Master Biologie-Santé
UE Microbiologie-Pathologies

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

F. Pagniez

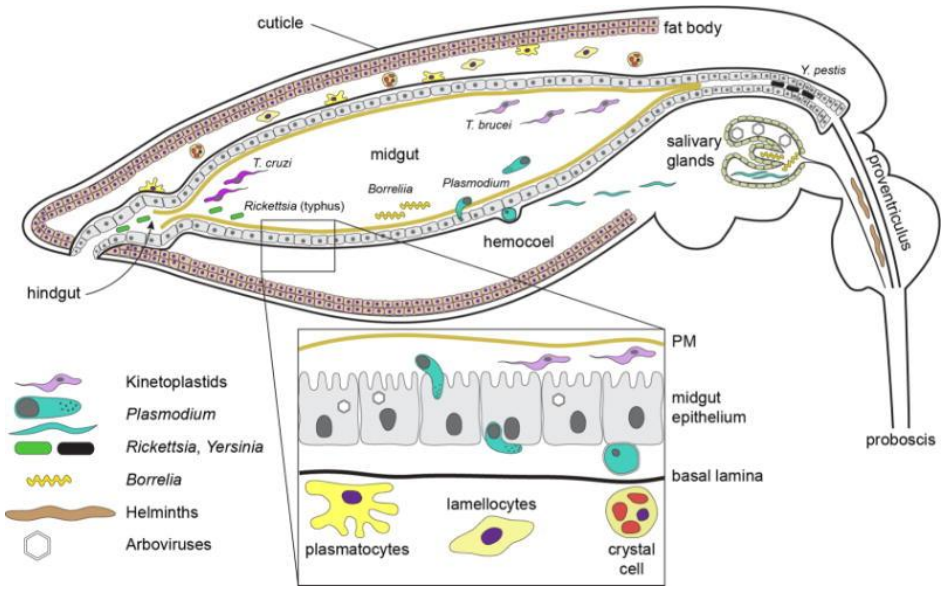
Introduction

Table 1 Taxonomic classification of major vector-borne diseases

Vectors			Diseases
Order	**Family**	**Genius**	
Diptera	Culicidae	*Anopheles*	Malaria,
			Lymphatic filariasis
		Culex	West Nile disease
			Japanese encephalitis
		Aedes	Yellow fever
			Chikungunya
			Dengue
	Psychodidae	*Phlebotomus*	Leishmaniasis
		Lutzomyia	
	Glossinidae	*Glossina*	Human African Trypanosomiasis
	Simulidae	*Simulium*	Onchocerciasis
	Tabanidae	*Tabanus*	Loiasis
Hemiptera	Reduviidae	*Triatoma*	Chagas disease
		Rhodnius	
Ixodida	Ixodidae	*Amblyomma*	Rickettsiosis
			Tularemia
		Ixodes	Lyme disease
			Babesiosis
		Haemaphysalis	Tularemia
			Tick borne encephalitis
	Argasidae	*Ornithodoros*	Relapsing fever

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

Fontaine *et al. Parasites & Vectors* 2011, **4**:187



Baxter et al.
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leishmaniose

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

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

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.

P.A. Bates / International Journal for Parasitology 37 (2007) 1097–1106

leishmaniose

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

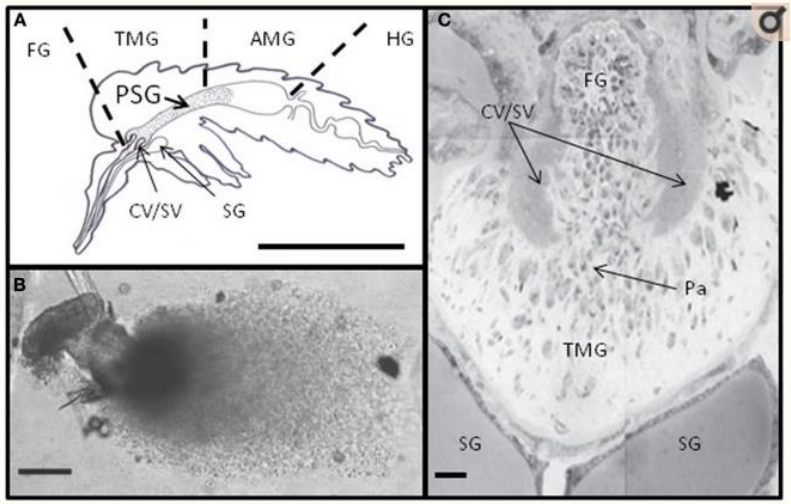

Figure 3

The PSG plug. **(A)** The typical position of *Leishmania* PSG in the gut of heavily infected sand flies (FG, foregut; TMG, thoracic midgut; AMG, abdominal midgut; HG, hindgut; CV/SV, cardiac or stomodeal valve; SG, salivary gland; scale bar: 1 mm). **(B)** Freshly dissected PSG from *L. mexicana*-infected *Lu. longipalpis* (scale bar: 100 μm). **(C)** Sagittal section through the anterior thoracic midgut of a heavy *L. mexicana-Lu. longipalpis* infection, showing numerous attached and unattached parasites (Pa) and occlusion to the stomodeal valve (Scale bar: 10 μm).

leishmaniose

- PSG :
  - Protéophosphoglycanes
  - Cicatrisation accélérée chez la souris
  - Recrutement macrophages/neutrophiles
  - Activation des macrophages

    Mais Inhibition indirecte production NO
- Échappement parasite : IL4/IL10
- Amélioration infection :
  - Modification comportement alimentaire/leishmanie

leishmaniose

- Salive
  - Composition
  - Rôle :
    - Vasodilatation : maxadilan, 5’AMP, adenosine
    - Hémostase : anti-aggregants, anticoagulants
    - Inflammatoire
    - immunologique

leishmaniose salive : 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 hydrolyzis of chondroitin sulfates	Purine metabolism hydrolysis of adenosine	Vasodilator and inhibitor of platelet aggregation	Nucleotidase	Vasodilator	
	Small odorant binding protein (OBP) – lile (~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
Lu. longipalpis (Valenzuela et al., 2004)	LJM04	LJM11[a], LJM17[a], LJM111[a] (Xu et al., 2011)	LJL143 (Lufaxin)[a] (Collin et al., 2012)	LuloAPY[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] (Grespan et al., 2012)
Lu. intermedia (De Moura et al., 2013)	Linb-7, 8, 28, 59	Linb-21	Linb-17	Linb-35	Linb-46	Linb-54				Linb-147	
Lu. ayacuchensis (Kato et al., 2013)	LayS32–37, 48–72	LayS22–24, 117, 118	LayS120–132	LayS8–14, 16–21	LayS147						
P. papatasi 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)			
P. duboscqi 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				
P. duboscqi 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				
P. sergenti (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)					
P. arabicus (Hostomska et al., 2009)	PabSP2, 45, 63–64, 93,	PabSP26, 53	PabSP34, 32	PabSP39, 40–41	PabSP49	PabSP72[b] (Rohousova et al., 2012)					
P. argentipes (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)			
P. ariasi (Oliveira et al., 2006)	ParSP03, 06, 08	ParSP04, 04B	ParSP09	ParSP01	ParSP10						
P. perniciosus (Anderson et al., 2006)	PpeSP02, 09, 11	PpeSP03, 03B	PpeSP06	PpeSP01, 01B [b] (Ribeiro et al., 1989b)	PpeSP32	[b]Rohousova et al. (2012)					
P. perniciosus Madrid Spain (Martin-Martin et al., 2013)	SP02, 09, 11	SP03B	SP06	SP01,01B [b] (Ribeiro et al., 1989b)		[b]Rohousova et al. (2012)					

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leishmaniose

- Salive
  - Composition
  - Rôle :
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Leishmania : hémostase

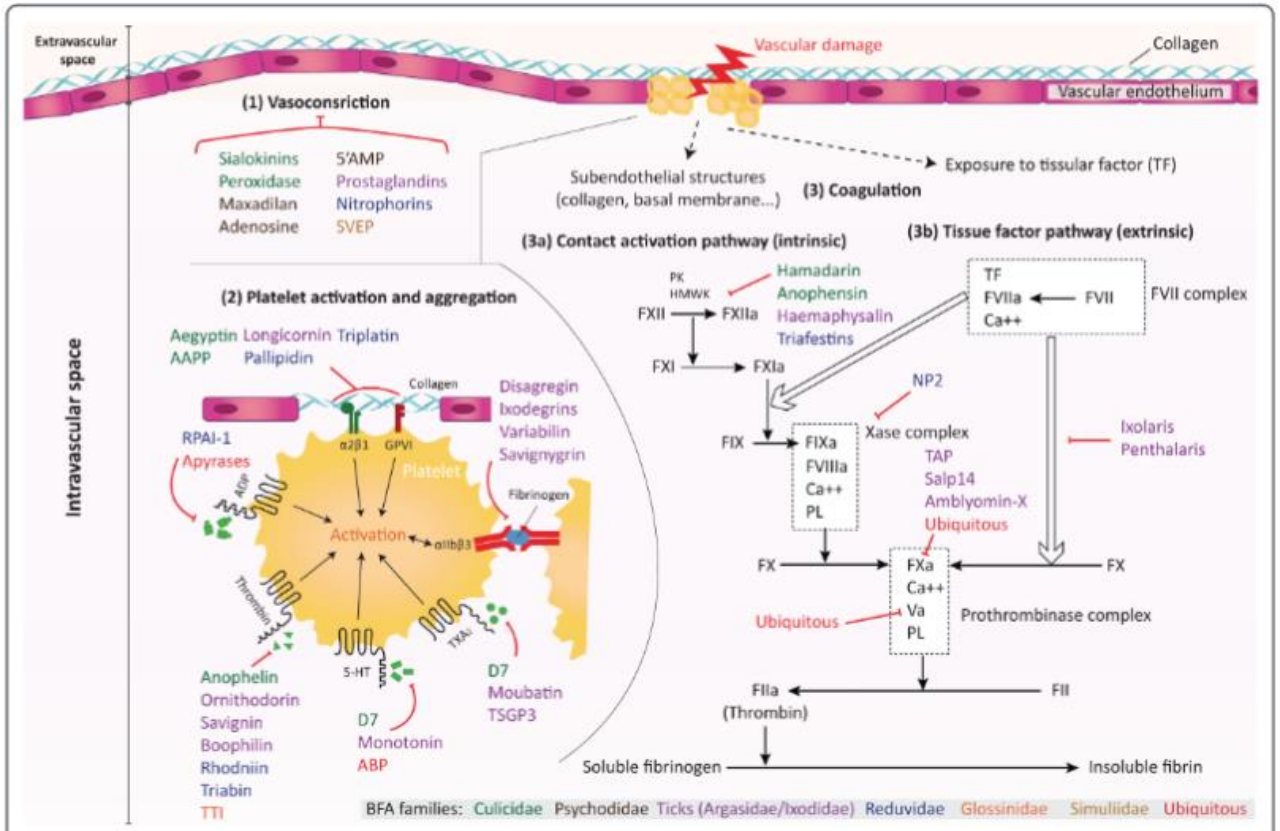

Figure 1 Schematic representation of arthropod salivary proteins acting on primary and secondary haemostasis. Haematophagous arthropods (HA) induce injuries to vascular endothelium when probing for a blood meal. The initial event of this vascular damage is vasoconstriction (1), which retards extravascular 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 A_2 (TXA_2), 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).

Fontaine *et al. Parasites & Vectors* 2011, **4**:187

leishmaniose salive : composition

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leishmaniose

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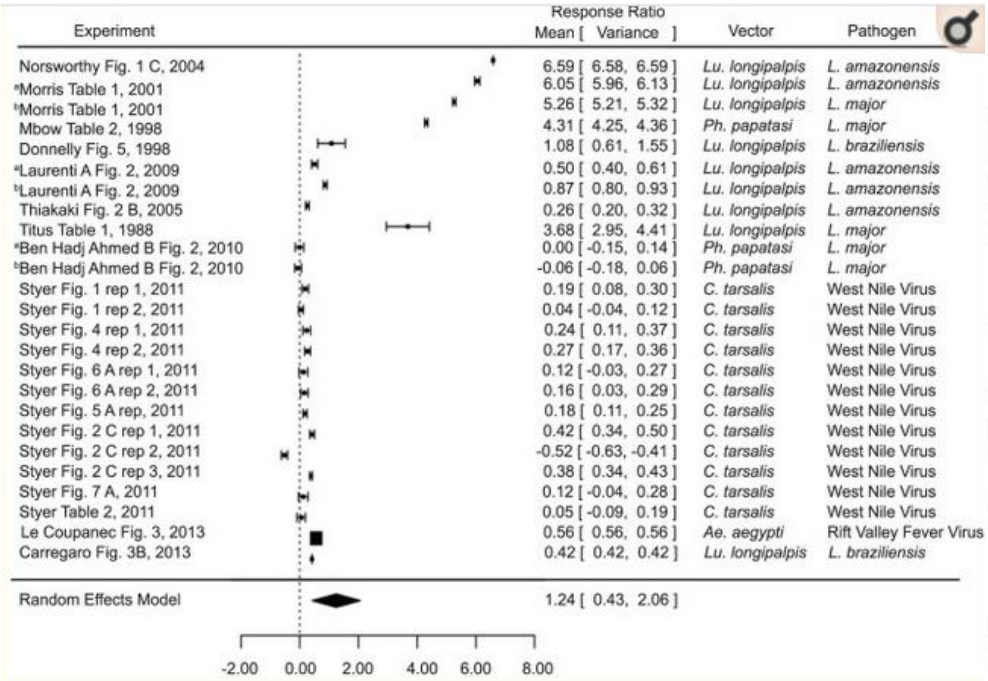
leishmaniose *: conséquences cliniques*



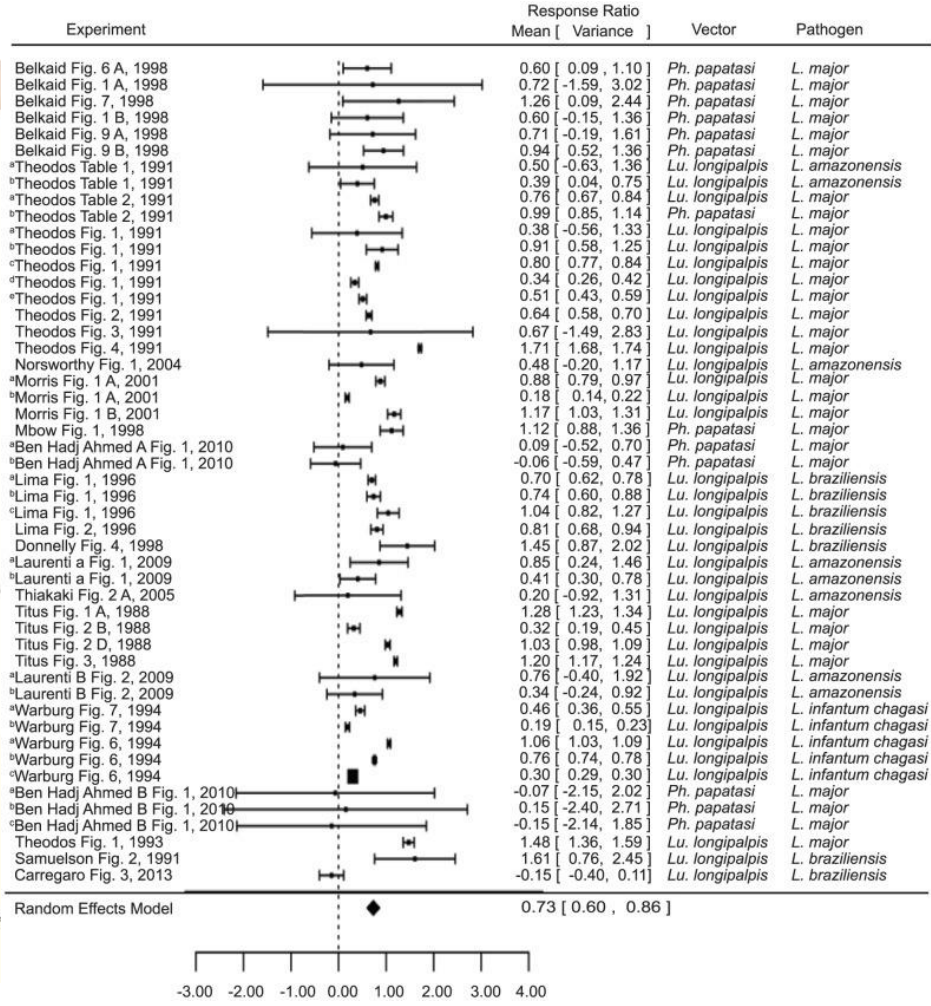


Figure 1

Forest plots of the relationship of vector saliva and infection level in naïve mice (Category 1).

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 (saliva) group, while those on the left indicate larger measurements in the control group. Those that cross the center indicate no significant difference.

leishmaniose *: conséquences cliniques*

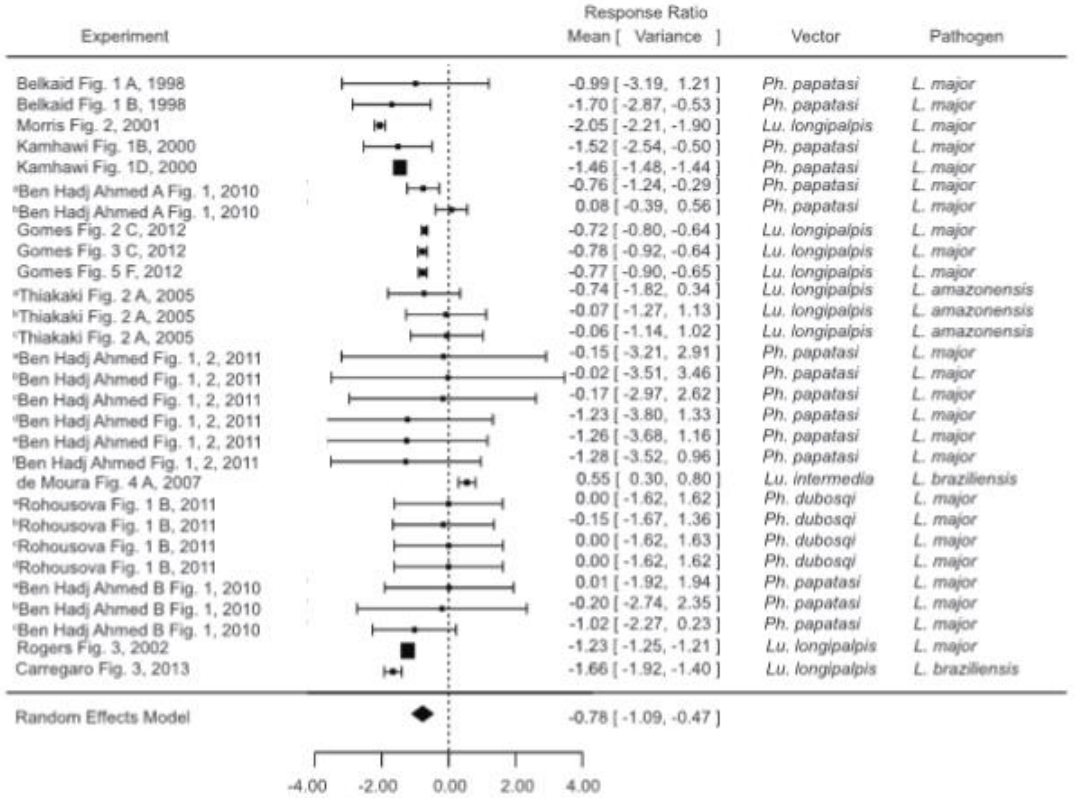


Figure 3. Forest plots of the relationship of exposure to vector saliva before infection and *Leishmania* lesion size (Category 2). Symbols represent the mean response ratio of the individual studies (squares) and of the entire analysis (diamond) using a Random Effects Model; the size of the square is 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.

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leishmaniose : salive/réponse immune

- *P. papatasi*/*P. duboscqi* inhibent présentation Ag par CD
- Cellule Dendritique : production PGE2 ; **IL4, IL10**
- Neutrophiles :
  - ↗ nombre
  - *Lu. Longipalpis favorise a*poptose neutrophiles
  - Leishmanies + salive : attraction macrophage
    => théorie du « Trojan rabbit »
- Macrophages : chimiotactisme +
  - Orientation M2 =>
  - Inhibition production NO
- Th :
  - Orientation Th2: IL4, IL10
  - Inhibition Th1 : IFN, IL12
- Protéines d'intérêt :
  - Maxadilan : inhibition Th1, « inactivation » macrophage
  - PpSP44 : ↗ infection
  - LinB-11 : ↘ infection mais salive (*Lu. intermedia*) ↗ infection
  - PpSP15 : IFN=> Th1
    => rPdSP15 => vaccin
- Anticorps : IgG1, IgE

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

Compound	Immunomodulatory effect		References
Promastigote secretory gel (PSG)	↑ Arg ↑ IL-1β ↑ IL-6 ↑ IL-10 ↑ TNF-α ↑ CCL2 ↑ CCL4 ↑ CCL3 ↑ CXCL2 ↑ FGFR2 ↑ EGF ↑ EGFR ↑ IGF1		(77) (78)
Salivary Gland Homogenate (SGH)	↑ MCP-1 ↑ CCR2 ↑ IL-10 ↑ Eosinophils ↑ Macrophages ↑ IFN-γ ↑ IL-13 ↑ IL-5	↓ INOS ↓ NO ↓ IFN-γ ↓ IL-13 ↓ IL-5	(79) (80, 81) (82)
Salivary Gland Lysate (SGL)	↑ IL-4 ↑ IL-6	↓ IFN-γ ↓ IL-12 ↓ INOS	(83, 84) (85–88)
Salivary Gland Extracts (SGE)	↑ IL-10 ↑ IL-4 ↑ CD8 ↑ INF-γ ↑ CD4	↓ NO	(89) (90)
Salivary Gland Sonicate (SGS)	↑ IL-4 ↑ PGE_2 ↑ Macrophages ↑ LTB_4	↓ IFN-γ	(91, 92)
Maxadilan (max)	↑ IL-6 ↑ IL-10 ↑ TGF-β ↑ CD86	↓ IL-1β ↓ IL-12p70 ↓ TNF-α ↓ IFN-γ ↓ CD80 ↓ CCR7	(87, 93, 94)
Adenosine	↑ IL-10 ↑ PGE_2		(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.

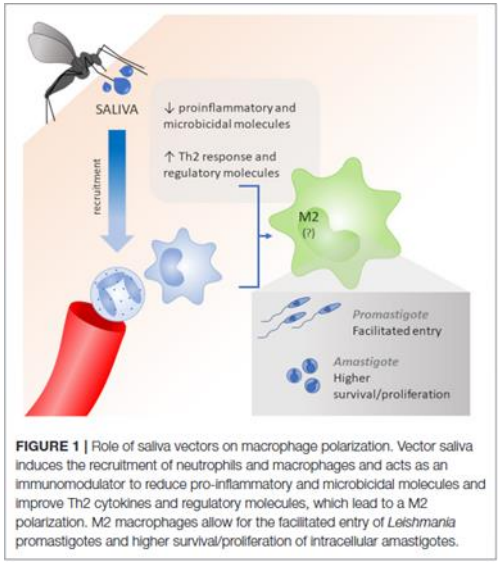

FIGURE 1 | Role of saliva vectors on macrophage polarization. Vector saliva induces the recruitment of neutrophils and macrophages and acts as an immunomodulator to reduce pro-inflammatory and microbicidal molecules and improve Th2 cytokines and regulatory molecules, which lead to a M2 polarization. M2 macrophages allow for the facilitated entry of *Leishmania* promastigotes and higher survival/proliferation of intracellular amastigotes.

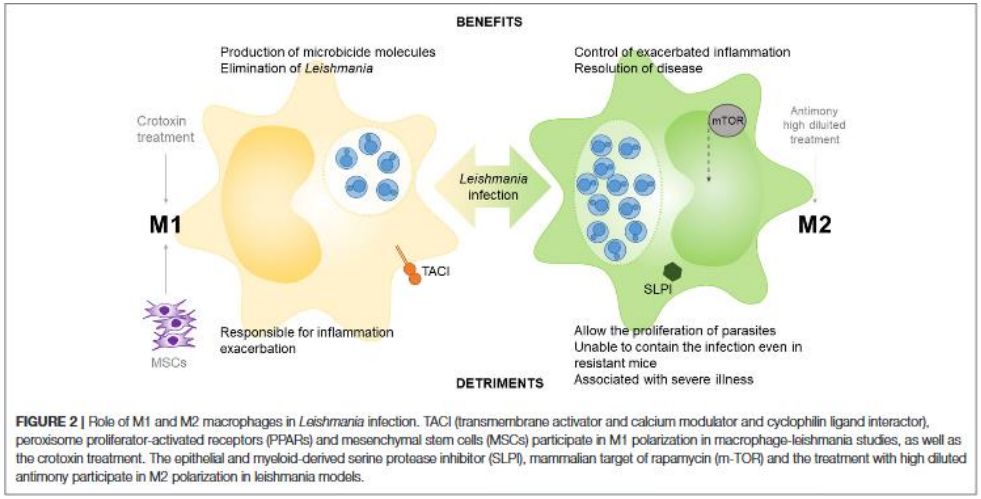

FIGURE 2 | Role of M1 and M2 macrophages in *Leishmania* infection. TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor), peroxisome proliferator-activated receptors (PPARs) and mesenchymal stem cells (MSCs) participate in M1 polarization in macrophage-leishmania studies, as well as the crotoxin treatment. The epithelial and myeloid-derived serine protease inhibitor (SLPI), mammalian target of rapamycin (m-TOR) and the treatment with high diluted antimony participate in M2 polarization in leishmania models.

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

leishmaniose : salive/réponse immune

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  => Cellule Dendritique : production PGE2 ; **IL4, IL10**
- Neutrophiles :
  - ↗ nombre
  - Apoptose par *Lu. Longipalpis*
  - Inhibition facteurs chimiotactiques : ↘ migration
  - « Trojan rabbit »
- Macrophages : chimiotactisme +
  - Orientation M2 =>
- Th :
  - Orientation Th2: IL4, IL10
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  - PdSP15 => rPdSP15 => vaccin
- Anticorps : IgG1, IgE

leishmaniose : salive/réponse immune

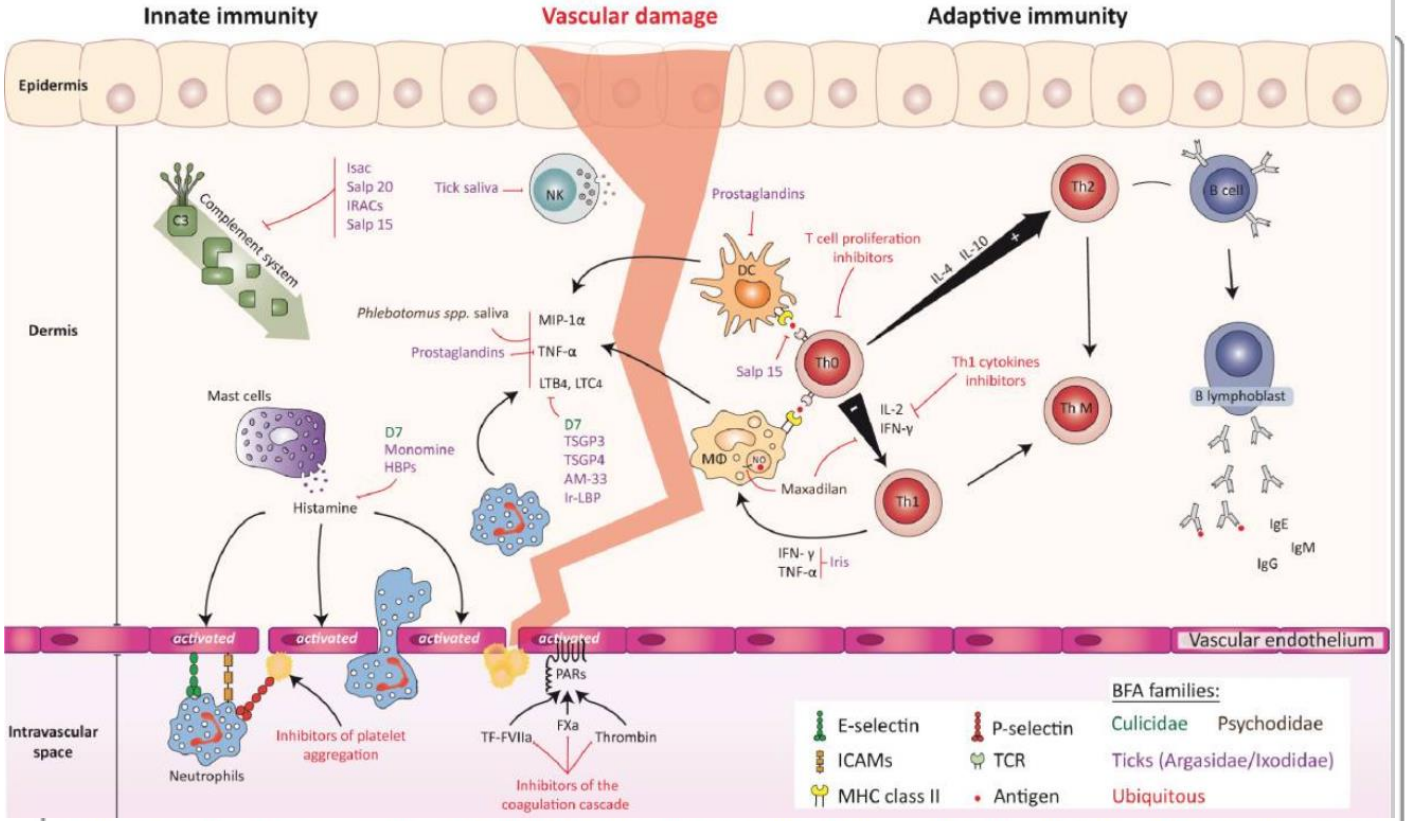

Figure 2 Schematic representation of arthropod salivary proteins involved in the modulation of innate and adaptive immunity. Protective immunity against haematophagous arthropods (HA) involves both innate and adaptive immunity. Cells involved in the innate response (*e.g.*, neutrophils, natural killers 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-1α), tumour necrosis factor- α (TNF- α) or leukotrienes (LB_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 naïve 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).

Fontaine *et al. Parasites & Vectors* 2011, 4:187

IL4 et salive

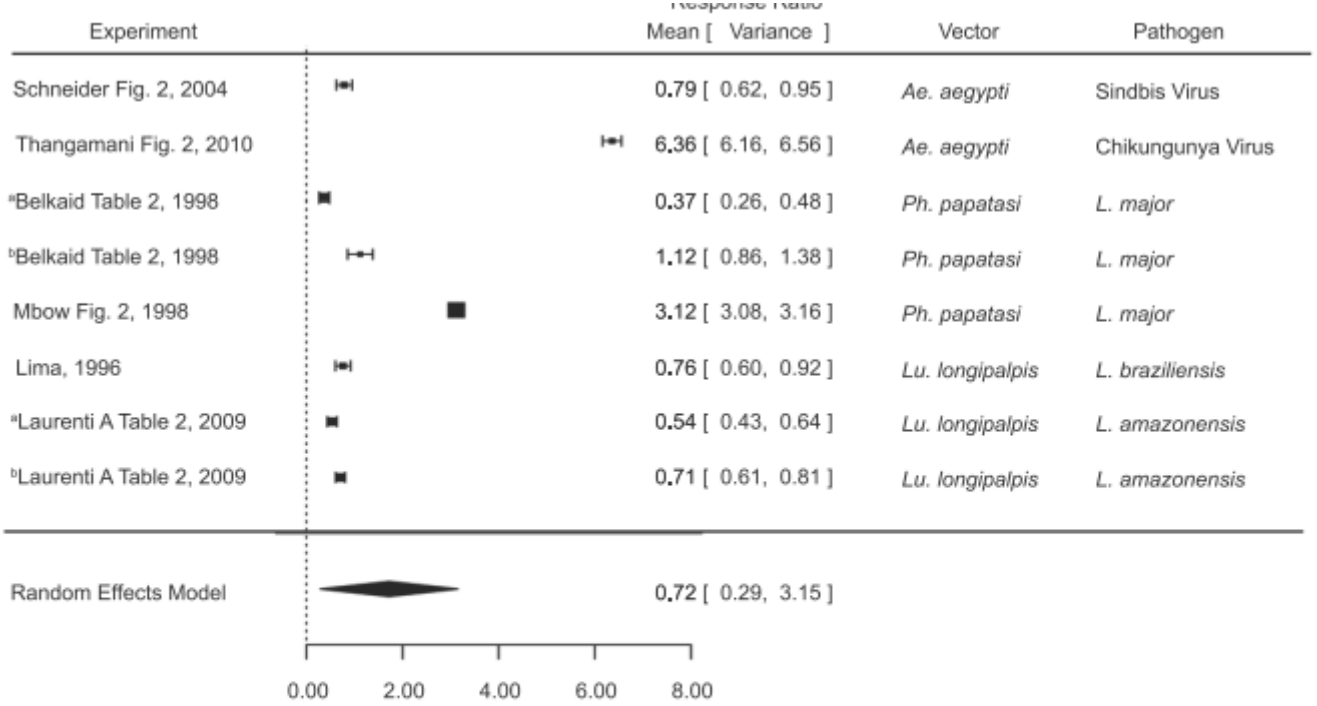

Figure 5. Forest plots of the relationship of vector saliva and IL-4 levels in naïve mice. Symbols represent the mean response ratio of the individual studies (squares) and of the entire analysis (diamond) using a Random Effects Model; the size of the square is proportional to the weight of an individual study. Error bars represent 95% Confidence Interval (CI). Squares to the right of the dotted line indicate larger measurements in the experimental (saliva) group, while those on the left indicate larger measurements in the control group. Those that cross the center indicate no significant difference.

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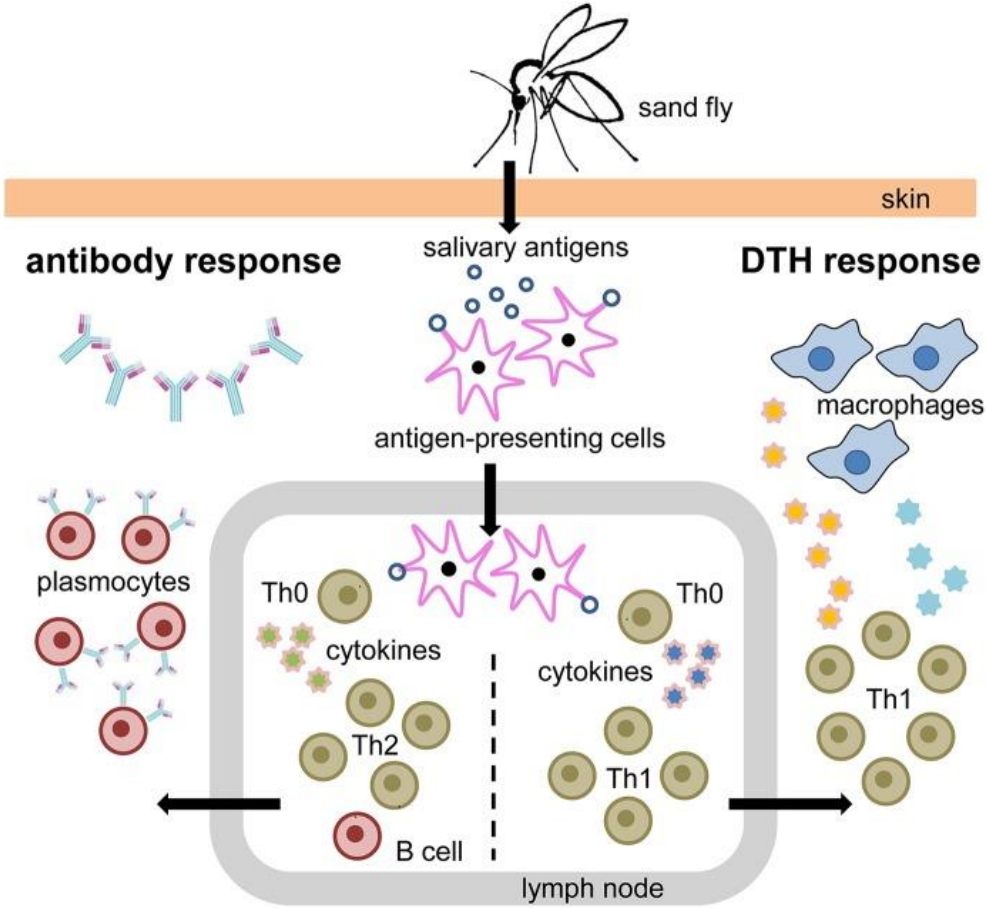
leishmaniose : salive/réponse immune



Hypersensibilité retardée => protection

Leishmania salive : application

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

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

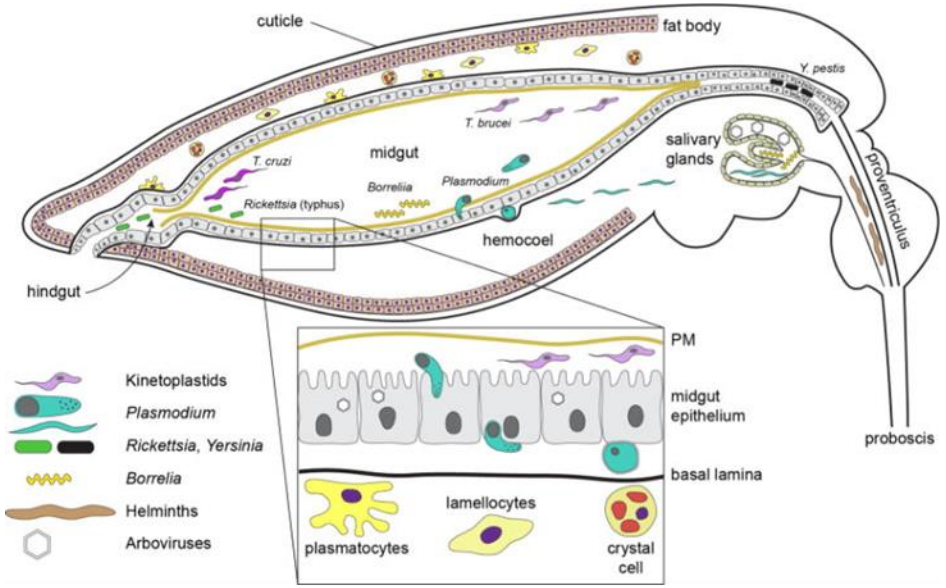
Fontaine *et al. Parasites & Vectors* 2011, **4**:187

leishmaniose : spécificité vecteur

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

Fontaine *et al. Parasites & Vectors* 2011, **4**:187

Plasmodium



Baxter et al.

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

Plasmodium

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

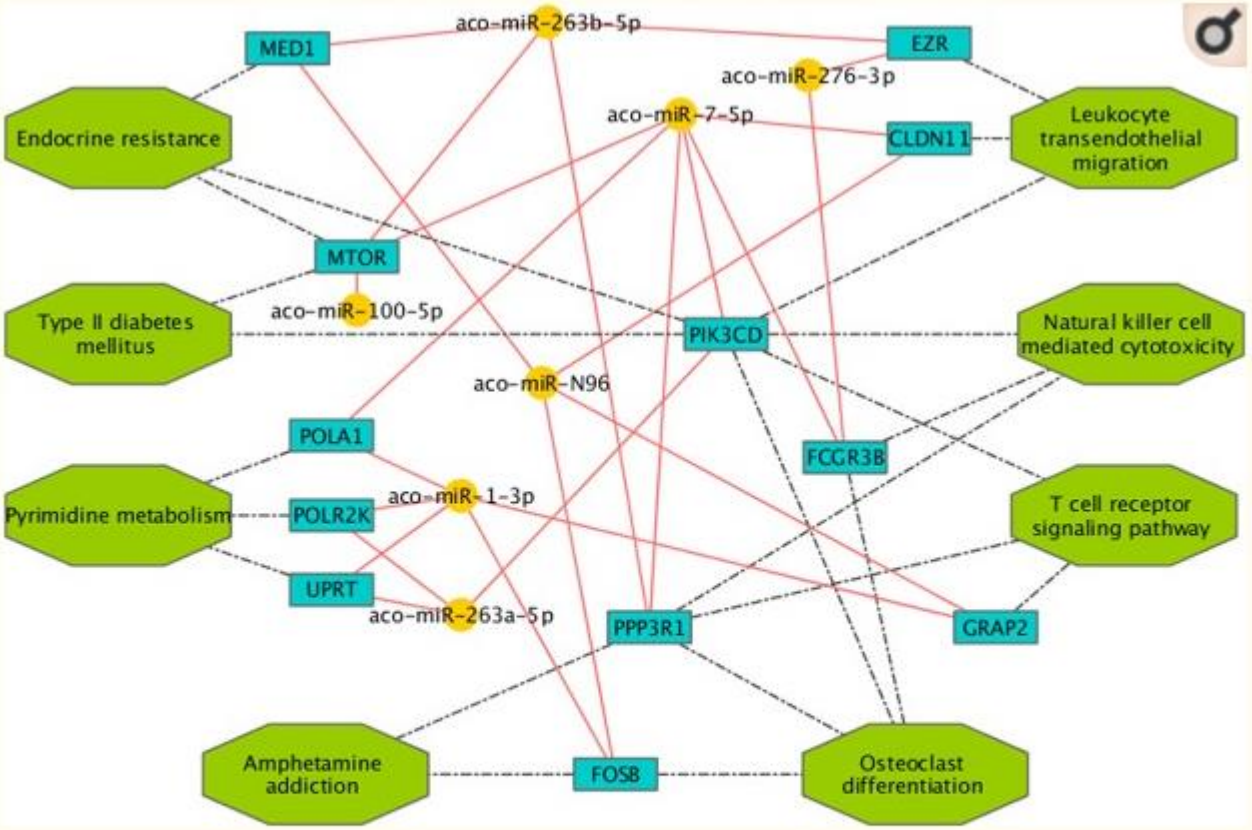


Figure 6

Target prediction analysis. Schematic representation of genes targeted by abundant miRNAs from *An. coluzzii* saliva and enriched categories. miRNAs are shown by yellow dots and targeted genes (blue boxes) indicated by solid red lines. Dotted lines connect genes to enriched KEGG pathways (green octagons).

Sci Rep. 2019 Feb 27;9(1):2955.

Autres parasitoses vectorisées

… protéines, miRNA…?

- Salive triatomes augmente infection T. cruzi

Autres agents infectieux vectorisés

Arboviroses +++

=> vaccins !

Borrelia/Tiques

Conclusion

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