers for vector exposure

Iliano V Coutinho-Abreu, Anderson B Guimarães-Costa and Jesus G Valenzuela

Functional genomic approaches based on expression of recombinant proteins linked to biochemical and disease model approaches resulted in the discovery of novel biological activities and the role some of these proteins play in disease transmission. Importantly, the expression of salivary proteins was recently shown to be affected by environmental factors and by the presence of the pathogen in the salivary gland. A practical application resulting from insect saliva research is the use of insect antigenic salivary protein as biomarkers of vector exposure in humans and animal reservoirs, an approach that is yielding interesting results in the field.

Address
Vector Molecular Biology Section, Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD 20878, USA

Corresponding author: Valenzuela, Jesus G (jvalenzuela@niaid.nih.gov)

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Introduction

The components and biological effects of the saliva of blood feeding arthropods is a growing area of research that is being cross-fertilized by various disciplines including biochemistry, immunology and molecular biology. Importantly, studies of saliva that focused only on a couple of insect species have expanded to other disease vectors in the last few years. Furthermore, the effect of insect saliva in pathogen transmission and establishment has been expanded to other pathogens.

This review highlights recent work in saliva from vectors of disease with emphasis in the discovery of novel biological activities from salivary proteins, the impact of insect saliva in infection, and the effect of environmental factors and pathogens in the expression of these salivary molecules. This review will also highlight an important contribution and practical application of insect salivary proteins: the use of antigenic proteins as novel biomarkers for vector exposure.

Insect saliva in blood feeding: old problems, smart solutions

To have a successful blood meal, hematophagous insects have developed several strategies to overcome the host hemostasis mechanisms. Vasodilators, inhibitors of the blood coagulation cascade, and inhibitors of platelet aggregation have been identified from the saliva of various vectors of disease [1]. Although we have achieved great knowledge on the composition of saliva (transcripts and proteins), the biological activity of many of the most abundant molecules has remained elusive. Functional genomics approaches based on the expression of recombinant proteins in heterologous systems and in gene silencing have propelled the discovery of novel activities from some of the highly abundant salivary proteins with previous 'unknown function'.

Aegyptin, a novel salivary collagen-binding protein from *Aedes aegypti*

It was recently shown that a 30 kDa recombinant protein, named Aegyptin, specifically binds to collagen, impeding the interaction of collagen with the platelet receptor glycoprotein VI, Integrin $\alpha 2\beta 1$, and von Willebrand factor. This ultimately leads to the inhibition of collagen-induced platelet aggregation and adhesion [2]. Chagas *et al.* [3••] used a gene-silencing approach to assess the relevance of Aegyptin in blood feeding. Saliva from transgenic mosquitoes lacking Aegyptin failed to inhibit collagen-induced platelet aggregation, exhibited increased probing time, and also ingested less amount of blood when feeding on mice as compared to control group.

The function and structure of the mosquito salivary D7 protein

D7 salivary proteins are found in Nematoceran Diptera and consist of a multigene family distantly related to the odorant binding proteins. The short molecular forms (D7r) have been characterized in the mosquito *Anopheles gambiae* [4]. The D7 proteins were shown to bind biogenic amines, which are important mediators of inflammation

and vascular tone. Among the long D7 proteins, the different domains have evolved to bind different ligands. Whereas the C-termini domains of some long D7 proteins, such as the *Aedes aegypti* AeD7, bind to biogenic amines, the N-terminal domains bind to cysteinyl leukotriene, another mediator of allergy and vascular permeability [4]. Interestingly, the N-terminal domain of AnSt-D7L1, a long D7 salivary protein of the mosquito *An. stephensi*, also binds to thromboxane A_2 [5]. The N-termini, on the other hand, lost its ability to bind to biogenic amines [5].

A salivary lipocalin from *Rhodnius prolixus* is a biogenic amine-binding protein

A salivary protein from *Rhodnius prolixus* was shown to bind biogenic amines and the structure of this protein was recently solved and shown to be a lipocalin [6•], a different structure compared to the D7 family of proteins, the biogenic amine binding proteins found in mosquitos [4] suggesting a case of convergent evolution. The amine-binding protein (ABP) from *R. prolixus* has some sequence similariry to the salivary nitrophorins but ABP does not bind heme. ABP binds serotonin and norepinephrine with high affinity and inhibits biogenic amine-mediated platelet activation.

Triplatin, a salivary protein from *Triatoma infestans*, is a novel platelet aggregation inhibitor and a vasoconstriction inhibitor

Triplatin was shown to be an inhibitor of collagen-induced platelet aggregation and proposed to antagonize the collagen receptor glycoprotein VI (GPVI). Recently, triplatin was shown to inhibit platelet aggregation induced with low dose of collagen but it did not bind the collagen receptor GPVI. Triaplatin was also shown to bind Thromboxane A_2 and prostanglandin $F2_{alpha}$ and PGJ_2 and to inhibit vasoconstriction [7].

The salivary Antigen 5 from *Triatoma infestans* and *Dipetalogaster maxima* functions as an antioxidant by scavenging O^-_2

The presence of antigen 5 family of proteins has been reported in the saliva of many blood feeding insects. However, the function of this protein remained elusive for many years. Recently, the biological function of the antigen 5 salivary protein from *Triatoma infestans* and *Dipetalogaster maxima* was elucidated and shown to be a superoxide dismutase that binds Cu^{2+} and scavenges O^-_2. The salivary antigen 5 inhibited platelet aggregation induced by collagen and blocked neutrophil oxidative burst [8••]. This family of proteins represents a novel family of antioxidants present in the saliva of blood-feeding insects.

The yellow salivary proteins from sand flies bind biogenic amines

One of the most abundant salivary proteins from sand flies with 'unknown function' is the yellow related family of proteins. It was recently shown that the yellow related proteins LJM17, LJM11, and LJM111 bind biogenic amines, including serotonin, catecholamines, and histamine, counteracting this way the hemostatic system [9]. The kissing bug *Rhodnius prolixus* has also a novel biogenic amine binding protein; however, the sequence and structure of this protein does not resemble the protein in sand flies and belongs to the lipocalin protein family, representing a case of convergent evolution [6•].

Lufaxin, the anticoagulant from sand flies

A salivary protein of 38 kDa of unknown function was demonstrated to be the anticoagulant in sand flies. The salivary protein named Lufaxin is a potent and specific inhibitor of Factor Xa [10] and a potent inhibitor of inflammation. Lufaxin has no homologs to any other proteins in accessible databases and so far it has only been identified in the salivary glands of sand flies [10].

Sand fly salivary protein SP15 is a novel inhibitor of contact pathway

The recombinant protein PdSP15 from the sand fly *Phlebotomus duboscqi* was shown to bind negatively charged surfaces. These anionic surfaces serve to stabilize complexes of the blood coagulation cascade. By binding to these negatively charge surfaces, PdSP15 inhibits the activation of factors FXII and FXI, therefore preventing the process of coagulation and bradykinin production [11•].

Insect saliva in pathogen transmission

Effect of mosquito saliva on virus infection

The powerful effects of saliva in the host hemostatic system and inflammatory system may have consequences in virus transmission as demonstrated in other diseases. The saliva from *Ae. aegypti* was shown to enhance Dengue virus infection in *ex vivo* human keratinocytes [12]. Importantly, this effect correlated with the down-regulation of the expression of several antimicrobial peptides, including β-defensin, LL-37, Elafin, and S100A7 and the down-regulation of the anti-virus cytokines, IFN-alpha, IFN-beta, and IFN-gamma [12]. Recently, a salivary protein with a molecular weight of 34 kDa only present in *Aedes* and *Culex* mosquitoes was shown to enhance Dengue virus replication and suppress the innate immune response of the host [13••]. Conway and colleagues have identified a mosquito salivary protease CLIPA3 that enhances DENV infectivity and dissemination both *in vitro* and *in vivo* models of infection [14••]. CLIPA3 is proposed to cleave extracellular matrix proteins, allowing DENV particles to ultimately interact with local permissive cells [14••].

A salivary endonuclease helps *Leishmania* to escape from the innate immune system

A sand fly salivary endonuclease named Lundep (LJL138) was shown to have a direct impact on *Leishmania* infection. Neutrophils are the first cells recruited to the

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