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REVIEW

Immunomodulatory effects of tick saliva

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Abstract

Ticks are bloodsucking ectoparasites that cause great damage to host organisms, so these ectoparasites are of great importance in medicine and veterinary medicine. All the biological success achieved by ticks is due to the action of bioactive components present in their saliva, which are synthesized by the salivary glands. These components have great diversity of functions such as enabling feeding and the permanence of ectoparasites on hosts, since they modulate immune system acting as complement inhibitors, immunosuppressors, cytokine expression modulator and chemokine binders of hosts. In addition, these components are an important source of protective antigens. In this sense, salivary glands/saliva are considered a potential source of multifunctional molecules. In this context, many studies have been conducted aiming at searching to establish a better understanding on the biology and morphophysiology of some organs such as salivary glands, as well as elucidate the complex relationship of these ectoparasites with their hosts. Such studies are conducted with the main objective of developing new immunobiological products aimed at the alternative control of ticks, as well as for the identification and isolation of bioactive molecules with pharmacological properties and with great therapeutic potential in the search for treatments for some diseases.

Key Words: tick saliva; immunomodulation; immunosuppression; salivary glands

Introduction

Ticks are bloodsucking ectoparasites that can parasitize animals of different groups such as mammals, birds, reptiles, amphibians (Keirans and Durden, 2005; Anderson and Magnarelli, 2008) and even spiders, including ticks themselves (Labruna *et al.*, 2007). These ectoparasites have broad geographic distribution, and can be found in all regions of the planet (Keirans and Durden, 2005; Anderson and Magnarelli, 2008).

Ticks are animals belonging to the phylum Arthropoda, subphylum Chelicerata, class Arachnida, subclass Acari, order Parasitiformes and suborder Ixodes. These ectoparasites are divided into four families, namely: Ixodidae, Argasidae, Nutalliellidae and Laelaptidae, the first two being the most important, totaling 878 species (Anderson and Magnarelli, 2008).

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Ticks are arthropods of great medical and veterinary importance because they are vectors of bacteria, viruses, protozoa and helminthes to their hosts, affecting domestic animals, wildlife and humans (Jongejan and Uilemberg, 2004; Dantas-Torres *et al.*, 2010), besides causing considerable economic losses.

Considering that ticks remain attached to their hosts feeding for weeks, they must have a large, diverse and effective pharmacological arsenal to ensure their survival and feeding (Wikel, 1999, Sauer *et al.*, 2000; Francischetti *et al.*, 2005; Steen *et al.*, 2006), which can be rapidly introduced into the host. Thus, throughout evolution, salivary glands have specialized in the production of a secretion called saliva, which has such capability.

The present review will focus only on immunomodulatory effects of tick saliva.

Salivary glands of ticks

The salivary glands of ixodid (family Ixodidae) are vital organs for the biological success of this group, since they have wide variety of functions such as the production of substances necessary for

the fixing and feeding of ectoparasites (Binnington, 1978; Walker *et al.*, 1985; Gill and Walker, 1987).

The presence of these organs and their role in hosts to give these ectoparasites the status of one of the most important groups within the group of arthropods. Their salivary glands are also responsible for the transmission of infectious agents to other groups of animals (Balashov, 1983).

Morphologically, salivary glands of ixodid ticks are formed by an excretory portion composed of a common excretory duct, intermediate ducts and acinar ducts responsible for collecting and secretion of saliva produced in the secretory portion. The latter consists of types I, II, III and IV acini, the latter present only in males (Binnington, 1978; Walker *et al.*, 1985; Fawcett *et al.*, 1986; Gill and Walker, 1987; Sonenshine, 1991; Furquim *et al.*, 2008a, b, 2010). Type I acini are nongranular and act in the water balance of the ectoparasite, while type II, III and IV acini are granular and act in the feeding process (Binnington, 1978; Walker *et al.*, 1985), in osmoregulation in the phase of large blood consumption (Kaufman and Sauer, 1982; Sonenshine, 1991) and in reproduction (Feldman-Muhsam *et al.*, 1970). The salivary glands of ticks have no reservoir to store secretion, which is released as soon as it is produced (Binnington, 1978; Balashov, 1983; Walker, 1985; Nunes *et al*., 2008).

Type I acini consist of a large central cell, surrounded by several smaller peripheral cells (Binnington, 1978; Walker *et al.*, 1985; Fawcett *et al.*, 1986; Gill and Walker, 1987).

Type II acini are formed by types a, b, c1, c2, c3 and c4 secretory cells (Binnington, 1978) and in females of *R. sanguineus*, and in addition to those, c5 and c6 cells have been recently described (Furquim, 2007). It is known that a cells are involved in the secretion of the cement (Binnington, 1978; Walker *et al.*, 1985; Fawcett *et al.*, 1986; Gill and Walker, 1987), and b and c are involved with the manipulation of the host response (Binnington, 1978; Walker *et al.*, 1985).

Type III acini, in turn, are composed of three cell types, d, e and f (Binnington, 1978; Walker *et al.*, 1985; Gill and Walker, 1987; Furquim, 2007), where d and e secrete components of the cement during attachment (Binnington, 1978; Walker *et al.*, 1985; Gill and Walker, 1987), and f cells secrete substances related to the consumption of blood by the ectoparasite (Binnington, 1978).

The new classification of the salivary gland cells of *Rhipicephalus sanguineus* established by Furquim (2007) included a larger number of secretory types present in type II acinus (females), unlike those previously described in literature (Binnington, 1978, Walker *et al.*, 1985). Moreover, the author has shown that these new types (c5 and c6), and f of type III acini would be activated and inactivated at specific moments of the glandular cycle (when the tick had already fed for two and four days), while the other types would remain continuously active until the complete engorgement of the female, becoming inactive, beginning the death process (Furquim *et al.*, 2008a, b). This was evidence that the activity of c5, c6 and f cells would be essential for feeding and permanence of ticks in the host, therefore acting specifically in the manipulation of their immune response.

Type IV acinus, exclusive to males, consists of a single cell type, g (Binnington, 1978; Furquim *et al.*, 2008a, 2010). In some ixodid, its product participates in the secretion of the cement (Fawcett *et al.*, 1986) and can also produce other secretions important in the transfer of the spermatophore to the female (Feldman-Muhsam *et al.,* 1970).

Functions of the tick saliva

The tick saliva is a mixture that plays a variety of roles during parasitism and non-parasitism periods, as: modulating the immune system of the host (Fawcett *et al.*, 1986; Ribeiro *et al.*, 1985; Wikel, 1999; Sauer *et al.*, 2000); attaching the tick to the host skin through the secretion of cement to form the cone (Fawcett *et al*., 1986); excreting excess water and ions from the food (blood) (Sauer *et al.*, 2000); secreting hygroscopic solution, which is deposited in the mouth region and absorbs atmospheric water, hydrating the ectoparasite during non-parasitism periods (Sauer *et al*., 2000; Bowman and Sauer, 2004); producing secretions that lubricate the spermatophore during its transfer to the female during copulation (Feldman-Muhsam *et al.*, 1970); releasing toxins that cause paralysis in the host (Fawcett *et al.*, 1986) and conveying pathogens to the host (Fawcett *et al.*, 1986; Wikel, 1999; Sauer *et al.*, 2000; Bowman and Sauer, 2004).

Immunomodulation of host immune responses

Given the importance of components synthesized by type II and III acini for the feeding and fixing of ticks (Binnington, 1978; Walker *et al.*, 1985), these components should be studied in more depth (Jittapalapong *et al.*, 2008).

Proteins, glycoproteins, lipoproteins and lipids are among products with pharmacological and immunological properties present in the saliva of ticks (Binnington, 1978; Wheeler *et al.*, 1991; Shipley *et al.*, 1993), such as acid phosphatase, esterases, aminopeptidases, metalloproteases, calreticulin, esterase, prostaglandins, lipocalins (Binnington, 1978; Gill *et al.*, 1986; Jaworski *et al.*, 1995; Brossard and Wikel, 2004; Steen *et al.*, 2006; Harnoi *et al.*, 2007; Mulenga *et al.*, 2007; Kaewhom *et al.*, 2008; Konnai *et al.*, 2010; Oliveira *et al.*, 2011), among many others.

Although the function of the cement of keeping the ectoparasite attached to the host has been widely reported, this substance has proteins that act both in the host modulation and in the formation and maintenance of the feeding lesion (Mulenga *et al.*, 2007). In this sense, the chemical composition of the cement consists of a mixture of antigenic and non antigenic proteins containing carbohydrates and lipids in the inner layers of the cone, the outer layers being formed by lipoproteins and glycoproteins (Sonenshine, 1993).

Binnington (1978) studied the salivary glands of females of *Boophilus microplus* and demonstrated the production of: a) glycoproteins by b, c1, c2, c3 cells of type II acinus, and f cells of type III acinus, b) acid phosphatase by the three types of acini,

mainly by type I acinus and by d cells of type III acinus , c) protease by cell of type II acinus, d) esterase by cells of all types of acini, especially b and c cells of type II acini and e) lipoproteins by a cells of type II acinus and d and e cells of type III acinus.

The tick saliva is a complex and sophisticated pharmacological arsenal effectively interacting with elements of the immune-inflammatory and hemostatic system of the host that can hold its defenses quickly since the first days of ectoparasite feeding (Ribeiro *et al.*, 1985; Wikel, 1989; Brossard and Wikel, 1997, 2004; Francischetti *et al.*, 2005, Steen *et al.*, 2006). Moreover, the tick saliva immunosuppresses the host, making these ectoparasites skilled transmitters of pathogens that are transmitted through their own saliva (Wikel, 1999; Singh and Girschick, 2003; Kovár, 2004).

In this sense, the saliva of ticks plays vital functions in the hemostatic, inflammatory and immune processes of the host by: a) increasing blood flow (circulation) in the bite region through the secretion of vasoactive agents; b) inoculating anticoagulants that keep the host's blood in the fluid form; c) inhibiting the inflammatory process in the host d) immunosuppressing the host and enabling the attachment of ticks, making their rejection by the host difficult (Sauer *et al.*, 2000).

The following elements present in the saliva of ticks with pharmacological and immunological properties stand out: a) enzymes (apyrase, kininase), enzyme inhibitors, b) proteins homologous to host proteins, c) proteins that bind to immunoglobulins, d) lipocalin that bind to amines, e) agonists / antagonists of receptors, f) calcium-carrier elements (calreticulin), g) cytokine expression modulators, and h) other non-protein bioactive components such as prostaglandins (PGE2) (Steen *et al.*, 2006; Brossard and Wikel, 2004).

The action of the tick saliva is a complex process, since this mixture has quantitative and qualitative variations due to the different glandular cycle periods within the same species (Binnington, 1978; McSwain *et al.*, 1982; Sauer *et al.*, 1982; Shipley *et al.*, 1993; Sanders *et al.*, 1996; Furquim, 2007; Mulenga *et al.*, 2007; Xiang *et al.*, 2009) or when considering different species (Kazimírová, 2007). In addition, another important factor that contributes to the heterogeneity of the tick saliva and that should be considered is the fact that the immunereactive activity of tick-derived factors may vary depending on the host species parasitized (Lawrie *et al.*, 1999).

Harnnoi *et al.* (2007) demonstrated the occurrence of the expression of six types of metalloproteases along the glandular cycle of *Haemaphysalis longicornis*. In addition, Oliveira *et al.* (2011) detected the presence of molecules of non protein origin, prostaglandin (PGE2) and purine nucleoside adenoside (Ado), with strong immunomodulatory properties in the saliva of *R. sanguineus* and found that isolated molecules have different ways of action, whereas when combined, their action becomes enhanced.

Moreover, some elements produced by the salivary glands of ticks are likely to have more than one biological activity, for example, molecules that inhibit coagulation and enhance vasodilation contribute to the formation of fixation and feeding lesion, anti-inflammatory and immunosuppressive molecules those reduce host defenses impairing the feeding of ticks (Wikel, 1996).

The bioactive molecules present in the saliva of ticks of different species and genera are: apyrase, which inhibits platelet aggregation through the hydrolysis of ATP and ADP into AMP and orthophosphate (Titus and Ribeiro, 1990; Kazimírová, 2008), and prevents neutrophil aggregation and degranulation of mastocytes (Ribeiro *et al.*, 1985). Prostaglandins (PGs), found in high concentrations in the saliva of some species of ticks (Bowman *et al.*, 1996) such as prostaglandin E_2 (PGE_2), with anti-hemostatic, vasodilator and immunosuppressive activity (Bowman *et al.*, 1996), which inhibit platelet aggregation and cause vasodilation (Champagne, 1994; Ribeiro *et al.*, 1985; Kazimírová, 2008), suppress the production of interferon (IFN)-γ (Hasler *et al.*, 1983; Betz and Fox, 1991) and interleukin (IL)-2 (Hasler *et al.*, 1983; Betz and Fox, 1991; Krause and Deutsch, 1991) and inhibit the bioactivity of IL-2 in cells that dependent on this cytokine by reducing the expression of IL- 2 receptors in these cells (Krause and Deutsch, 1991) - thus, prostaglandins can inhibit the function of T lymphocytes (Singh and Grischick, 2003), and in *Ixodes dammini*, inhibit IL-2 production by these lymphocytes (Ribeiro and Spielman, 1986); prostacyclin (PGI_2), found in the saliva of *I. dammini*, which blocks platelet aggregation, inhibits degranulation of mastocytes and induces vasodilation (Ribeiro and Spielman, 1986; Kazimírová, 2008). Elements that in *Dermacentor andersoni* act in factors V and VII inhibiting intrinsic (activated tissue factor) and extrinsic pathways (activated collagen) of the blood coagulation cascade (Gordon and Allen, 1991). Peptides found in the saliva of *Ornithodoros savigny* also inhibit the extrinsic pathway of the coagulation cascade (Ehebauer *et al.*, 2002). Variegin found in the saliva of *Amblyomma variegatum*, which is a thrombin inhibitor (Koh, 2007). Anti-coagulant, which in *R. appendiculatus* inhibits the activity of factor Xa or other components of the prothrombinase complex (Limo *et al.*, 1991). Another factor Xa inhibitor, TAP protein, was found both in the saliva of *O. moubata* (Waxman *et al.*, 1990) and in *O. Savigny* (Joubert *et al.*, 1998). Kininase, found in *I. dammini*, has the capacity to act in the cleavage of bradykinin (enhanced by PGE 2) (Ribeiro *et al.*, 1985) and reduce skin irritation (itching) caused by this substance, leading to reduced removal of ticks by self-cleaning mechanism through licking. Molecules with anti-chemokine activity in adult ticks of the species *R. sanguineus*, which act against human chemokines CXCL8, CCL2, CCL3, CCL5, and CCL11 (Vancová *et al.*, 2010). According to these authors, males of *I. ricinus* have molecules that act against these chemokines, while in females of the same species, no activity against chemokines CCL5 and CCl11 was detected (Vancová *et al.*, 2010). Elements that bind to growth factors transforming them. In *A. variegatum*, these elements react with growth

factor-β (TGF-β1), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF-2) and hepatocyte growth factor (HGF), In *D. reticulatus* and *R. appendiculatus* with TGF-β1, FGF-2 and HGF and in *I. ricinus* and *I. scapularis* with PDGF (Hajinická *et al.*, 2010). Peptides found in *I. scapularis* are potent inhibitors of the complement system (Tyson *et al.*, 2007). Calcium-binding proteins (calreticulins), whose functions in the parasite-host relationship would facilitate feeding through their actions in the immune system, immunosuppressive and antihemostatic (Jaworski *et al.*, 1995; Brossard and Wikel, 2004; Jittapalapong *et al.*, 2008; Steen *et al.*, 2006). Lipocalins, present both in ixodid and argasids, act in the modulation of the immune response by inhibiting platelet (Keller *et al.*, 1993) or complement aggregation (Nunn *et al.*, 2005; Mans and Ribeiro, 2008a), inflammation through association with histamine, serotonin, leukotrienes C4, D4, E4 (Paesen *et al.*, 1999; Sangramnatdej *et al.*, 2002; Mans and Ribeiro, 2008b; Mans *et al.*, 2008c) and induction of toxicoses (Mans *et al.*, 2001, 2002, 2003). Metalloproteases detected in the saliva of *I. scapularis* with anti-fibrinogen activity (Francischetti *et al.*, 2003). Peptides that form and maintain feeding lesion (Mulenga *et al.*, 2007). Elements that are potent inhibitors of angiogenesis and proliferation of endothelial cells (Francischetti *et al.*, 2005). Anti-inflammatory proteins that bind to lipocalin and histamines (Mulenga *et al.*, 2007).

In relation to the modulating capacity of tick saliva, it is known that this mixture acts on hosts affecting the proliferation of lymphocytes (Kopecky *et al.*, 1999), decreasing the oxidative activity of macrophages (Kuthejlova *et al.*, 2001), inhibiting neutrophils, including their oxidative and phagocytic activity (Ribeiro *et al.*, 1990), inhibiting the activity of "natural killer-NK" cells (Kubes *et al.*, 1994), reducing the development of the primary IgM response (Fivaz, 1989; Wikel, 1985), which remains evident for a few days after the infestation (Wikel, 1985), and decreasing cytokine production by Th1 lymphocytes (IL-2 and IFN-γ) and cytokines of macrophages, while increasing the production of cytokines by Th2 lymphocytes (IL-4, IL-5 and IL-10) (Wikel, 1999), in order to influence the class of immunoglobulin produced, causing the host to the preferential production of IgG1 and IgE immunoglobulins instead of IgG2 (Wikel, 1996). Cytokines IL-2 and IFN-γ are vital to the development of an effective immune response in the attachment and feeding lesion of the tick, including the recruitment, activation and proliferation of immunocompetent cells, thereby mediating an inflammatory response to the ectoparasite (Singh and Grischick, 2003).

Recent studies have shown that the saliva of different tick species, among them *R. sanguineus*, modulates different steps of the biology of dendritic cells, such as maturation and migration (Oliveira *et al.*, 2008, 2010). Anticoagulant proteins have been identified in the saliva of ticks such as Boophilina (obtained from the saliva of *B. microplus*) (Macedo-Ribeiro *et al.*, 2008) and ixolaris and penthalaris (obtained from the saliva of *I. scapularis*) (Francischetti *et al.*, 2002, 2004).

Also with regard to the biochemical and functional complexity of the saliva, Ribeiro (1987) reported that the pharmacology of tick saliva can adapt to specific homeostatic defenses of the host. In this sense, Furquim *et al.* (2011) demonstrated that the secretory behavior of the salivary glands of females of *R. sanguineus* is modified according to the resistance of the host through immunization. These authors found that the glandular secretion of these females showed increased amounts of many components such as proteins, lipids, polysaccharides, acid phosphatase and calcium (probably calreticulin), which enhanced the pharmacological action and biochemical complexity of the saliva produced by them, thereby modifying its action on the parasite-host relationship.

Resistance acquisition of hosts

In ticks, the salivary glands are important sites for producing antigens (Wikel *et al.*, 1978; Gill *et al.*, 1986; Almeida *et al.*, 1994; Ferreira *et al.*, 1996; Szabó and Bechara, 1997; Jittapalapong *et al.*, 2000a; Nunes *et al.*, 2011). Therefore, after the first contact of these ectoparasites with some hosts, the latter develop resistance (Wikel *et al.*, 1978; Gill *et al.*, 1986; Jittapalapong *et al.*, 2000a, Zhou *et al.*, 2006). In this sense, many studies have been carried out to verify the acquisition of resistance by hosts when they are immunized by successive infestations (Jittapalapong *et al.*, 2000a, b; Monteiro *et al.*, 2008, 2011; Caperucci *et al.*, 2009, 2010; Veronez *et al.*, 2010; Nunes *et al.*, 2011) or by inoculation of extracts made of whole ticks (or parts of them) (Wikel, 1981; Ferreira *et al.*, 1996; Szabó and Bechara, 1997; Jittapalapong *et al.*, 2000a, b, 2008).

The acquisition of resistance by hosts is measured analyzing food and reproductive parameters of ticks infesting animals previously immunized (Wikel, 1981; Szabó and Bechara, 1997; Jittapalapong *et al.*, 2000b), as well as analyzing the impact of this resistance on the salivary glands (Sanders *et al.*, 1996; Jittapalapong *et al.*, 2008; Furquim *et al.*, 2011; Nunes *et al.*, 2011) and intestine (Caperucci *et al.*, 2009, 2010; Veronez *et al.*, 2010) of different species.

According to Wikel (1981) and Jittapalapong *et al.* (2000b, 2008), immunization obtained from antigens derived from salivary glands would stimulate the host immune response that would affect ticks of subsequent infestations due to the direct action of resistance acquired by the host in the secretory cycle of the salivary glands, reducing the efficiency of the feeding process and pathogen transmission by ticks (Jittapalapong *et al.*, 2008).

Considering that ticks are able to modulate local hemostatic reactions in the host, this ability can be affected by the immune status (resistance) of the host. In resistant hosts, large amounts of inflammatory cells are recruited and the expression of anti-coagulant molecules in the salivary glands of ticks is reduced, and this glandular alteration may hinder the consumption of blood by ticks (Carvalho *et al.*, 2010).

According to Turner *et al.* (2002), much information can be obtained on the resistance

Table 1 Examples of bioactive components in tick saliva

Tick species	Molecule name	Target/ Function	Reference
Ticks in general	Salp15 (Anti-alarmin)	Chemotactic properties of Chemokines	Marchal *et al*., 2010
Ixodidae	Salp 25	Antioxidant	Kovar, 2004
	MIF homologue (cytokine homologue)	Inhibits the migration of human macrophages similarly of humam MIF	Kovar, 2004
	HBPs (lipocalins with 1 or 2 binding sites)	Suppress inflammation by hystamin or serotonin binding	Kovar, 2004
Hyalomma asiaticum	BIF	Inhibits LPS-induced proliferation of B-Cells	Yu *et al*., 2006
Ixodes	TSLPI	Lectin pathway inhibitor	Schuijt *et al.*, 2011
Ixodes scapularis	PGs	Inhibits lymphocytes L2	Ribeiro and Splielman, 1986
	Isac	Alternate complement pathway, interacts with C3 convertase	Valenzuela et al., 2000
	Salp20	C3 convertase	Tyson *et al*., 2007
	Salp15	Impairs IL-2 production and T-Cell proliferation; binds *Borrelia burgdorferi* OspC, protects the spirochete from antibody-mediated killing	Ramamoorthi *et al*., 2005
	IL-2 binding protein	Inhibits proliferation of human T-Cells and CTLL2 Cells	Gillespie *et al*., 2001
	Sialostatin L	Inhibits cathepsin L activity	Kotsyfakis *et al*., 2006
Ixodes ricinus	BIP	Inhibitorof B-Cell proliferation	Hannier *et al.*, 2004
	Iris	Modulates T-lymphocytes and macrophage responsiveness, induce T-h2 type responses; inhibitor of homeostasis	Leboulle *et al*., 2002
	IRAC I, II, Isac paralogues	Alternate complement pathway, interacts with C3 convertase	Daix *et al*., 2007
Ornithodoros moubata	OMCI	C5, prevention of interaction C5 with C5 convertase	Nunn *et al*., 2005
Rhipicephalus sanguineus	Evasin-1	binds Chemokines CCL3, CCL4 and CCL18	Frauenschuh *et al*., 2007
	PGE2	Modulations of DCs	Oliveita *et al*., 2011

acquired by hosts sensitized to different tick species or even to the same species, because immunosuppressive molecules synthesized by the salivary glands are differentially expressed during tick feeding. In addition, the salivary glands of different species have different antigens, in quantities and concentrations also different (Jaworski *et al.*, 1990; Inokuma *et al.*, 1994). Data are summarized in Table 1.

Therapeutic properties and prospects of tick saliva

The saliva of ticks has several types of molecules that modulate the immune-inflammatory and hemostatic system of their hosts (Wikel and Bergman, 1997; Steen *at al.*, 2006; Hajnická *et al.*, 2011). This complex mixture is considered to be a potential reservoir of multifunctional molecules, *i.e.*, the saliva of these ectoparasites, as well as the saliva of hematophagous organisms in general has bioactive compounds of great interest (Batista *et al.*, 2010). Thus, tick saliva has been the subject of different studies due to the great interest in the identification and isolation of bioactive molecules with vasodilating, anti-inflammatory, immunosuppressive and anticoagulant activity (Oliveira *et al.*, 2010).

The tick saliva has presented mitigating action of angiogenesis (Francischetti *et al.*, 2005), as well as anti-tumor properties (Simons *et al.*, 2011).

In relation to the bioactive molecules present in the saliva of ticks, the evasin-1, a chemokine binding protein is used in the idiopathic pulmonary fibrosis therapy (Russo *et al.*, 2011) a protein recently found in the saliva of *A. cajennense* that acts in the coagulation process, also showed cytotoxic activity in different tumor cells, among them pancreatic cells and melanomas (Chudzinski-Tavassi *et al.*, 2010). The effects of crude saliva are also promising, since it triggered cell death and morphological changes in human melanoma cells (SK-MEL-28) and human pancreatic carcinoma (MIA PaCa-2), without causing changes in normal human fibroblasts exposed to it (Simons *et al.*, 2011). Previous results have shown that molecules present in extracts of the salivary glands of *R. appendiculatus* and *A. variegatum* were able to hold the growth of human HeLa cells (cervical cancer cells) through an apoptotic process (Kazimírová *et al.*, 2008).

Thus, ticks seem to be a source of bioactive molecules with great potential for the treatments for some diseases, including cancer, because as already mentioned, among the known species of ticks, as well as among genera, there are differences in bioactive compounds present in their salivary glands (Kazimírová, 2008). Moreover, the acquisition of resistance by the host can affect the biochemical composition of the salivary glands / saliva of ectoparasites that feed on them. This change becomes an additional factor that contributes to the quantitative and qualitative variation of bioactives found in the saliva of ticks (Furquim *et al.*, 2011).

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