

Master Biologie-Santé

UE Microbiologie-Pathologies

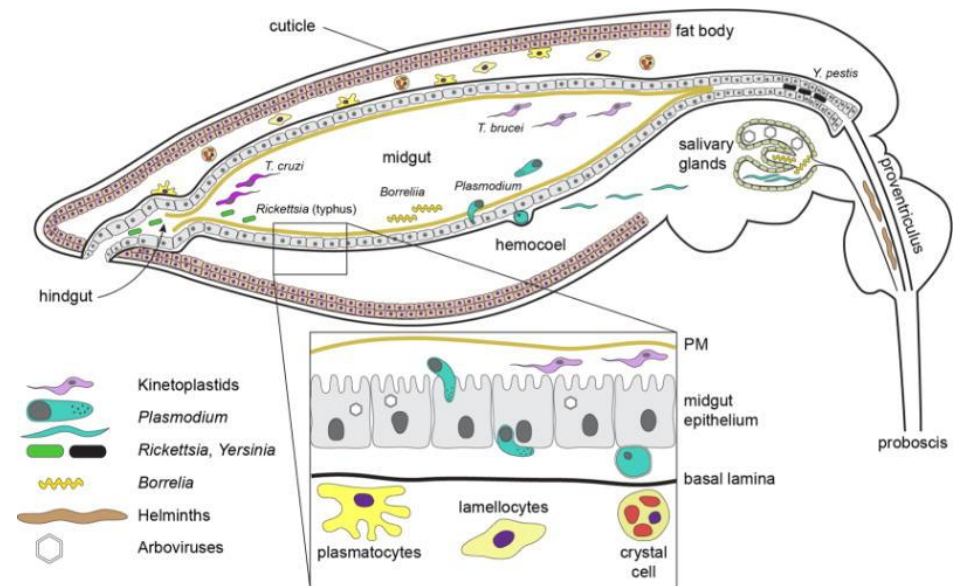
Rôle des vecteurs dans la
transmission des parasites :
Effet de la salive sur l'infection

Introduction

Table 1 Taxonomic classification of major vector-borne diseases

| Vectors | | Diseases |
|-----------|-----------------|----------------------|
| Order | Family | |
| Diptera | Culicidae | <i>Anopheles</i> |
| | | <i>Culex</i> |
| | | <i>Aedes</i> |
| | | |
| | | |
| | Psychodidae | <i>Phlebotomus</i> |
| | | <i>Lutzomyia</i> |
| | Glossinidae | <i>Glossina</i> |
| | Simuliidae | <i>Simulium</i> |
| | Tabanidae | <i>Tabanus</i> |
| Hemiptera | Reduviidae | <i>Triatoma</i> |
| Ixodida | Ixodidae | <i>Rhodnius</i> |
| | | <i>Amblyomma</i> |
| | | <i>Ixodes</i> |
| | Haemaphysalidae | <i>Haemaphysalis</i> |
| | | |
| | | |
| | Argasidae | <i>Ornithodoros</i> |

The taxonomic classification of the major hematophagous arthropod vectors described in the present review is given with their corresponding diseases.



Baxter et al.

Biochemistry. Author manuscript; available in PMC 2018 February 21.

leishmaniose

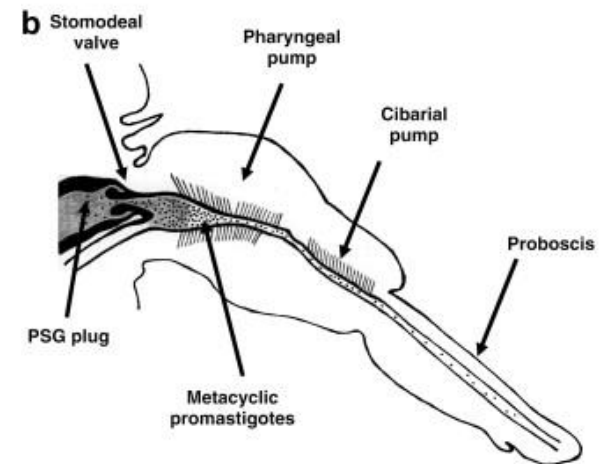
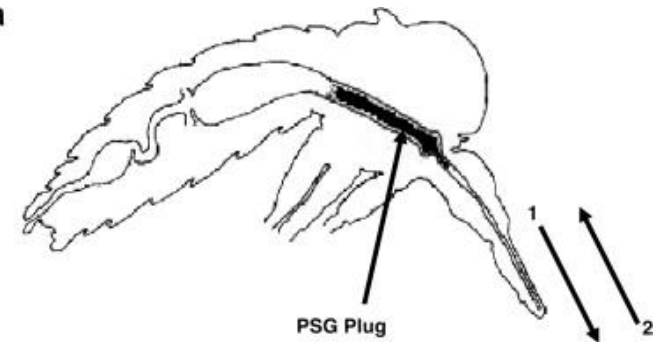
Table 1
Medically important species of phlebotomine sand fly and transmission of leishmaniasis

| Sand fly species | Geographical distribution | Species of <i>Leishmania</i> | Main disease(s) in humans | Transmission | Important mammalian hosts |
|--|---|--|---|------------------------|--|
| <i>Phlebotomus papatasi</i> , <i>Phlebotomus dubosqi</i> , <i>Phlebotomus salehi</i> | Central and West Asia, North Africa, Sahel of Africa, Central and West Africa | <i>Leishmania (Leishmania) major</i> | Cutaneous (oriental sore) | Rural zoonotic | Great gerbil (<i>Rhombomys opimus</i>), fat sand rat (<i>Psammomys obesus</i>) |
| <i>Phlebotomus sergenti</i> | Central and West Asia, North Africa | <i>Leishmania (Leishmania) tropica</i> | Cutaneous (oriental sore) | Urban anthroponotic | Humans, rock hyraxes |
| <i>Phlebotomus longipes</i> , <i>Phlebotomus pedifer</i> | Ethiopia, Kenya | <i>Leishmania (Leishmania) aethiopica</i> | Cutaneous diffuse cutaneous | Rural zoonotic | Rock hyraxes (<i>Heterohyrax brucei</i> , <i>Procavia</i> spp.) |
| <i>Phlebotomus argentipes</i> , <i>Phlebotomus orientalis</i> , <i>Phlebotomus martini</i> | Indian subcontinent, East Africa | <i>Leishmania (Leishmania) donovani</i> | Visceral (kala azar) | Epidemic anthroponotic | Humans |
| <i>Phlebotomus ariasi</i> , <i>Phlebotomus perniciosus</i> | Mediterranean basin, Central and West Asia | <i>Leishmania (Leishmania) infantum</i> | Infantile visceral | Zoonotic peridomestic | Domestic dog |
| <i>Lutzomyia longipalpis</i> | Central and South America | <i>L. (L.) infantum (syn. chagasi)</i> | Infantile visceral | Zoonotic peridomestic | Domestic dog, foxes (<i>Lycalopex vetulus</i> , <i>Cerdocyon thous</i>) |
| <i>Lutzomyia olmeca olmeca</i> | Central America | <i>Leishmania (Leishmania) mexicana</i> | Cutaneous (chiclero's ulcer) | Sylvatic zoonotic | Forest rodents (<i>Ototylomys phyllotis</i> + others) |
| <i>Lutzomyia flaviscutellata</i> | South America | <i>Leishmania (Leishmania) amazonensis</i> | Cutaneous | Sylvatic zoonotic | Forest rodents (<i>Proechimys</i> spp. + others) |
| <i>Lutzomyia wellcomei</i> , <i>Lutzomyia complexus</i> , <i>Lutzomyia carrerai</i> | Central and South America | <i>Leishmania (Viannia) braziliensis</i> | Cutaneous mucocutaneous (espundia) | Sylvatic zoonotic | Forest rodents (<i>Akodon</i> spp., <i>Proechimys</i> spp. + others) |
| <i>Lutzomyia peruensis</i> , <i>Lutzomyia verrucarum</i> | Peru | <i>Leishmania (Viannia) peruviana</i> | Cutaneous (uta) | Upland zoonotic | Reservoir unknown, dog? |
| <i>Lutzomyia umbratilis</i> | South America | <i>Leishmania (Viannia) guyanensis</i> | Cutaneous, often metastatic (pian-bois) | Sylvatic zoonotic | Sloth (<i>Choloepus didactylus</i>), anteater (<i>Tamandua tetradactyla</i>) |
| <i>Lutzomyia trapidoi</i> | Central America | <i>Leishmania (Viannia) panamensis</i> | Cutaneous | Sylvatic zoonotic | Sloth (<i>Choloepus hoffmanni</i>) |

Various species in the genus *Phlebotomus* are responsible for transmission of leishmaniasis in the Old World and *Lutzomyia* species in the New World. Each sand fly species typically transmits only one species of parasite and each parasite leads to a particular type of disease. Animal reservoirs are important for maintaining the life cycle of many *Leishmania* species and consequently transmission is frequently zoonotic and rural/sylvatic. Important exceptions are *Leishmania tropica* and *Leishmania donovani*, which are transmitted between human beings.

leishmaniose

- Transmission promastigotes : a
 - Nouveau monde : *Lutzomya*
 - Ancien monde : *Phlébotomus*
- Promastigote secretory gel
 - fPPG
- saliva



leishmaniose

- PSG :
 - Protéophosphoglycanes :
 - Cicatrisation accélérée chez la souris
 - Recrutement macrophages
 - Activation des macrophages
- Échappement parasite
- Amélioration infection

leishmaniose

- Salive
 - Composition
 - Rôle :
 - Hémostase
 - Inflammatoire
 - immunologique

leishmaniose saline : composition

Table 2
Sand fly salivary proteins with known biological activity.

| Sand fly salivary transcriptomes | Biological activities of salivary proteins (molecular weight) | | | | | | | | | | Anti-inflammatory /anti-arthritis |
|---|---|---|---|---|--|--|--|--|--|---|--|
| | Inhibitor of contact activation, heparin binding | Biogenic amine binding proteins | Anti-coagulant, inhibitor of factor Xa | Ecto ADPase, inhibitor of platelet aggregation | DNAse activity | Degradation of hyaluronan hydrolysis of chondroitin sulfates | Purine metabolism hydrolysis of adenosine | Vasodilator and inhibitor of platelet aggregation | Nucleotidase | Vasodilator | |
| | Small odorant binding protein (OBP) – like (~15 kDa) | Yellow protein (~45 kDa) | Lufaxin/ Lufaxin like (~32 kDa) | Apyrase (~36 kDa) | Endonuclease (~44 kDa) | Hyaluronidase (~42 kDa) | Adenosine deaminase (~56 kDa) | Adenosine | 5' Nucleotidase (~61 kDa) | Maxadilan peptide (6 kDa) | LJM111 |
| <i>Lu. longipalpis</i> (Valenzuela et al., 2004) | LJM04 | LJM11 ^a , LJM17 ^a , LJM111 ^a (Xu et al., 2011) | LJL143 (Lufaxin) ^a (Collin et al., 2012) | LuloAP ^a (Charlab et al., 1999) | LJL138 (Lundep) ^a (Chagas et al., 2014) | LuloHYA ^a (Cerna et al., 2002; Charlab et al., 1999; Rohousova et al., 2012) ^b | ADA ^a (Charlab et al., 1999) | | Lulo5NUC ^a (Charlab et al., 1999) | Maxadilan ^a (Lerner and Shoemaker, 1992) | LJM111 ^a (Crespan et al., 2012) |
| <i>Lu. intermedia</i> (De Moura et al., 2013) | Linb-7, 8, 28, 59 | Linb-21 | Linb-17 | Linb-35 | Linb-46 | Linb-54 | | | | Linb-147 | |
| <i>Lu. ayacuchensis</i> (Kato et al., 2013) | LayS32–37, 48–72 | LayS22–24, 117, 118 | LayS120–132 | LayS8–14, 16–21 | LayS147 | | | | | | |
| <i>P. papatasi</i> Tunisia (Abdeladhim et al., 2012) | PPTSP12–15 | PPTSP42, 44 | PPTSP34 ^b (Collin et al., 2012) | PPTSP36 ^b (Ribeiro et al., 1989b) | | ^b Cerna et al. (2002)) | ^b Ribeiro et al. (1999), Charlab et al. (1999), Carregaro et al. (2011) | Adenosine and 5'-AMP ^b (Ribeiro et al., 1999) | | | |
| <i>P. duboscqi</i> Mali (Kato et al., 2006) | PduM02–03, 06–07, 12, 31–32, 49–50, 57–58, 60, 62, 99 ^a (Alvarenga et al., 2013) | PduM10, 35 | PduM04–05 ^b (Collin et al., 2012) | PduM38–39 ^a (Hamasaki et al., 2009) | | ^b Cerna et al. (2002) | PduM73 | | | | |
| <i>P. duboscqi</i> Kenya (Kato et al., 2006) | PduK01–03, 40–42, 49, 56–58, 109–110 ^a (Alvarenga et al., 2013) | PduK04–06, 86 | PduK70 ^b (Collin et al., 2012) | PduK50 ^a (Hamasaki et al., 2009) | | ^b Cerna et al. (2002) | PduK60 | | | | |
| <i>P. sergenti</i> (Rohousova et al., 2012) | PsSP9–11, 14–15, 54–55 | PsSP18–20, 22, 26 | PsSP49 | PsSP40–42 | | ^b Cerna et al. (2002), Rohousova et al. (2012) | | | | | |
| <i>P. arabicus</i> (Hostomska et al., 2009) | PabSP2, 45, 63–64, 93, | PabSP26, 53 | PabSP34, 32 | PabSP39, 40–41 | PabSP49 | PabSP72 ^b (Rohousova et al., 2012) | | | | | |
| <i>P. argentipes</i> (Anderson et al., 2006) | PagSP01, 02, 07, 12, 13 | PagSP04 | PagSP09 | PagSP03 ^b (Ribeiro et al., 1989b) | PagSP11 | ^b Rohousova et al. (2012) | | Adenosine and 5'-AMP ^b (Ribeiro et al., 1999) | | | |
| <i>P. ariasi</i> (Oliveira et al., 2006) | ParSP03, 06, 08 | ParSP04, 04B | ParSP09 | ParSP01 | ParSP10 | | | | | | |
| <i>P. perniciosus</i> (Anderson et al., 2006) | PpeSP02, 09, 11 | PpeSP03, 03B | PpeSP06 | PpeSP01, 01B ^b (Ribeiro et al., 1989b) | PpeSP32 | ^b Rohousova et al. (2012) | | | | | |
| <i>P. perniciosus</i> Madrid Spain (Martin-Martin et al., 2013) | SP02, 09, 11 | SP03B | SP06 | SP01,01B ^b (Ribeiro et al., 1989b) | | ^b Rohousova et al. (2012) | | | | | |

(continued on next page)

leishmaniose

- Salive
 - Composition
 - Rôle :
 - Hémostase
 - Inflammatoire
 - immunologique

Leishmania : hémostase

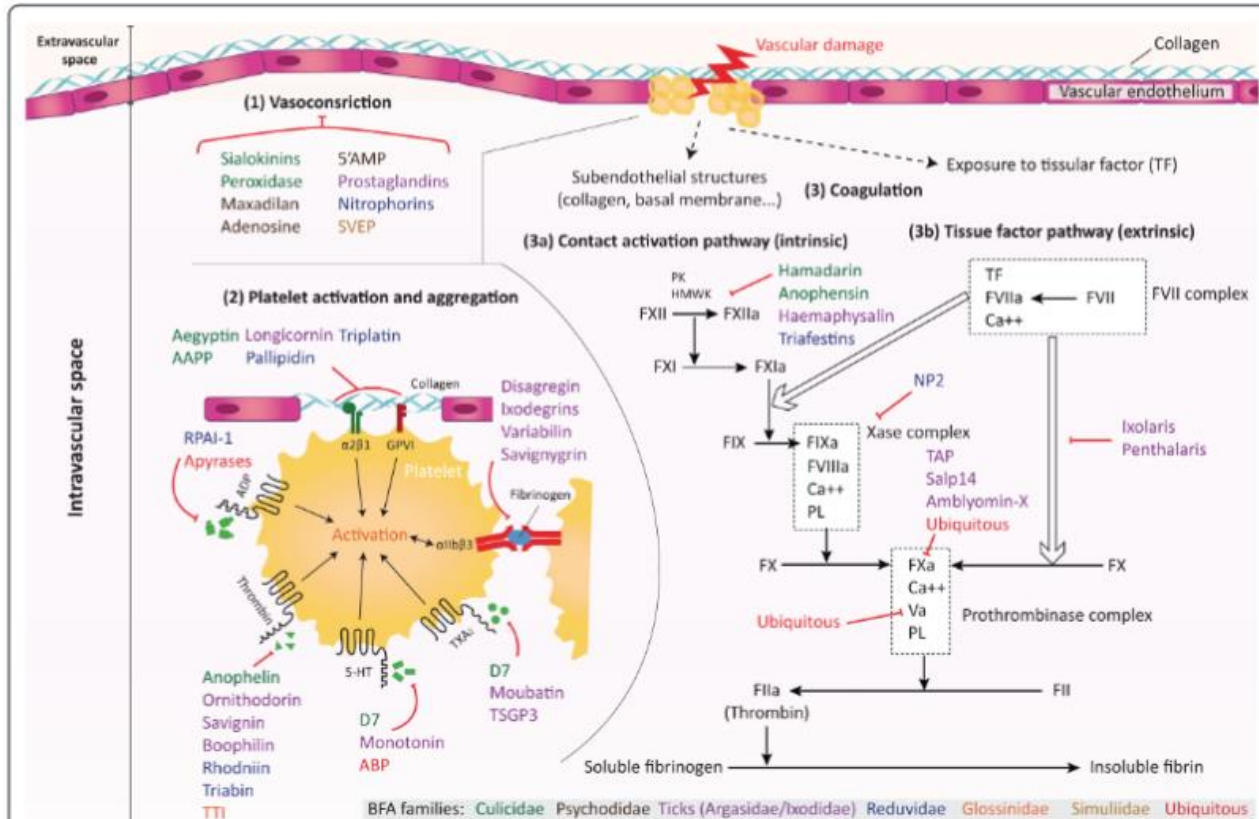
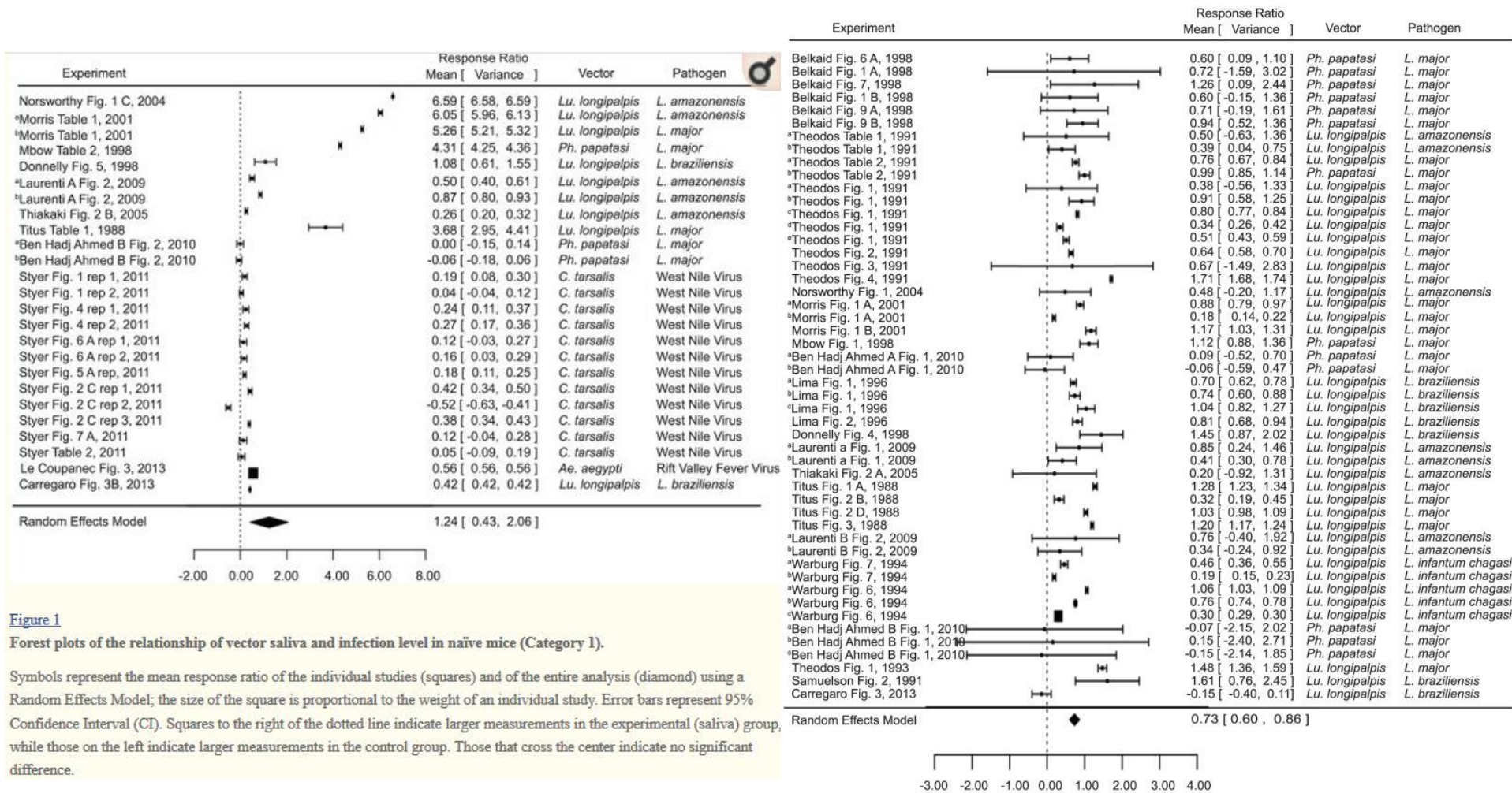


Figure 1 Schematic representation of arthropod salivary proteins acting on primary and secondary haemostasis. Haematophagous arthropods (HA) induce injuries to vascular endothelium when probing for a blood meal. The initial event of this vascular damage is vasoconstriction (1), which retards extravascular blood loss and enhances the adhesion of platelets to exposed subendothelial collagen. This adhesion activates platelets (2) and causes the release of platelet activation agonists (Adenosine diphosphate (ADP), Thrombin, Thromboxane A₂ (TXA₂), serotonin (5-HT)) as well as platelet membrane integrin receptor αIIbβ3. Fibrinogen binds to this receptor and crosslinks platelets to form a platelet plug. The blood coagulation cascade (3) is then initiated to strengthen the platelet plug with fibrin at the site of injury. The coagulation cascade is separated into two pathways converging into a common pathway. The contact activation pathway (intrinsic) involves high-molecular weight kininogen (HMWK), prekallikrein (PK), factor XII, factor XI and factor IX (3a), and the tissue factor pathway (extrinsic) involves the tissue factor and factor VII complex (3b). Both pathways lead to the activation of factor X. The common pathway leads to the generation of thrombin from prothrombin and the ultimate production of insoluble fibrin from fibrinogen. HA have evolved anti-haemostatic salivary proteins that inhibit specific agonists and factors of platelet aggregation and the blood coagulation cascade. The known actions of some HA salivary proteins listed in Additional file 1 are indicated. (Salivary protein affiliation to HA families is indicated by colour as represented on the bottom right corner legend).

leishmaniose

- Salive
 - Composition
 - Rôle :
 - Hémostase
 - Inflammatoire
 - immunologique

leishmaniose : conséquences cliniques



leishmaniose : conséquences cliniques

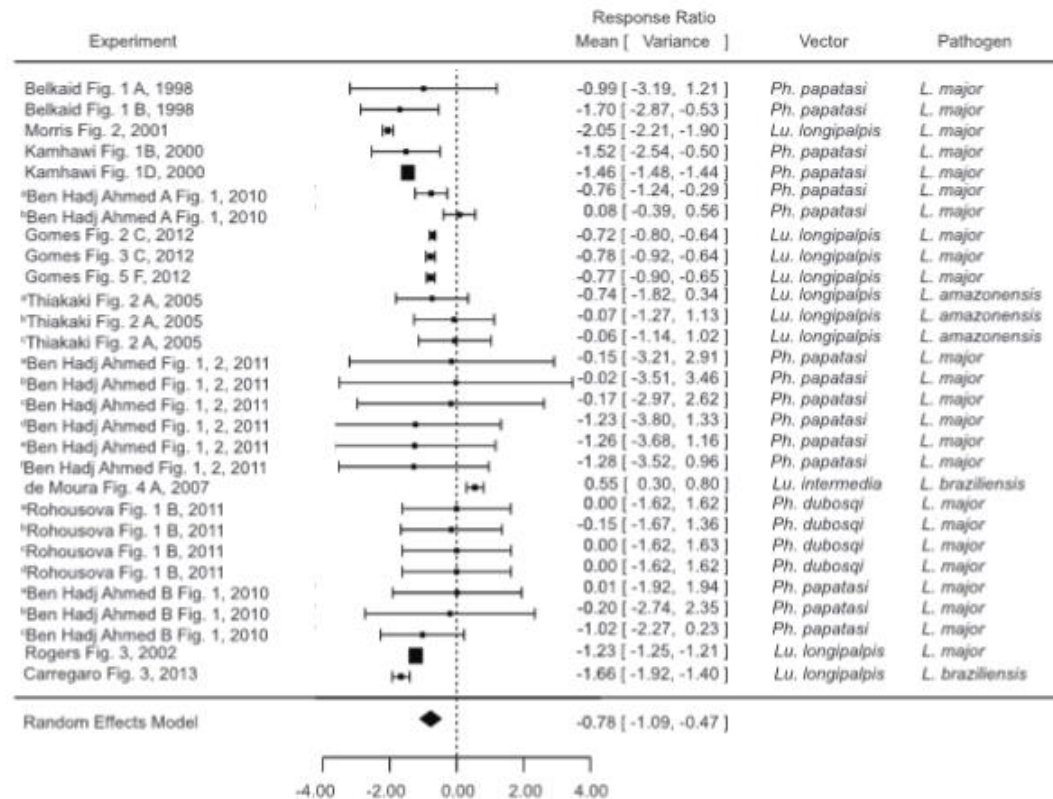


Figure 3. Forest plots of the relationship of exposure to vector saliva before infection and *Leishmania* lesion size (Category 2). Symbols represent the mean response ratio of the individual studies (squares) and of the entire analysis (diamond) using a Random Effects Model; the size of the square is proportional to the weight of an individual study. Error bars represent 95% Confidence Interval (CI). Squares to the right of the dotted line indicate larger measurements in the experimental (pre-exposed) group, while those on the left indicate larger measurements in the control group. Those that cross the center indicate no significant difference.
doi:10.1371/journal.pntd.0003197.g003

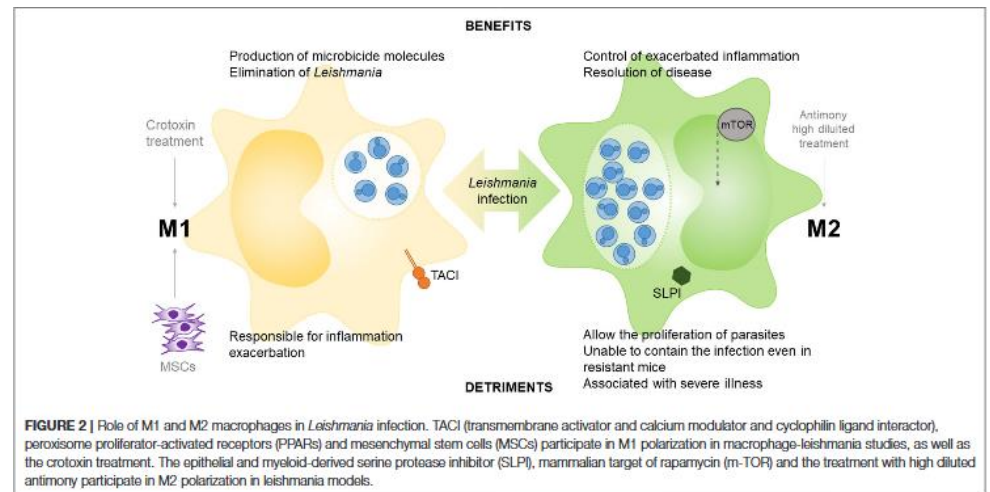
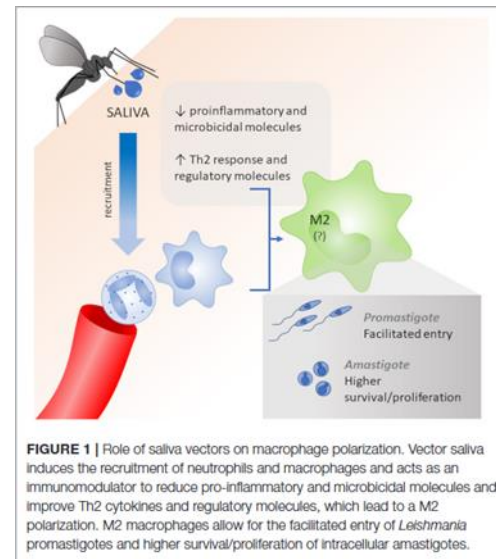
leishmaniose : salive/réponse immune

- *P. papatasi*/*P. duboscqi* inhibent présentation Ag par CD
- Cellule Dendritique : production PGE2 ; **IL4, IL10**
- Neutrophiles :
 - ↗ nombre
 - Apoptose par *Lu. Longipalpis*
 - Inhibition facteurs chimiotactiques
 - « Trojan rabbit »
- Macrophages : chimiotactisme +
 - Orientation M2 =>
- Th :
 - Orientation Th2: IL4, IL10
 - Inhibition Th1 : IFN, IL12
- Protéines d'intérêt :
 - Maxadilan : Th1, « inactivation » macrophage
 - PpSP44 : ↗ infection
 - LinB-11 : ↘ infection mais salive (*Lu. intermedia*) ↗ infection
 - PpSP15 : IFN=> Th1
 - PdSP15 => rPdSP15 => vaccin
- Anticorps : IgG1, IgE

TABLE 2 | Salivary compounds and their effects on *Leishmania* infection.

| Compound | Immunomodulatory effect | References |
|----------------------------------|---|---|
| Promastigote secretory gel (PSG) | <ul style="list-style-type: none"> ↑ Arg ↑ IL-1β ↑ IL-6 ↑ IL-10 ↑ TNF-α ↑ CCL2 ↑ CCL4 ↑ CCL3 ↑ CXCL2 ↑ FGFR2 ↑ EGF ↑ EGFR ↑ IGF1 | <ul style="list-style-type: none"> (77) (78) |
| Salivary Gland Homogenate (SGH) | <ul style="list-style-type: none"> ↑ MCP-1 ↑ CCR2 ↑ IL-10 ↑ Eosinophils ↑ Macrophages ↑ IFN-γ ↑ IL-13 ↑ IL-5 | <ul style="list-style-type: none"> ↓ INOS ↓ NO ↓ IFN-γ ↓ IL-13 ↓ IL-5 <ul style="list-style-type: none"> (79) (80, 81) (82) |
| Salivary Gland Lysate (SGL) | <ul style="list-style-type: none"> ↑ IL-4 ↑ IL-6 | <ul style="list-style-type: none"> ↓ IFN-γ ↓ IL-12 ↓ INOS <ul style="list-style-type: none"> (83, 84) (85–88) |
| Salivary Gland Extracts (SGE) | <ul style="list-style-type: none"> ↑ IL-10 ↑ IL-4 ↑ CD8 ↑ INF-γ ↑ CD4 | <ul style="list-style-type: none"> ↓ NO <ul style="list-style-type: none"> (89) (90) |
| Salivary Gland Sonicate (SGS) | <ul style="list-style-type: none"> ↑ IL-4 ↑ PGE₂ ↑ Macrophages ↑ LTB₄ | <ul style="list-style-type: none"> ↓ IFN-γ <ul style="list-style-type: none"> (91, 92) |
| Maxadilan (max) | <ul style="list-style-type: none"> ↑ IL-6 ↑ IL-10 ↑ TGF-β ↑ CD86 | <ul style="list-style-type: none"> ↓ IL-1β ↓ IL-12p70 ↓ TNF-α ↓ IFN-γ ↓ CD80 ↓ CCR7 <ul style="list-style-type: none"> (87, 93, 94) |
| Adenosine | <ul style="list-style-type: none"> ↑ IL-10 ↑ PGE₂ | <ul style="list-style-type: none"> (73) |

CCR, chemokine receptor; CD, cluster of differentiation; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; PG, prostaglandin; TNF, tumor necrosis factor; TGF, transforming growth factor; CCL, chemokines; CXCL, motif chemokine ligand; FGFR, fibroblast growth factor receptor; EGF, epidermal growth factor; EGFR, epidermal growth factor; IGF, insulin-like growth factor.



Tomiotto-Pellissier
(2018) Macrophage Polarization in
Leishmaniasis: Broadening
Horizons. *Front. Immunol.* 9:2529.

leishmaniose : salive/réponse immune

- *P. papatasi*/*P. duboscqi* inhibent présentation Ag par CD
- Cellule Dendritique : production PGE2 ; **IL4, IL10**
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leishmaniose : saliva/réponse immune

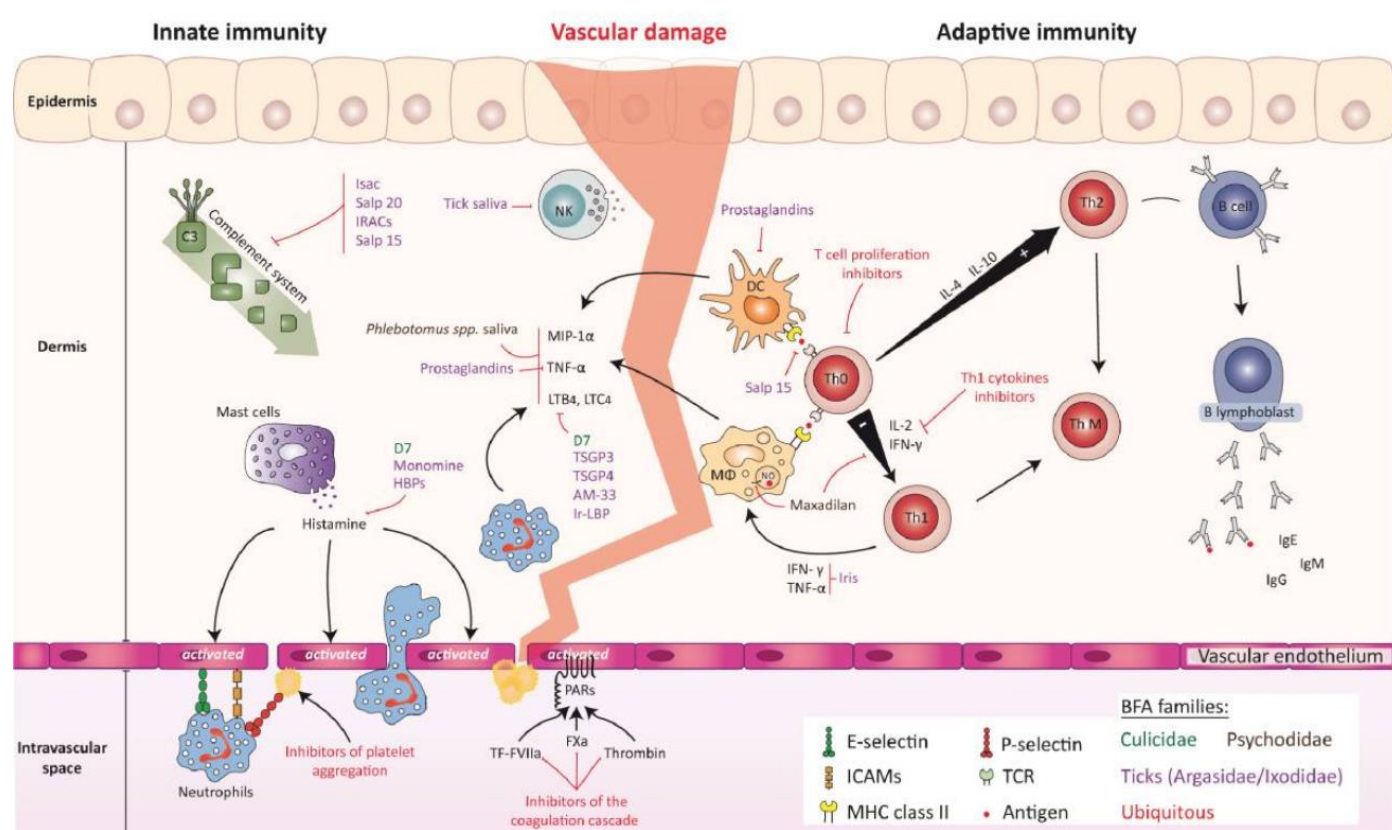
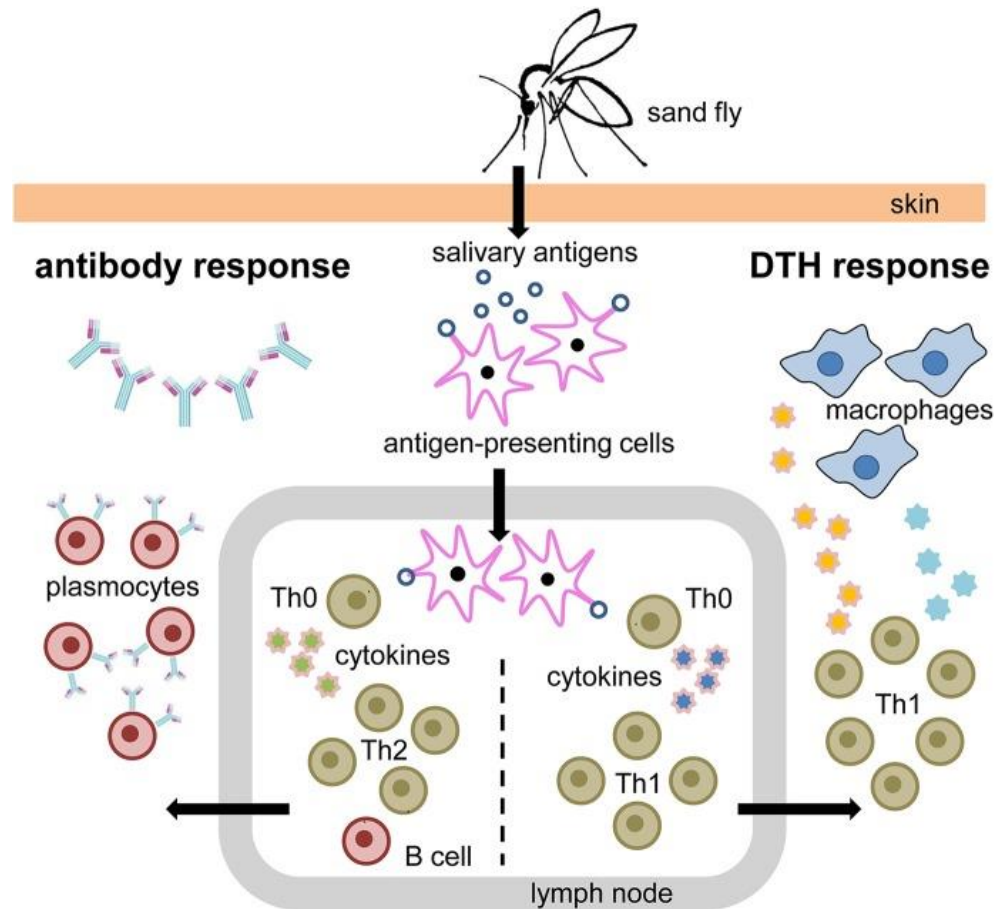


Figure 2 Schematic representation of arthropod salivary proteins involved in the modulation of innate and adaptive immunity.

Protective immunity against haematophagous arthropods (HA) involves both innate and adaptive immunity. Cells involved in the innate response (e.g., neutrophils, natural killers cells (NK), mast cells and macrophages (MΦ)) represent the first line of defence. Once activated, these cells release molecules (e.g., macrophage inflammatory proteins-1 α (MIP-1 α), tumour necrosis factor- α (TNF- α) or leukotrienes (LTB $_4$, LTC $_4$) that initiate the inflammation process. This local inflammation can further be triggered by the activation of complement, which has chemotactic and inflammatory properties. Endothelial cells and platelets can be activated by the binding of factors of the coagulation cascade to PAR receptors, leading to an over-expression of surface adhesive molecules (ICAMs, E-selectin, P-selectin) that participate in neutrophil migration. Antigen presenting cells, such as dendritic cells (DC) migrate to the lymph nodes where they interact with naive CD4 $^{+}$ helper T lymphocytes (Th0 cells) via the interplay of their T cell receptors (TCR) and major histocompatibility complex (MHC) class II proteins. Th0 cells have the potential to proliferate and to differentiate into two distinct lineages of effectors cells: Th1 and Th2 cells. Memory T helper (Th M) cells, which can improve the quality of the response to a subsequent exposure by developing more efficient memory capacity over time, are also produced. In a general pattern, HA saliva down-regulates the expression of Th1 cytokines (such as IL-2) modulating the adaptive immune response to an antibody mediated Th2 response. The action of saliva or salivary proteins is indicated in the figure as well as their corresponding organism's family. (Salivary protein affiliation to HA families is indicated by colour as represented on the bottom right corner legend).

leishmaniose : saliva/réponse immune



Hypersensibilité retardée => protection

Leishmania salive : application

- Marqueur d'exposition
- Marqueur du risque de transmission
- Marqueur de réservoir

Leishmaniose saline: application

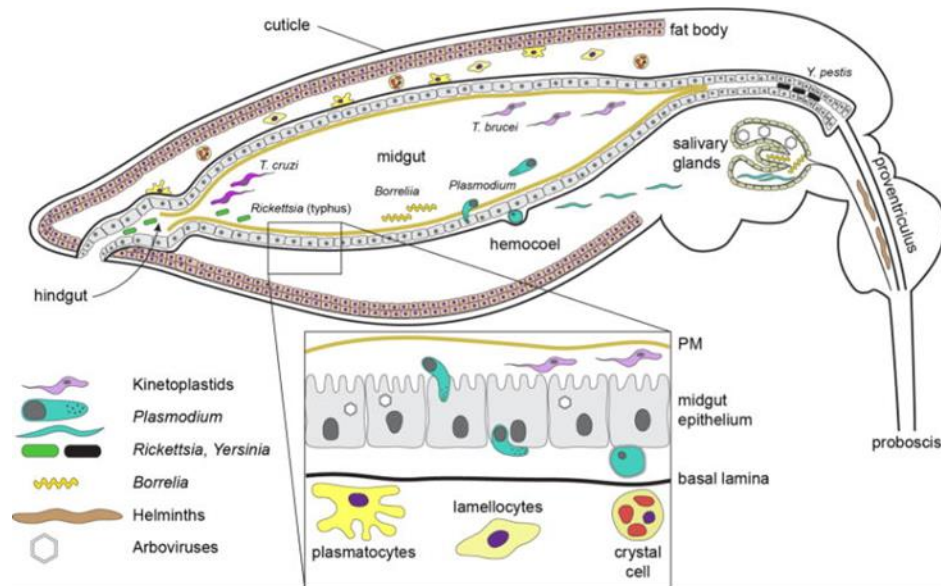
Table 2 Recombinant salivary proteins characterized in hematophagous arthropods and their immunological applications

| Protein names | Organisms | Additional informations | MW [kDa] | Application | Ref. |
|---------------|------------------------------|---|----------|----------------------------------|-------------------|
| rAed a1 | <i>Aedes aegypti</i> | Salivary apyrase | 68 | Allergy | [151,152] |
| rAed a2 | <i>Aedes aegypti</i> | Belong to the D7 family | 37 | Allergy | [151,152] |
| rAed a3 | <i>Aedes aegypti</i> | 30 kDa salivary gland allergen | 30 | Allergy | [151,152] |
| Procalin | <i>Triatoma protracta</i> | Belong to the lipocalin family | 20 | Allergy | [225] |
| Arg r 1 | <i>Argas reflexus</i> | Belong to the lipocalin family | 17 | Allergy | [227] |
| Der-p2 | <i>Ixodes ricinus</i> | <i>Dermatophagoides pteronyssinus</i> allergen-like | 15.6 | Allergy | [226] |
| TAg5 | <i>Glossina m. morsitans</i> | Tsetse Antigen 5 | 28.9 | Allergy | [228] |
| Maxadilan | <i>Lutzomyia longipalpis</i> | - | 9.5 | Vaccine candidate | [123] |
| SP15 | <i>Phlebotomus papatasi</i> | - | 15 | Vaccine candidate | [162] |
| rLJM19 | <i>Lutzomyia longipalpis</i> | - | 11 | Vaccine candidate | [229] |
| Salp15 | <i>Ixodes scapularis</i> | - | 14.7 | Vaccine candidate | [163] |
| gSG6 | <i>Anopheles gambiae</i> | - | 10 | Immunological marker of exposure | [218,219,230,220] |
| rTC | <i>Amblyomma americanum</i> | Calreticulin | 47.5 | Immunological marker of exposure | [221] |
| rLJM11 | <i>Lutzomyia longipalpis</i> | Yellow-related protein | 43 | Immunological marker of exposure | [223,224] |
| rLJM17 | <i>Lutzomyia longipalpis</i> | Yellow-related protein | 45 | Immunological marker of exposure | [223,224] |

leishmaniose : spécificité vecteur

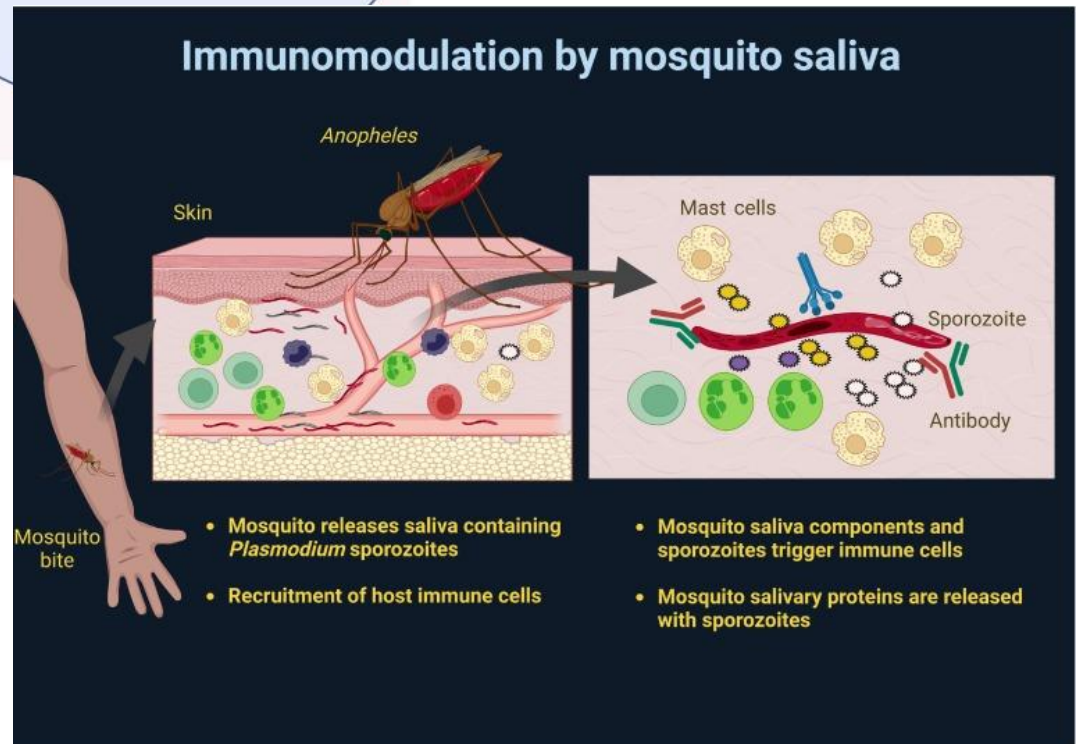
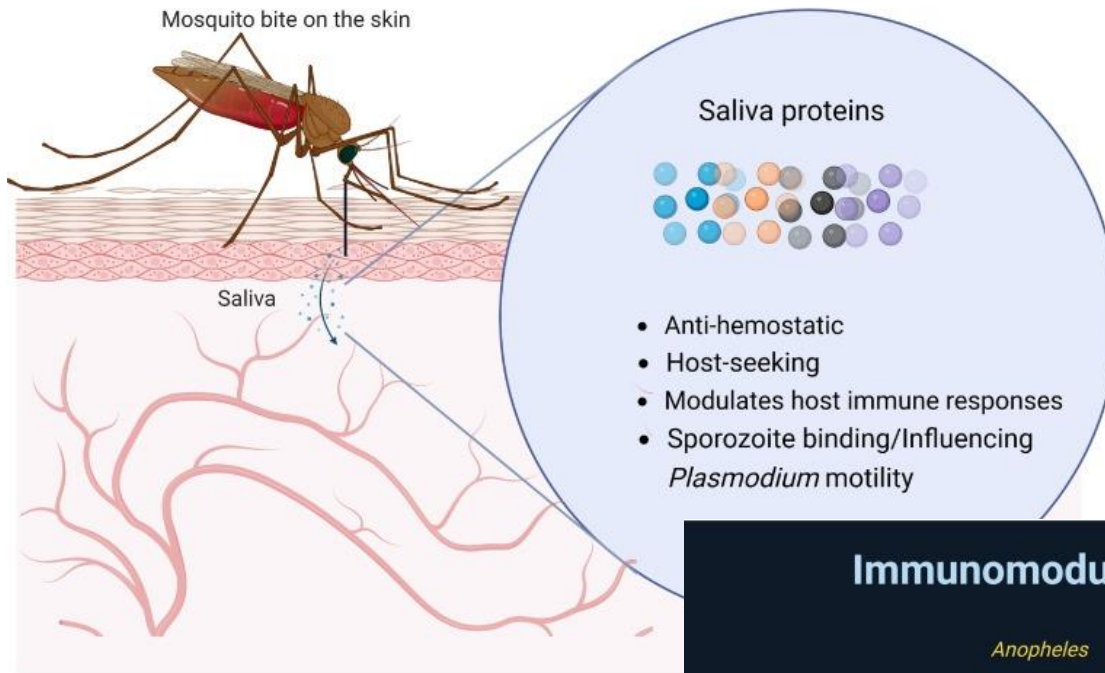
- Relation privilégiée vecteur/parasite
- Homologie de la salive/PSG
- *Phlebotomus* vs *Lutzomya*
 - Variation entre genres
 - Conservation intragenre
- Zone endémique/occasionnelle/saisonnalité

Plasmodium



Baxter et al.
Biochemistry. Author manuscript; available in PMC 2018 February 21.

Mosquito saliva



Plasmodium

- Mastocytes
 - recrutement
 - Dégranulation => afflux sanguin ?
- Neutrophiles :
 - Afflux mais pas d'impact sur l'infection
- Augmentation production INF
- Macrophage migration inhibitory factors

Plasmodium

- **Anopheline antiplatelet protein**
 - Baisse coagulation
- **AgTRIO**
 - Augmentée par présence Plasmodium
 - Augmente le niveau d'infection
- **mosGILT**
 - Baisse motilité sporozoïtes
 - Protection des oocystes
- **SAMSP1**
 - Améliore mobilité sporozoïtes
 - Role sur niveau infection
- **AgSAP**
 - Baisse immunité locale
 - Role sur niveau infection
- **D7 protein family**
 - Inhibition vasoconstriction
 - Anticoagulant

Autres parasitoses vectorisées

... ?

Autres agents infectieux vectorisés

Arboviroses +++

=> vaccins !

Borrelia/Tiques

Conclusion

- Rôle du vecteur
 - Évident pour *Leishmania*... autres parasites ?
- Activité pharmacologique de la salive ++
- Immunisation bénéfique?