A Nod to disease vectors: mitigation of pathogen sensing by arthropod saliva

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INTRODUCTION

Vector-borne diseases impact individuals worldwide and, with their frequencies increasing, they are becoming a crucial public health problem in need of attention (McGrane and O’Neill, 2013). With more than 200 million affected individuals, malaria is spreading rampant in tropical and subtropical regions and dengue fever is following close behind (Table 1). The spread of these illnesses, as well as other vector-borne diseases, has been attributed to rapid globalization, anthropomorphic and environmental changes, and the lack of effective vaccines (Kovats et al., 2001). These maladies have been combated by preventive care and therapeutics as well as other vector-borne diseases, has been attributed to rapid globalization, anthropomorphic and environmental changes, and the lack of effective vaccines (Kovats et al., 2001). These maladies have been combated by preventive care and therapeutics (Mejia et al., 2006; Fontaine et al., 2011). In order to develop novel treatments, scientists are continuously attempting to elucidate the mechanism of microbial transmission and aspects of the immune system that are involved in pathogen recognition (Titus et al., 2003; Chmelar et al., 2012).

Arthropod saliva possesses anti-hemostatic, anesthetic, and anti-inflammatory properties that facilitate feeding and, inadvertently, dissemination of pathogens. Vector-borne diseases caused by these pathogens affect millions of people each year. Many studies address the impact of arthropod salivary proteins on various immunological components. However, whether and how arthropod saliva counters Nod-like (NLR) sensing remains elusive. NLRs are innate immune pattern recognition molecules involved in detecting microbial molecules and danger signals. Nod1/2 signaling results in activation of the nuclear factor-kB and the mitogen-activated protein kinase pathways. Caspase-1 NLRs regulate the inflammasome – a protein scaffold that governs the maturation of interleukin (IL)-1β and IL-18. Recently, several vector-borne pathogens have been shown to induce NLR activation in immune cells. Here, we provide a brief overview of NLR signaling and discuss clinically relevant vector-borne pathogens recognized by NLR pathways. We also elaborate on possible anti-inflammatory effects of arthropod saliva on NLR signaling and microbial pathogenesis for the purpose of exchanging research perspectives.

Keywords: Nod-like receptors, inflammasome, vector-borne pathogens, vector-borne diseases, arthropod saliva, salivary proteins

Table 1

| Vector-borne diseases                                      | Annual incidence |
|------------------------------------------------------------|------------------|
| Malaria                                                    | 200 million      |
| Dengue fever                                               | Following close behind |

Since their discovery, numerous groups have identified the role of NLRs in the recognition of self-derived danger associated molecular patterns (DAMPs), such as ATP, and pathogen associated molecular patterns (PAMPs), such as those from fungi, bacteria, and viruses (Strigwol et al., 2012). However, the association between NLRs and vector-borne pathogens still remains unclear. Only recently have researchers drawn attention to the detection of these pathogens by NLRs, even more ambiguous is the connection between salivary proteins and NLRs.

Here, we will address what occurs once a crucial barrier, the skin, is breached by an arthropod vector. We will discuss the subsequent recognition of key vector-borne pathogen by NLRs, and potential mechanisms by which salivary proteins may modulate this interaction. Though not all-encompassing, our focus is on acknowledging major examples by which saliva can modify immunity during infection. For a more comprehensive discussion about proteinaceous and non-proteinaceous salivary molecules, and their function during arthropod feeding, the reader is referred to accompanying reviews in this thematic research topic.

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| Disease                          | Pathogen                      | Vector                        | Number of affected individuals | Mortality | Nod-like receptor(s) | Reference                                                                 |
|---------------------------------|-------------------------------|-------------------------------|--------------------------------|-----------|---------------------|---------------------------------------------------------------------------|
| 1. Malaria                      | *Plasmodium* spp.             | Anopheles gambiae             | 216 million                     | 655,000   | NLRP3               | Ockenhouse et al. (2006), Coban et al. (2007), Dostert et al. (2009),    |
|                                 |                               |                               |                                |           | Nod1, Nod2          | Finney et al. (2008), Griffith et al. (2009), Shio et al. (2009),         |
|                                 |                               |                               |                                |           |                     | World Health Organization (2013a)                                        |
| 2. Dengue fever                 | Dengue virus                  | *Aedes aegypti, Aedes albopictus* | 10 million annually            | 22,000    | NLRP3               | World Health Organization (2013b), Centers for Disease Control and        |
|                                 |                               |                               |                                |           |                     | Prevention (2012a), Wu et al. (2013)                                      |
| 3. West Nile neuroinvasive      | West Nile virus               | Culex quinquefasciatus        | *                              | *         | NLRP3               | Demers et al. (2009), World Health Organization (2013a),                |
| disease                         |                               |                               |                                |           |                     | Kaushik et al. (2012), Ramos et al. (2012), Centers for Disease Control  |
|                                 |                               |                               |                                |           |                     | and Prevention (2013b)                                                    |
| 4. Leishmaniasis                | *Leishmania* spp.             |                               | 12–15 million                   | 60,000    | NLRP3               | Centers for Disease Control and Prevention (2013b), Lima-Junior et al.  |
|                                 |                               |                               |                                |           |                     | (2013), Sah et al. (2013)                                                |
| 5. Chagas disease               | Trypanosoma cruzi            |                               | 10 million                      | >10,000   | Nod1, NLRC4         | Silva et al. (2010), Aoki et al. (2012), Centers for Disease Control    |
|                                 |                               |                               |                                |           |                     | and Prevention (2013b), World Health Organization (2013a)                |
| 6. Lyme Borreliosis              | *Borrelia burgdorferi*        | Ixodes spp.                   | 11,000**                       | 1**       | Nod2                | Lindgren and Jaenson (2006), Ouzou et al. (2018), Wilmanski et al. (2018), |
|                                 |                               |                               |                                |           |                     | Liu et al. (2009), Berendes et al. (2011), Oosting et al. (2011),        |
|                                 |                               |                               |                                |           |                     | Patricki-Oswaj et al. (2011), Centers for Disease Control and Prevention  |
|                                 |                               |                               |                                |           |                     | (2013b), The New York Times (2013)                                      |
| 7. Plague                       | *Yersinia pestis*             | Xenopsylla cheopis            | 1,000–3,000 annually           | 80–300    | NLRP12              | Fenwerta et al. (2009), Brodsky et al. (2010), Zheng et al. (2011),      |
|                                 |                               |                               |                                |           |                     | Centers for Disease Control and Prevention (2012d), Vladimir et al. (2012), |
|                                 |                               |                               |                                |           |                     | Healthline (2013)                                                         |
| 8. Human granulocytic anaplasmosis | *Anaplasma* spp.              | Ixodes spp.                   | 1,000 annually**               | <10***    | NLRC4               | Pedra et al. (2007), Centers for Disease Control and Prevention (2013d)  |
| 9. Tularemia                     | Francisella tularensis        | Dermacentor spp., Amblyomma americanum | 130*** | 1–29*** | AW2               | Fernandes-Almanni et al. (2010), Alain et al. (2011), Centers for Disease |
|                                 |                               |                               | 500,000                          |           |                     | Control and Prevention (2014b), Center for Infectious Disease Research    |
|                                 |                               |                               |                                |           |                     | and Policy (2013), MD Guidelines (2013), Medscape (2013)                 |
| 10. Yellow fever                 | Yellow fever virus            | *Aedes aegypti*               | 300,000                         | 30,000    | NLRC4?              | Gauthier et al. (2018), Centers for Disease Control and Prevention (2011a, |
|                                 |                               |                               |                                |           |                     | World Health Organization (2013e)                                       |
| 11. Lymphatic filariasis         | *Wuchereria* spp., *Brugia* spp. |                               | 120 million                     | —         | Nod1, Nod2          | Babu et al. (2009), Centers for Disease Control and Prevention (2013a)   |
|                                 |                               |                               |                                |           |                     | —                                                                          |

*Estimates are not available.
**Estimates in the United States and Europe.
***Estimates in the United States.
—Not applicable.
? Potential association, needs further confirmation.
ARTHROPOD SALIVA AND SALIVARY PROTEINS

Hematophagous arthropods have developed ways to promote the extraction of blood from their hosts while evading detection. The penetration of an arthropod mouthpart into the mammalian host promotes the release of saliva and allows for the acquisition of a blood meal. Though some components of saliva are ubiquitous to all arthropods, specific molecules for different vectors have also been reported (Mans and Francischielli, 2011). For over a hundred years, researchers have identified and dissected the components of saliva and found it to contain anti-hemostatic and anti-inflammatory properties (Sabattani, 1899). In order to maintain a fluid supply of blood, salivary proteins act as vasodilators, inhibitors of platelet activity, and anti-coagulants (Champagne, 2005). To avoid recognition by the host, saliva not only modulates the inflammatory response, but it can also inhibit immune signaling (Chmelař et al., 2012). Arthropod saliva is composed of a plethora of salivary proteins that possess unique immunomodulatory functions (Table 2). Effects of tick saliva can be seen in a range of immune cell types, such as macrophages, neutrophils, T cells, B cells, and others (Gillespie et al., 2006; Titus et al., 2006; Chen et al., 2012). Salivary proteins with immunomodulatory properties from a myriad of arthropods, include but are not limited to: Rbohinsus protease, Rhipicephalus appendiculatus, Lutzomyia longipalpis, Aedes aegypti, and Aedes aegypti and Anopheles gambiae have been described. These proteins do not simply target one immune constituent but rather they span the gamut of cellular and molecular immunity.

An example of an immunomodulatory molecule in saliva is evasin. This protein manipulates immune signaling by binding key chemokines, thus, inhibiting the production of cytokines (Frauenschuh et al., 2007; Déruaz et al., 2008). The tick proteins ISL929, ISL1373, sialostatin L, IRS-2, IR-LBP, and TSLP1 all target neutrophils, usually the first immune cell to respond to a pathogen (Kotsyfakis et al., 2006, 2007; Beaufays et al., 2008; Gao et al., 2009; Sá-Nunes et al., 2009; Chmelař et al., 2011; Schuitt et al., 2011). Antigen presenting cells are the focus of the following salivary molecules: japonin, sialostatin L, PG2, IRS, Salp15, Ado, and maxadilan (Gillespie et al., 2000; Anguita et al., 2002; Leboulle et al., 2002; Garg et al., 2006; Kotsyfakis et al., 2006, 2007; Hovius et al., 2008; Schuitt et al., 2008; Prevot et al., 2009; Sá-Nunes et al., 2009; Berende et al., 2010; Fontaine et al., 2011). Increased infectivity in the presence of arthropod saliva has been shown for pathogens transmitted by sandflies, mosquitoes and ticks (Titus et al., 2006). Specifically, mosquito saliva enhances transmission of malaria parasites (Vaughan et al., 1999; West Nile (Sterr et al., 2011), La Crosse (Ostorio et al., 1996) and Cache Valley (Edwards et al., 1998) viruses. Similarly, tick saliva counteracts host-derived inflammation (Francischetti et al., 2009; Fontaine et al., 2011) by impairing the function of innate and adaptive immune cells (de Silva et al., 2009), and inhibiting cytokine secretion (Fontaine et al., 2011). Borellia burgdorferi – the Lyme disease agent - appears shielded by a salivary protein called Salp15 from the tick L. scapularis, and in turn, protected from antibody-mediated killing (Ramamoorthi et al., 2005) and dendritic cell function (Valenzuela et al., 2000; Hovius et al., 2008). However, this effect is not unique to Salp15 because sialostatin L2, another protein, also facilitates pathogen transmission at the skin site (Kotsyfakis et al., 2010). Interestingly, in the Aedes aegypti mosquito model, saliva appears to protect dendritic cells from infection with dengue virus as vethe (Linder et al., 2004).

An intriguing aspect of the pathogen-saliva interaction lies in the response of the skin to infection (Frischknecht, 2007; Kruse et al., 2009). During the infectious blood meal, the arthropod mouthpart dilacerates and penetrates the epidermis and reaches the dermis. The skin injury leads to a local inflammatory response involving secretion of chemokines, cytokines, and antimicrobial molecules as well as dermal mast cell degranulation, fluid
| Protein component | Vector | Cellular | Molecular | Reference |
|-------------------|--------|----------|-----------|-----------|
| ISL129            | I. scapularis | Neutrophils | ↓ Superoxide production | Guo et al. (2009) |
| ISL173            | I. scapularis | β2-integrins | | |
| ISAC              | I. scapularis | Complement | Disassociates C3 convertase | Valenzuela et al. (2000), Soares et al. (2009) |
| IL2 binding protein | I. scapularis | T cells | Binds IL2 | Gillespie et al. (2001) |
| Salp 21D          | I. scapularis | | Catalyzes the reduction of hydrogen peroxide with glutathione and glutathione reductase (antioxidant) | Das et al. (2001) |
| Salp30            | I. scapularis | Complement | Disassociates C3 convertase | Tyson et al. (2007), Tyson et al. (2008) |
| Csalastatin L     | I. scapularis | Neutrophils, dendritic cells, mast cells | ↓ Neutrophil influx, CD80/86, IL-12p70, TNF-α, MHC II, cathespins L, IL-12 T cell proliferation | Kotsyfakis et al. (2008), Kotsyfakis et al. (2007), Sá-Nunes et al. (2009), Horka et al. (2012) |
| Il2MAse           | I. scapularis | T cells | ↓ IL-4 | Alarcon-Chaidez et al. (2009) |
| PGEs              | I. scapularis | Dendritic cells | ↓ IL-12, TNF-α, CD40, inhibitor of differentiation | Sá-Nunes et al. (2007), Oliveira et al. (2011) |
| Histamine release factor (HRF) | Dermacentor variabilis | Basophils, mast cells | Release of histamine | Dai et al. (2010), Malta et al. (2003) |
| DAP26             | Dermacentor andersoni | T cells | | |
| IRS-2             | I. ricinus | Neutrophils | Inhibits cathepsin G and chymase | Chimalar et al. (2011) |
| IRAC1 and II      | I. ricinus | Complement | Disassociates C3 convertase | Schroeder et al. (2007) |
| IRF               | I. ricinus | Monocytes, macrophages, T cells | ↓ TNFα and IFNγ | Pavot et al. (2008), Fontaine et al. (2011) |
| Ir-LBP            | I. ricinus | Neutrophils, monocytes, B cells | Binds leukotriene B4 | Beauchesne et al. (2008) |
| BIP                | I. ricinus | B cells | Inhibits B cell activation | Hannier et al. (2004) |
| TSLP               | Haemagogus | Complement, neutrophils | Inhibits mannose-binding lectin | Schuji et al. (2011) |
| Salp/15           | Haemagogus | Dendritic cells, T cells, complement | Ra-1/MEK activation | Huix et al. (2008), Anguita et al. (2002), Garg et al. (2008), Berende et al. (2010) |
| Histamine binding proteins (HBP) | Rhodnius prolixus | Basophils, mast cells | ↓ T cell activation and IL-2 | Piessen et al. (1999), Santamati et al. (2002), Andersen et al. (2009) |
| Lipocalins         | | | | |

(Continued)
| Protein component | Vector | Cellular | Molecular | Reference |
|-------------------|--------|----------|-----------|-----------|
| Nitrophorins      | Rh. prolixus | IgG | Binds histamine | Gazit-Lapin et al. (2012) |
| IgGBP             | Ixodes spp | IgG | Binds IgG | Wang and Nuttall (1995), Wang and Nuttall (1998), Wang et al. (1998) |
| Maxadilan         | Lutzomyia longipalpis | T cells, macrophages | ↑ Nitric oxide, TNF-α, ↓ Prostaglandin E2, IL-10, IL-6 | Gillespie et al. (2000) |
| Adenosine and adenosine monophosphate | Rh. appendiculatus | T cells, macrophages, NK cells, dendritic cells | ↑ Nitric oxide and IFN-γ | Hitch and Titus (1995), Katz et al. (2003), Oliveira et al. (2011) |
| Evasin-1, -3, -4  | R. sanguineus | Tick spp | Binds chemokines | Frauenschuh et al. (2005), Dinaz et al. (2008) |
| Ado               | R. sanguineus | Dendritic cells | Induce cAMP/PKA to reduce cytokine production | Oliveira et al. (2015) |
| D7 proteins       | Aedes aegypti | Anopheles gambiæ | Binds histamine | Calvo et al. (2006) |
| Sialokinins       | Aedes aegypti | T cell | Binds histamine | Zeitmaster et al. (1999) |
extravasation and neutrophil influx (Boulanger et al., 2006; Rubin and Strayer, 2012). This response has a major impact on furthering the establishment of infection because pathogen inoculation follows an arthropod bite. Cellular responses promoted by mast cells, neutrophils, dendritic cells and infiltrated macrophages aim not only to repair the skin injury, but also to remove a microbial threat during vector transmission. This series of steps also reverberates on the later activation of adaptive immunity and recruitment of cell types that may promote pathogen propagation in the host, especially for intracellular microorganisms.

**NOD-LIKE RECEPTORS**

Approximately two decades ago, a group of sensors were added to the pattern recognition receptor family, expanding what was known about intracellular recognition of endogenous and exogenous molecules (Inohara et al., 1999). NLRs are appropriately named due to their characteristic nucleotide binding and oligomerization domain (NOD). NLRs may also contain leucine-rich repeats (LRR) at their C-terminus and a variable effector domain at their N-terminal end, all of which play a role in pathogen recognition and immunity (Moreira and Zamboni, 2012). Although 22 human and 30 mouse NLRs have been discovered, to stay within the scope of our review, we will only address those that have been associated with crucial vector-borne diseases (Table 1; Schroder and Tschopp, 2010; Moreira and Zamboni, 2012).

**NOD1 AND NOD2**

Nod1 and Nod2 are crucial for the recognition of peptidoglycan components (Figure 1). Signaling through Nod1 and Nod2 begins with the initiation of Nod1 by D-glutamyl-meso-diaminopimelic acid (DAP) and/or Nod2 by muramyl dipeptide (MDP; Chamillard et al., 2003; Girardin et al., 2003a). While the NOD portion acts as a receiver in the presence of these pathogenic molecules, the effector CARD domain(s) of Nod1 and Nod2 perpetuate the signal transduction by interacting with receptor-interacting serine/threonine protein kinase-2 (RIP2/RICK; Kobayashi et al., 2002). Classically, RIP2/RICK is polyubiquitinated by TNF receptor-associated factor 6 (TRAF6), this signal is required for the recruitment of the adaptor molecules TAK1-binding protein 2 and 3 (TAB2/3) and activation of TAK1 (Besse et al., 2007). Together this forms the TGF-β-activated kinase 1 (TAK1) complex that promotes the degradation of the inhibitor of nuclear factor (NF)-κB, thereby allowing the translocation of NF-κB into the nucleus. This is only one signaling cascade that is activated by Nod1/2, the mitogen-activated protein kinases (MAPK) pathway is another branch that can be driven by these NLRs (Pauleau and Murray, 2003; Park et al., 2007). Nod1 and Nod2 can activate three key MAPK: extracellular signal-related kinases (ERK), jun amino-terminal kinases (JNK), and p38. The latter two can also be signaled by Nod2 through the adaptor caspase recruitment domain-containing protein 9 (CARD9; Colonna, 2007). The activation of each pathway results in the expression of pro-inflammatory mediators, such as cytokines and antimicrobial peptides. Nod1 and Nod2 can be regulated by A20-mediated ubiquitin modifications and caspase-12 inhibition of RIPK2-TRAF6 complex formation (Hinoitumatsu et al., 2008; LeBlanc et al., 2008).

Recent developments have identified a new role for Nod1 and Nod2 in the recognition of pathogens lacking peptidoglycan. Studies have reported that Nod proteins can respond to protozoan parasites, like Toxoplasma gondii (Shaw et al., 2009). Surprisingly, Nod2 has been shown to respond to single-stranded RNA (Sabbah et al., 2009). The activation of Nod2 in this case is dependent upon the mitochondrial antiviral signaling protein MAVS and results in the facilitation of interferon regulatory factor 3 (IRF3) mediated interferon (IFN) gene expression. Another protective measure that Nod1 and Nod2 are involved in is the induction of autophagy related 16-Like 1 (ATG16L1)-dependent autophagy in response to bacterial invasion, such as the case with Listeria monocytogenes (Travassos et al., 2010). Nod1 and Nod2 are gradually revealing their complex nature. Most commonly acknowledged as a sensor for peptidoglycan molecules, there is also debate that Nod1 and Nod2 may possess regulatory abilities (Murray, 2005). Studies regarding Nod1 and Nod2 function are continuously being assessed in order to develop a comprehensive understanding of these key proteins.

**INFLAMMASOME**

The inflammasome is a potent innate immune structure characterized by its ability to activate pro-caspase-1 in response to PAMPs or DAMPs (Figure 2). The inflammasome scaffold is created by the oligomerization and recruitment of several proteins. One component, the receptor, defines the inflammasome; it can either originate from the NLR family or contain the HIN-200 domain (Lamkanfi and Dixit, 2011). Depending upon the receptor type, the adaptor molecule ASC may or may not be implicated. Since ASC possesses both a pyrin and CARD domain, it facilitates the association between the CARD-containing pro-caspase-1 and a receptor lacking the CARD domain (Schroder and Tschopp, 2010). Classically, inflammasome-mediated cytokine secretion is the product of a two-tiered signaling system (Figure 2; Franchi et al., 2012). The first signal concerns the activation the NF-κB pathway in order to promote the gene expression of IL-1β and IL-18 and other pro-inflammatory genes, such as Nlrp3. The second signal involves the assembly of the inflammasome, which results in the secretion of the abovementioned cytokines. Common to all canonical inflammasomes is the presence of the enzyme pro-caspase-1. Caspase-1 is responsible for the maturation of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18 and the inflammation-related cell death process termed pyroptosis (Davis et al., 2011). Other caspases have also been shown to be involved in the inflammasome-signaling pathway. Caspase-11 was recently discovered to modulate caspase-1 in response to certain Gram-negative bacteria, such as Citrobacter rodentium (Kayagaki et al., 2011; Rathinam et al., 2012). Another non-canonical inflammasome involvesASC and CASP-8 is a negative regulator of pro-inflammatory NLRP3 inflammasome activity (Kang et al., 2013). During macrophage infection with Francisella tularensis subspecies novicida, caspase-8 can form a complex with AIM2 and ASC (Pierini et al., 2012). Caspase-8 associates with dendin-1 in the presence of fungi and mycobacteria (Gringhuis et al., 2012). Caspase-8 can also bind with an inflammasome, namely NLRP1 (Martinon et al., 2002). Not only can caspases bind to the inflammasome, they can also be cleaved by the caspase-1 component of
FIGURE 1 | Nod1 and Nod2 signaling. Nod1 and Nod2 are activated by the pathogenic components iE-DAP and MDP, respectively. Recognition of PAMPs triggers TRAF6, RICK/RIP2, TAB 2/3, and TAK1. These can signal downstream to two major signaling networks: (1) MAP kinase and the (2) NF-κB pathways. Transcription factors, such as AP1 and the NF-κB complex (p50/p65), translocate to the nucleus to promote the transcription of pro-inflammatory cytokines and antimicrobial peptides.

the protein scaffold, similar to IL-1β. This phenomenon is seen in caspase-7 activation by caspase-1 during Legionella pneumophila infection (Akhter et al., 2009). Taken together, multiple checkpoints are crucial for inflammasome regulation due to its strength as a pro-inflammatory initiator.

RECOGNITION OF VECTOR-BORNE PATHOGENS BY NLRs

Medically relevant vector-borne pathogens have plagued the health of individuals all over the globe (Table 1). Even more concerning is the rate at which these diseases are escalating and claiming the lives of thousands of people (Hotez et al., 2009). The relationship between these daunting pathogens and recognition by NLRs is not fully understood.

NOD1 AND NOD2

Being one of the first NLRs discovered, many studies have been aimed to the role of Nod1 in the context of bacterial pathogenesis (Chamaillard et al., 2003; Girardin et al., 2003b; Ray et al., 2009). Research involving the sensing of bacteria in the intracellular compartment of a wide range of cell types has dominated the Nod1 field. However, Silva et al. (2010) were able to classify Nod1 as a crucial component for the resistance to the parasite Trypanosoma cruzi. T. cruzi is transmitted by the kissing bug, Rhodnius prolixus, primarily in Latin American countries. It is the causative agent of Chagas disease, which can be characterized by fever, edema, or inflammation in the heart and/or brain (Centers for Disease Control and Prevention, 2010). These authors observed, through the use of Nod1−/− and Nod2−/− mice, that IL-12 and TNF-α levels were reduced after infection. Since nitric oxide is a key factor for T. cruzi containment, interferon gamma (IFN-γ) was used to treat Nod1−/− and Nod2−/− bone marrow-derived macrophages. This resulted in a high load of parasites for the Nod1−/− macrophage, highlighting the specificity of Nod1, not Nod2, for T. cruzi infection.

B. burgdorferi is a spirochete transmitted by Ixodes spp. Infection by B. burgdorferi causes Lyme disease, the most common vector-borne disease north of the equator (Parola and Raoult, 2001; Lindgren and Jaenson, 2006; Berende et al., 2010). Lyme disease can manifest into a three stage infection: (1) erythema migrans is characterized by localized infection, (2) early disseminated infection results in inflamed joints and CNS, and (3) persistent infection, which consists of chronic inflammation of joints and the CNS and sensory polyneuropathy (Berende et al., 2010). It has been established that TLR2 plays an important role in the recognition of B. burgdorferi. Recent evidence points to Nod2 as an important factor in the sensing of this pathogenic spirochete (Petnicki-Ocwieja et al., 2011). Nod2 is upregulated in mouse microglia and individuals with mutated Nod2 were not
able to mount an efficient cytokine response after infection with *B. burgdorferi* (Sterka et al., 2006; Oosting et al., 2010). The plague causing vector-borne pathogen *Yersinia* has also been shown to be recognized by Nod2 (Verwold et al., 2009).

Nod1 and Nod2 also appear to possess redundancy because they are able to detect similar arthropod-borne pathogens. Individuals who encountered an antigenic component from the *Brugia* malayi adult demonstrated an increase in Nod1 and Nod2 expression (Balu et al., 2009). *Brugia* and *Wuchereria bancrofti* species can cause lymphatic filariasis which can manifest as elephantiasis, lymphedema, and hydrocele (Centers for Disease Control and Prevention, 2013a). Independently, the obligate intracellular pathogen *Anaplasma phagocytophilum*, transmitted by *Ixodes* spp., is involved in the increased expression of Rip2, a critical molecule in Nod1 and Nod2 signaling (Sukumaran et al., 2012). More importantly, the ability for Rip2−/− mice to control and clear *A. phagocytophilum* was severely hindered. The *Plasmodium* parasite is also detected by Nod proteins (Coban et al., 2007). Certain instances result in upregulation of Nod2 in the presence of *Plasmodium* sporozoites, while in other cases Nod1 and Nod2 confer changes in cytokines but do not promote survival after infection (Ockenhouse et al., 2006; Finney et al., 2009).

**NLRP1 INFLAMMASOME**

The NLRP1 inflammasome was the first to be characterized (Martinon et al., 2002). NLRP1 has been shown to recognize the *Bacillus anthracis* lethal toxin and, like Nod2, MDP (Boyden and Dietrich, 2006; Faustin et al., 2007). The activation of pro-caspase-1 activity elicited by these bacterial components is distinct. Cleavage of the NLRP1 inflammasome by the lethal toxin is required for inflammasome activation, as mutation of NLRP1 demonstrates reduced caspase-1 activation (Levinsohn...
Wu et al. (2013) elucidated that, in human macrophages, dengue virus is transmitted by the mosquito Aedes aegypti. Inoculation of yellow fever virus by a mosquito can lead to mild reactions, such as fever, ache, and nausea, or more serious ones, such as organ failure (Centers for Disease Control and Prevention, 2011a). More studies need to be done in order to clarify what components trigger a NLRP1 inflammasome response to the yellow fever virus.

**NLRP1 INFLAMMASOME**

Of all NLRs, NLRP3, currently, has the most known associations with vector-borne diseases. It is well known that NLRP3 is triggered by three signals: (1) potassium efflux, (2) phospho-tyrosine, and (3) ROS production (Schroder and Tschopp, 2010). Recently, mitochondrial DNA and calcium levels were suggested to be other activators of the NLRP3 inflammasome (Rossel et al., 2012; Shimada et al., 2012). The malarial parasite has demonstrated the ability to activate the NLRP3 inflammasome through the crystalline particle hemozoin (Doustert et al., 2009; Gràffith et al., 2009; Shi et al., 2009). Monosodium urate (uric acid), together with hemozoin, has also been reported to result in pro-inflammatory reactions through the MAPK signaling pathway (Gràffith et al., 2009; Shi et al., 2009). Hemozoin is a byproduct of heme detoxification by Plasmodium. The phagocytosis of hemozoin initiates signals through spleen tyrosine kinase (Syk) and v-yes-1 Yamaguchi sarcoma viral related oncogene homolog (LYN), tyrosine kinases, in order to initiate the NLRP3 inflammasome (Shio et al., 2009). Another mosquito-borne pathogen, the dengue virus is transmitted by A. aegypti or A. albopictus. Dengue virus can cause dengue fever or dengue shock syndrome. As was previously mentioned, the NLRP1 inflammasome mediated IL-1β secretion. Additionally, IL-1β combined with type I IFN results in the reduction of dengue infection (Centers for Disease Control and Prevention, 2013b). In murine macrophages, Sani et al. (2013) found that the expression of NLRP3 is increased after exposure to Leishmania major. Furthermore, Lima-Junior et al. (2013) confirmed NLRP3 activation after L. amazonensis infection that led to the protective restriction of parasites. Another non-mosquito-borne pathogen is Francisella tularensis, which is commonly transmitted by ticks. Tularemia can cause sepsis and respiratory complications. Uniquely in human leukemia cell line (THP-1) but not in mouse cells, Francisella is capable of activating the NLRP3 inflammasome (Atianand et al., 2011). Supporting this, the use of NLRP3 inflammasome inhibitors and NLRP3 siRNA revealed that the IL-1β secretion in response to Francisella was lessened. The type III secretion system (T3SS) from Yersinia pestis is also able to activate the NLRP3 inflammasome in vitro (Bredsky et al., 2010). With the addition of K3, the NLRP3 inflammasome activity was nullified. However, other inflammasomes are also involved in the detection of Yersinia as well. Although nod2 has been acknowledged as a protein that recognizes Bordetella, there is controversy on whether inflammasomes are activated in response to this vector-borne pathogen. Though independent of the NLRP3 inflammasome, multiple groups have found that caspase-1 is activated after exposure to Bordetella while another group was unable to detect caspase-1 dependence (Cruz et al., 2008; Liu et al., 2009; Oostrag et al., 2011).

**NLRC4 INFLAMMASOME**

The CARD-containing NLRC4 inflammasome mediates pro-inflammatory responses to the recognition of flagellin and type III/IV secretion systems from gram-negative bacteria (Schroder and Tschopp, 2010). NLRC4, also called IPAF inflammasome confers protection against bacteria, such as Salmonella typhimurium and Pseudomonas aeruginosa (Miao et al., 2008). It is also able to directly and indirectly associate with pro-caspase-1, via its CARD domain or the adaptor molecule ASC, respectively. Additionally, another level of specificity is added by the NLRC4 interaction with NAIP5 or NAIP2, which modifies NLRC4 activation in response to flagellin and the type III secretion system (T3SS), respectively (Zhao et al., 2011). As of yet, NLRC4 has been implicated in two vector-borne illnesses, Human granulocytic anaplasmosis and Leishmaniasis. Nlrc4−/− mice showed heightened susceptibility to Anaplasma phagocytophilum and decreased levels of IL-18 relative to the wild-type. However, the effect of NLRC4 was partial; thereby, suggesting additional mechanisms of inflammasome activation (Pedra et al., 2007). Sani et al. (2013) found that Nlrc4 expression increased after exposing macrophages to L. major. As was previously mentioned, Y. pestis is able to activate several inflammasomes, and it is also able to combat this recognition with effector proteins (Bredsky et al., 2010). The NLR4 inflammasome is another protein complex involved in the recognition of Y. pestis T3SS (Bredsky et al., 2010).

**NLRP12 INFLAMMASOME**

The NLRP12 inflammasome is a member of the NLR family that has been suggested to reduce and potentiate inflammatory cytokine secretion (Vang et al., 2002; Lich et al., 2008; Arthur et al., 2010; Zaki et al., 2011; Allen et al., 2012). Currently, NLRP12 has been shown to play a role in hereditary period fever syndromes, but very little is known with respect to vector-borne diseases. Vladimir et al. (2012) discovered that NLRP12 regulates IL-1β secretion in response to Y. pestis. More specifically, after infection of Nlrc12−/− mice with Y. pestis, they observed an increase in bacterial load and death which was associated with decreased levels of IL-18 and IL-1β.
NON-NLR INFLAMMASOME

The AIM2 (absent in melanoma 2) inflammasome does not contain the typical NLR domain as do other inflammasomes. Rather, it carries the HIN-200 domain (Case, 2011). In particular, AIM2 is known for sensing double stranded DNA in the cytosol (Bauerfeind et al., 2011). The formation of the AIM2 inflammasome consists of the AIM2 receptor, ASC, and pro-caspase-1. Upon recognition of cytoplasmic DNA, AIM2 is able to coordinate pyroptosis and the release of IL-1β and IL-18 via pro-caspase-1 maturation (Doris et al., 2011). Of the vector-borne pathogens discussed in this review, AIM2 is able to recognize F. tularensis in mouse macrophages (Fernandes-Alnemri et al., 2010). Moreover, IFR3 is needed for a type I IFN response to help mount an effective AIM2-dependent activation after F. tularensis infection (Fernandes-Alnemri et al., 2010).

CONCLUDING REMARKS

The importance of NLRs and vector saliva has been demonstrated through numerous elaborate studies. Further research in this area has the potential to reveal more intricate relationships, as well as the salivary effectors that can modulate these interactions. This review has highlighted the role of NLRs and salivary components in vector-borne diseases. Due to the vast amount of literature available in the field of arthropod saliva and the diverse mechanisms of vertebrate-host immunomodulation, we elected to focus only on those pertinent to the vectors discussed here. Elucidating the mechanisms behind NLR recognition and salivary modulation of pathogenic agents will shed light on the fundamental basis of pathogen-vector-host interactions. Additionally, it should provide novel targets for therapeutic intervention of devastating vector-borne diseases.

Based on our current knowledge, we suggest that arthropod saliva could regulate NLR inflammasome activity during pathogen transmission or after infection. Vector saliva has been shown to minimize reactive oxygen species (ROS, Guo et al., 2009). ROS has been identified as an agonist for inflammasomes; therefore salivary proteins can potentially reduce ROS to decrease inflammasome activity. Another mechanism by which arthropod saliva can hinder the inflammasome is by acting on caspase-1. Caspase-1, the key enzymatic component of the inflammasome, is a member of the cysteine protease family. Salivary proteins have demonstrated the ability to target cysteine proteases, such as caspase-1. The role of salivary components regulating vector-borne pathogens and NLR interaction could allow us to gain a foothold on controlling these infectious diseases.

AUTHOR CONTRIBUTIONS

Olivia S. Sakhon, Maiara S. Severo, Michael Kotsyfakis, and Joao H. F. Pedra wrote the manuscript. Olivia S. Sakhon created the tables and figures.

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