PLOS | NEGLECTED TROPICAL DISEASES

REVIEW

The enemy within: Targeting host–parasite interaction for antileishmanial drug discovery

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Abstract

The state of antileishmanial chemotherapy is strongly compromised by the emergence of drug-resistant *Leishmania*. The evolution of drug-resistant phenotypes has been linked to the parasites' intrinsic genome instability, with frequent gene and chromosome amplifications causing fitness gains that are directly selected by environmental factors, including the presence of antileishmanial drugs. Thus, even though the unique eukaryotic biology of *Leishmania* and its dependence on parasite-specific virulence factors provide valid opportunities for chemotherapeutical intervention, all strategies that target the parasite in a direct fashion are likely prone to select for resistance. Here, we review the current state of antileishmanial chemotherapy and discuss the limitations of ongoing drug discovery efforts. We finally propose new strategies that target *Leishmania* viability indirectly via mechanisms of host–parasite interaction, including parasite-released ectokinases and host epigenetic regulation, which modulate host cell signaling and transcriptional regulation, respectively, to establish permissive conditions for intracellular *Leishmania* survival.

Citation: Lamotte S, Späth GF, Rachidi N, Prina E (2017) The enemy within: Targeting host–parasite interaction for antileishmanial drug discovery. PLoS Negl Trop Dis 11(6): e0005480. https://doi.org/10.1371/journal.pntd.0005480

Editor: Michael P. Pollastri, Northeastern University, UNITED STATES

Published: June 8, 2017

Funding: All authors are funded by Institut Pasteur and INSERM U1201. SL, GFS, and EP are also supported by the FP7 A-ParaDDisE program funded under the European Union's Seventh Framework Programme (grant agreement 602080) and NR by the ANR-13-ISV3-0009-01 TranSig and the LabEx IBEID. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Leishmaniases are neglected diseases that prevail in tropical and subtropical areas. A recent WHO report indicates 399 million people in 11 high-burden countries and 556 million people in 12 high-burden countries are at risk for cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL), respectively [1]. The incidence of human leishmaniases shows an important increase over the last decades due to multiple factors, including failing preventive and therapeutic measures, human migration caused by conflicts and political instability, global warming, and the emergence of drug-resistant parasites in developing countries [2–5]. Causal agents of leishmaniases are protozoan parasites of the *Leishmania* genus belonging to the Trypanosomatidae family. During the parasite's life cycle, the promastigote form is transmitted by blood-feeding sandflies to vertebrate hosts, where they develop into the disease-causing amastigote form inside host phagocytes.

Control of intracellular *Leishmania* development relies primarily on chemotherapy but also on the ability of the parasitized host to mount an efficient immune response. The macrophage plays a key role in antiparasitic resistance but also immuno-pathology. These sentinel cells participate directly in the containment and clearance of *Leishmania* through their innate immune functions and stimulation of a protective Th1 response [6, 7]. Intracellular *Leishmania* and their host cells have coevolved intricate and dynamic interactions (Fig 1). In particular,

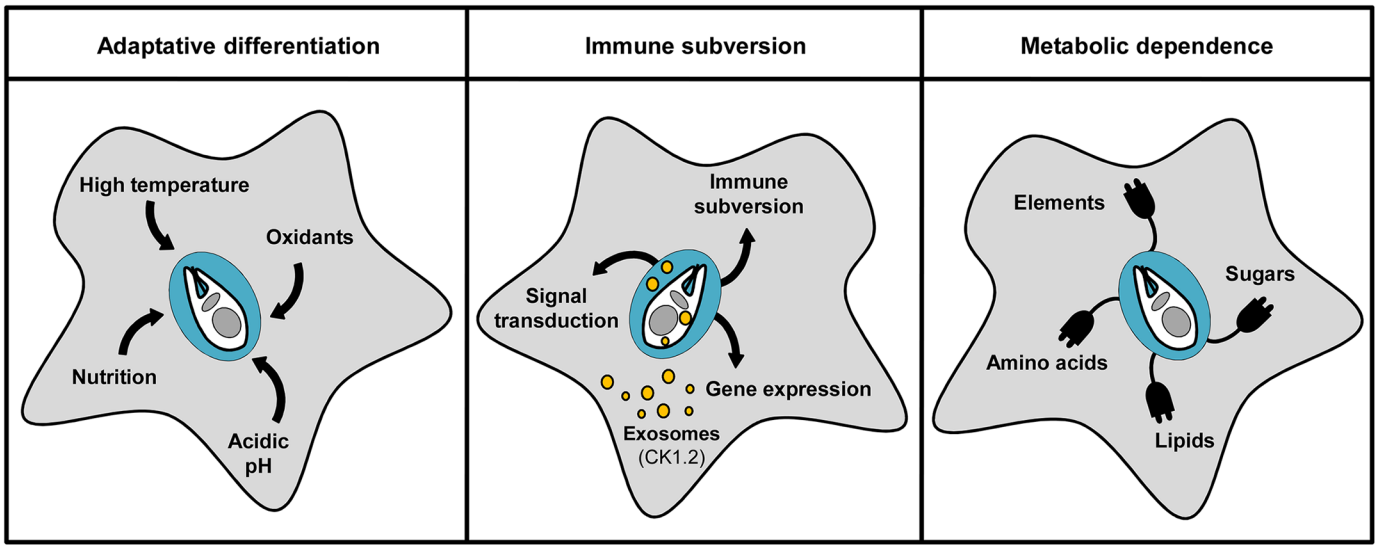

Fig 1. Different aspects of macrophage–*Leishmania* interaction. *Leishmania* responds to the intramacrophagic environment by adaptive differentiation (left panel) and hijacks vital macrophage functions via release of parasite ectoproteins (such as the ectokinase casein kinase 1 isoform 2 [CK1.2]), which affect host defense mechanisms, causing immune subversion (middle panel), and modulate host metabolic pathways, promoting parasite growth (right panel).

https://doi.org/10.1371/journal.pntd.0005480.g001

Leishmania has evolved mechanisms to subvert both innate and adaptive immune responses that cause immune dysregulation and the pathologies characteristic of CL and VL and ultimately allow parasite proliferation and persistent infection inside the mammalian host [8–10]. Surprisingly, even though it is very well established that *Leishmania* reprograms its host cell to subvert the immune response and to meet the nutritional and metabolic needs for intracellular parasite survival and proliferation [11, 12], there is only little effort to exploit these crucial effects of the parasite on the host cell for antiparasitic drug discovery. Here, we review the current literature on antileishmanial therapy and *Leishmania* host–pathogen interaction and discuss novel strategies to target host cell rather than parasite biology for drug discovery—a strategy that likely will be more refractory to the emergence of drug-resistant parasites.

Limitations of new and emerging therapies

Recent strategies to replace antimonials as first-line treatment to circumvent their limitations with respect to toxicity [13] and drug resistance [14] largely rely on repurposing of existing drugs [15]. These include the antifungal drug amphotericin B, the off-patent antibiotic paromomycin, the oral anticancer drug miltefosine, and the antimalarial drug sitamaquine, all of which were shown efficient for treating leishmaniases. Despite the success of this repurposing strategy, all these therapies have important limitations: (1) miltefosine is teratogenic, can provoke acute gastrointestinal side effects, and the length of the treatment (several weeks) causes poor treatment compliance with the risk of relapse [16], (2) conventional amphotericin B deoxycholate is not only nephrotoxic but also costly and cannot be stored at high temperature, rendering it unaffordable in some countries [17], and (3) paromomycin needs long parenteral regimens, involving qualified personnel and hospitalization [18].

In addition, depending on *Leishmania* species and geographical area, the parasite response to the drugs can vary substantially, with, for example, a cure rate of paromomycin treatment for VL ranging from 14.3% to 93.1% in Sudanese and Ethiopian patients, respectively [19]. Relapse can occur, and post-kala-azar dermal leishmaniasis can appear even months after the

end of therapy [20]. These drawbacks, together with the high attrition rate observed in the leishmaniases drug discovery pipeline, caused a recent shift from the discovery of new drugs to the use of combination therapies involving 2 or more drugs at lower dosage and shorter treatment duration [21]. This is believed to overcome 2 major handicaps of current drugs, i.e., toxicity and emergence of drug-resistant parasites.

The most important limitation of current antileishmanial drugs, however, is represented by treatment failures and the emergence of drug-resistant parasites. In Bihar state (India), efficiency of antimonial therapy fell to 40% in certain hyperendemic areas [22] due to the presence of drug-resistant strains [14]. A *Leishmania infantum* strain isolated from a patient who suffered various relapses and received multiple antimonial and amphotericin B treatments was shown to be resistant to both drugs [23], suggesting that even combination therapy may be of only limited use.

Drug target discovery exploiting *Leishmania*-specific biology

Current efforts towards antileishmanial drug discovery largely rely on the identification of target molecules that present significant structural and/or functional differences to their mammalian orthologs and are implicated in biochemical and metabolic pathways essential for parasite viability or infectivity. Following this rationale, a number of potential target candidates have been identified (reviewed in [24]) and implicated in a large variety of biological functions (S1 Table). The possibility to selectively inhibit the proteasomes of the 3 pathogenic trypanosomatids, i.e., *Leishmania* spp., *Trypanosoma cruzi*, and *T. brucei*, without interfering with the mammalian orthologous pathway holds great promise to discover novel treatments with broad applicability on the most important neglected tropical diseases (NTDs) [25]. Such a pan-anti-kinetoplastid drug may motivate Big Pharma to engage in NTD drug development, as it will increase the potential for economic return.

Despite the success of biochemical, pharmacological, and genetic approaches to validate a large number of *Leishmania* molecules as potential drug targets, any new drug that directly targets the parasite (including pan-kinetoplastid therapies) will likely have only a short therapeutic use, given the capacity of *Leishmania* to rapidly evolve towards drug-resistant phenotypes, which is partly linked to its remarkable genome plasticity. It is well established that *Leishmania* can escape drug action by modulating its gene content through various mechanisms, including gene tandem duplication, deletion, or extrachromosomal amplification, which rely on homologous recombination via interspersed repeated sequence elements [26–30]. In the absence of transcriptional regulation, *Leishmania* often resorts to chromosomal amplification as a means to modulate gene expression and to override drug pressure or adapt to a changing environment [31–34]. Likewise, mutation or deletion of transporter genes, such as those coding for aquaglyceroporine, the miltefosine transporter, or its accessory protein, LdRos3, have been linked to drug resistance [28, 35, 36].

In the following, we therefore propose host-directed therapeutic strategies as a new venue for antileishmanial drug discovery and discuss why they may be more refractory to the emergence of drug resistance.

The impact of intracellular *Leishmania* infection on the host cell phenotype

The *Leishmania*–macrophage interaction provides an excellent example of coevolution that promotes parasite survival and causes diseases [10, 37, 38]. Conceivably, interfering with these processes represents a promising new strategy for antileishmanial intervention. In the following, we will explore the possibility to target macrophage–*Leishmania* interaction by reviewing the current literature on host cell pathways that are modulated by intracellular *Leishmania*.

Impact on host innate and adaptive responses

Macrophages eliminate pathogenic microorganisms directly via nitric oxide (NO) or reactive oxygen species (ROS), or indirectly via the production of pro-inflammatory cytokines that initiate antimicrobial responses. *Leishmania* evades and subverts these host cell functions through the use of parasite proteins and glycolipid effectors, which are either expressed on the parasite surface or released into the cytoplasm, where they target host cell signaling processes [39–42]. Additionally, *Leishmania* interferes with the antigen-presentation capacity of their host cells through multiple mechanisms, implicating changes in abundance of costimulatory molecules or Major Histocompatibility Complex (MHC)-peptide complexes, destabilization of lipid rafts, or sequestration of *Leishmania* antigens [42–48]. Finally, *Leishmania* can interfere with the expression of microRNAs, which are considered as master regulators of the cellular transcriptome with important immunomodulatory functions (reviewed in [49]). In conclusion, a better understanding of how *Leishmania* interferes with macrophage immune functions may open important new venues to rescue the host cell's immune potential by immunotherapy or immunochemotherapy, for example, using pro-inflammatory cytokines and chemokines alone or in combination with antileishmanial drugs (reviewed in [50, 51]).

Impact on host cell viability

One of the striking features of the molecular dialogue between *Leishmania* and its host cell is the increased life span observed for parasite-infected macrophages. Since the seminal study of Moore and Matlashewski suggesting a *Leishmania*-dependent inhibition of host cell apoptosis [52], this observation has been confirmed by various reports [53, 54]. More recent reports studying the anti-apoptotic effect observed in the VL mouse model proposed molecular mechanisms involving *Leishmania*-CpG motifs, host myeloid cell leukemia 1 factor (MCL-1), and the cAMP response element binding protein (CREB) transcription factor [55, 56].

Impact on host cell metabolism

Auxotrophy of the intracellular *Leishmania* amastigote developmental stage for various essential nutrients renders this parasite dependent upon host resources for its growth during mammalian colonization [38, 57]. It is therefore not surprising that the impact of *Leishmania* infection on the host cell transcriptome translates into important metabolic changes that fuel parasite intracellular growth. Indeed, various reports demonstrated the up-regulation of genes coding for key molecules involved in sterol and fatty acid metabolisms during the early phase of infection and during active multiplication of intracellular parasites [11, 12, 58]. These transcriptional studies were supported by proteomics findings demonstrating the establishment of a *Leishmania*-specific macrophage protein expression profile with singular features related to major metabolic pathways [59–61]. Together, these data confirm that *Leishmania* turn their host cells into metabolic factories to ensure intracellular amastigote growth. Conceivably, this metabolic dependence of the parasite on the host cell may open new venues to eliminate intracellular *Leishmania*, for example, by pharmacological restoration of normal macrophage metabolic functions that may cause parasite death by starvation.

Targeting host–pathogen interaction for chemotherapeutic intervention

Targeting the host for antimicrobial therapy has been recognized as a new and fertile venue to treat viral, bacterial, and fungal diseases that provides the advantage to dramatically increase the genetic barrier for drug resistance [62–64]. Such host-directed therapies largely depend

either on drugs developed for noncommunicable diseases that show good safety profiles or various forms of immunotherapeutic intervention [65, 66]. The possibility to adopt the same strategy against *Leishmania* is supported by reports on the antileishmanial effects of imiquimod, which acts as a Toll-Like Receptor (TLR) agonist [67], or the compound Naloxonazine, which kills intracellular *Leishmania* by targeting host cell vATPases [68].

In the following, we propose parasite-released ectoproteins that can affect host cell signal transduction *in trans* and host histone-modifying enzymes that may be subverted by intracellular *Leishmania* as possible targets for the discovery of host-directed drug candidates (S2 Table).

Targeting *Leishmania* ectokinases and modulation of host cell signaling

Although the impact of intracellular *Leishmania* on host cell immune signaling and pathogenesis has been recognized [9, 43, 69], little information is available on how parasite signaling proteins, particularly released protein kinases, are involved in the modulation of host cell signaling. The importance of released kinases in the survival of intracellular parasites is well illustrated by members of the *Toxoplasma* ROP kinases family, with ROP16 phosphorylating and activating STAT3 [70, 71], thus mimicking anti-inflammatory signal transduction. Likewise, members of the *Plasmodium* FIK kinase protein family [72] that are exported into the erythrocyte cytoplasm shortly after infection were implicated in remodeling host cell membrane and cytoskeleton, with a likely impact on cytoadhesion [73]. In contrast, the role of *Leishmania* ectokinases in intracellular infection has not been studied in detail. Studies on the secretome and the exosomal proteome in *L. donovani* promastigotes identified over 400 putative ectoproteins [74, 75], including 13 secreted and 14 exosomal kinases, the majority of which are involved in biochemical processes (glycolytic pathways, nucleotide synthesis), suggesting an important effect on the host cell metabolism. Only 3 signaling kinases were identified, i.e., the mitogen-activated protein kinases MPK3 and MPK11 and Casein kinase 1 isoform 2 (CK1.2). Only CK1.2 has been functionally linked to infection and host cell immune subversion and, thus, is further described below.

CK1.2 (LmjF.35.1010) is a serine/threonine protein kinase that has attracted considerable interest as a putative drug target. Known CK1 inhibitors have been shown to block growth of extracellular *Leishmania* in in vitro culture [76] and intracellular parasites established in primary murine macrophages [77, 78]. *Leishmania* CK1.2 is a highly conserved kinase with over 70% of identity with its human ortholog, suggesting that the evolution of this kinase is driven by its interaction with host cell substrates. CK1.2 is also the most conserved kinase across all *Leishmania* species (over 99% of identity), further supporting the notion that its evolution may be uncoupled from species-specific constraints and driven by interaction with host proteins during intracellular infection [78]. Additionally, CK1.2 can directly phosphorylate host substrates, such as the human complement component C3a [79, 80] or the human receptor IFNAR1 attenuating the cellular responses to IFNα in vitro [81].

CK1.2 and other kinases thus likely impact on host cell signaling and metabolism to establish permissive conditions for intracellular *Leishmania* survival. Targeting such parasite-released "trans-acting" signaling factors constitutes a very interesting novel approach for the development of antileishmanials for 2 reasons: first, kinase inhibitors are prime candidates to treat various human pathologies, including cancer, diabetes, or inflammation. Thus, drug-discovery efforts directed to target *Leishmania*-released kinases can benefit from the availability of dedicated libraries that have already been well characterized. Second, it is conceivable that inhibitors that target *Leishmania*-released kinases that only affect the host may be more refractory for the development of drug resistance. Finally, mutation of these kinases may affect their role in host cell immune evasion and thus be strongly detrimental for parasite survival.

Targeting *Leishmania*-dependent epigenetic host cell reprogramming

The important impact of intracellular pathogens on the host cell transcriptome incited studies on the epigenetic consequences of infection. Epigenetics refers to heritable changes in gene expression that do not involve modifications of the underlying DNA sequence but depend on alteration of either DNA or of histone proteins influencing chromatin structure and local gene expression. Various pathogens modulate host cell DNA methylation levels to inhibit expression of genes that are involved in clearance of the infectious agent but also increase expression of genes that promote microbial growth and survival. For example, changes in DNA methylation levels were linked to (1) attenuated NFKB1- and IRF2-mediated pro-inflammatory signaling during *Mycobacterium tuberculosis* infection [82], (2) modulation of the inflammatory response, apoptosis, and pathogen-induced signaling during *Burkholderia pseudomallei* infection [83], and (3) changes in host behavior as observed in *Toxoplasma gondii*–infected mice, in which a decrease in the methylation levels of the arginine vasopressin promoter and subsequent increased neuronal gene expression were linked to fear reversion against the natural predator, promoting parasite transmission [84]. In contrast to these examples, only very limited information is available on the epigenetic impact of *Leishmania* infection on the host cell, with only 1 recent study showing that *L. donovani* causes epigenetic variation in macrophage DNA methylation, thus interfering with genes implicated in host cell antimicrobial defense [85].

Infectious microbes also remodel the chromatin and its accessibility by altering histone modifications. For example, *T. gondii* infection blocks Histone 3 (H3) phosphorylation of serine 10 and acetylation of lysines 4 and 9 in the promoter of TNFα, thus causing a transcriptional downregulation of this pro-inflammatory cytokine [86]. Likewise, decreased histone acetylation during *T. gondii* infection has been linked to altered STAT1 binding to INFγ-regulated promoters, which was reversed by treatment with histone deacetylase inhibitors [87]. *Theileria*-induced SMYD3 methyltransferase activity increases histone 3 lysine 4 trimethylation in the promoter of the host cell matrix metalloproteinase 9 gene, and increased expression of this protein has been linked to the invasive phenotype of infected cells [88].

In addition, secreted microbial proteins have been shown to interfere with host epigenetic control and gene expression. Influenza virus NS1 shares similarity with the H3 tail that binds the human polymerase-associated factor 1 complex, thus attenuating antiviral gene expression [89]. During *Listeria monocytogenes* infection, the host deacetylase sirtuin 2 (SIRT2) translocates to the nucleus, causing deacetylation of H3K18, thereby facilitating infection by repressing a specific set of genes [90]. *Chlamydia trachomatis* and *Legionella pneumophila* use a similar mechanism, secreting proteins with a conserved SET domain that specifically methylates host cell histones, allowing direct regulation of host gene expression [91, 92].

Surprisingly, despite the massive effect of *Leishmania* infection on the host cell transcriptome and the potential effect of parasite-released proteases on the nuclear proteome [93], no information is available on how the parasite affects histone modification of the host macrophage. The *Leishmania* genome encodes for an important number of putative histone-modifying enzymes (HMEs) [94]. In light of the largely constitutive gene expression in these early-branching eukaryotes, it is interesting to speculate that some of these proteins may be released and modify host cell histones to establish permissive conditions for intracellular survival. Alternatively, *Leishmania* infection may alter the activity of host cell HMEs that establishes an epigenetic profile permissive for intracellular parasite survival. Targeting parasite-released HMEs or directly modulating the host cell epigenome opens exciting new avenues for antileishmanial therapies that may be more refractory to the emergence of drug resistance. This possibility is supported by recent findings demonstrating that the antileishmanial effect

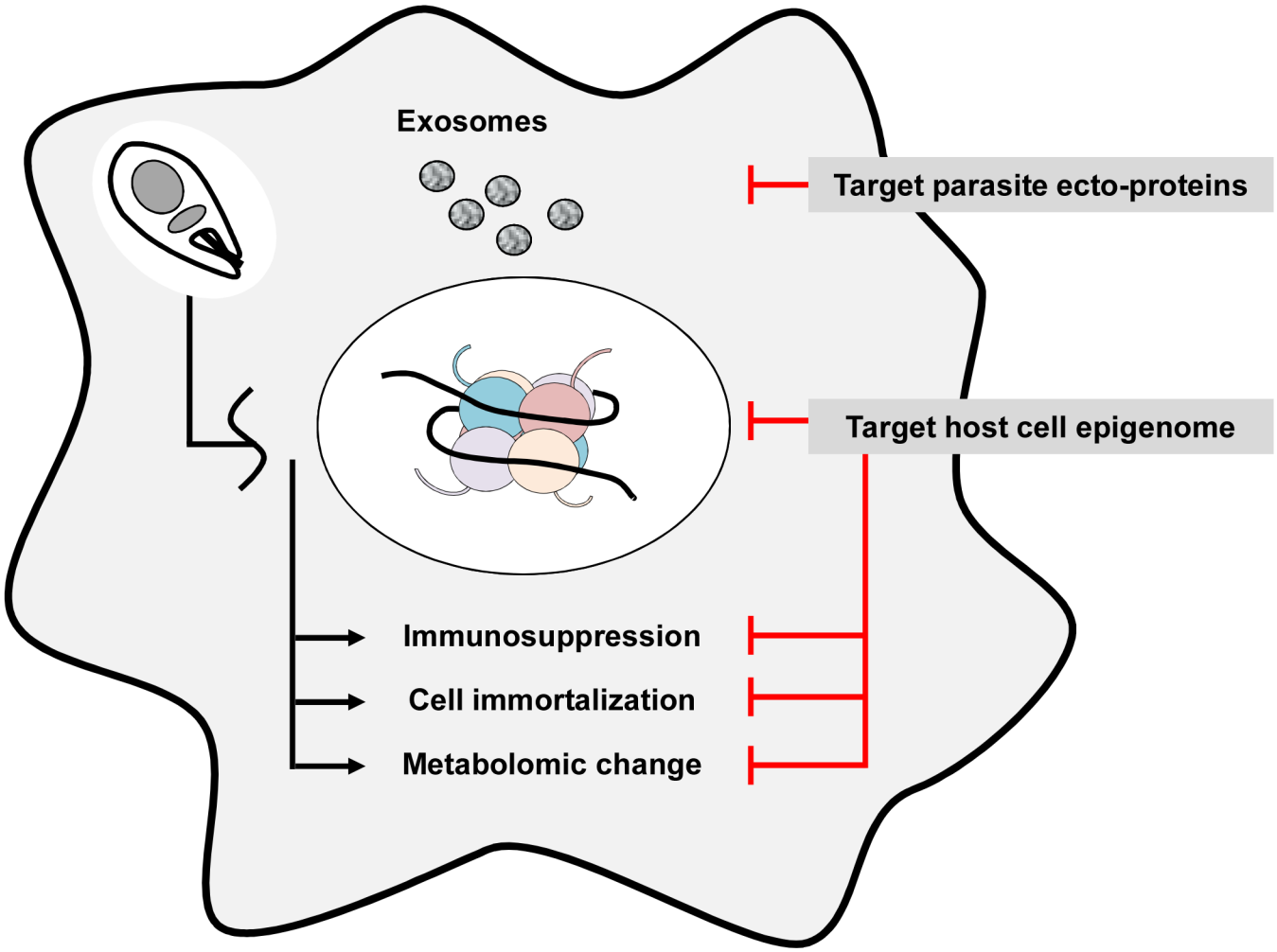

Fig 2. Targeting host–parasite interaction as a new venue for antileishmanial drug discovery. Exosomal or secreted parasite factors released into the host cell likely modulate the macrophage epigenome, causing phenotypic changes that favor parasite survival, including suppression of immune functions, prolongation of host cell survival, and metabolic changes necessary for parasite proliferation. Interfering with parasite factors that act *in trans* on the host cell or restoration of the normal host cell epigenome will likely interfere with intracellular parasite survival and may thus be exploited for antileishmanial drug discovery.

https://doi.org/10.1371/journal.pntd.0005480.g002

of imipramine, an antidepressant, is mediated via its effect on host cell HDAC11, which decreases IL10 expression [95], thus overcoming a host cell-dependent mechanism of antimony resistance.

Conclusions

In conclusion, the capacity of *Leishmania* to evolve towards a drug-resistant phenotype calls for new concepts for antileishmanial drug discovery. Our review proposes such new strategies by (1) targeting parasite ectokinases that modulate the host cell phenotype to establish permissive conditions for parasite survival, and (2) targeting host cell histone-modifying enzymes to restore a normal macrophage transcript profile that may be deleterious for intracellular *Leishmania* survival (Fig 2). Systems-level approaches combining high-throughput sequencing, proteomics and metabolomics analyses, RNAi screening, and pharmacological assessment need to be conducted to establish the proof-of-principle for these strategies and discover and validate

such novel targets. Drug targets that are not under the direct genetic control of the parasite may allow the discovery of inhibitors that are likely more refractory to classical mechanisms of drug resistance that often involves mutation of target gene or uptake systems, or amplification of efflux pumps.

Despite their great promise, host-directed therapies bear their own new challenges. First, given the differences in lifestyle and pathogenicity between the 3 major trypanosomatid pathogens, with *T. brucei* being an obligate extracellular pathogen and *T. cruzi* infecting various mammalian cells, the development of a pan-kinetoplastid therapy seems difficult. This fact is further illustrated by a recent high-throughput drug-screening campaign against all 3 trypanosomatids that identified only a few compounds with broad activity [96]. Even though one may expect that this will turn down Big Pharma from host-directed therapies, quite on the contrary, this strategy may actually incite important interest, as macrophages are the host cells of various viral, bacterial, and fungal pathogens with major global public health impact. It is conceivable that these pathogens have evolved intracellular survival strategies that are analogous to the ones employed by *Leishmania*, opening the exciting and yet unexplored possibility of pan-intracellular pathogen therapies.

A second major concern for host-directed therapies is toxicity. However, many host functions are the targets of successful therapies against various noncommunicable diseases, such as cancer or autoimmunity, and a repurposing strategy is already successfully applied on various infectious diseases. For example, protein kinases and epigenetic enzymes represent some of the most important groups of drug targets currently in development for various human diseases and are the subject of several U.S. Food and Drug Administration (FDA)–approved drugs, opening the interesting venue to repurpose existing treatments with good safety profiles for antileishmanial chemotherapy.

Key learning points

- High attrition rate in drug discovery pipeline for leishmaniases means very few new candidate drugs available.
- *Leishmania* genome plasticity allows swift adaptation to new antiparasitic drugs.
- Targeting *Leishmania*–host cell interactions is a novel strategy to circumvent *Leishmania* drug resistance.
- *Leishmania* ectoproteins are likely more refractory to drug resistance.
- Modulation of host cell epigenome is important to control intracellular *Leishmania* growth.

Top five papers

1. Nagle AS, Khare S, Kumar AB, Supek F, Buchynskyy A, Mathison CJ, et al. Recent developments in drug discovery for leishmaniasis and human African trypanosomiasis. Chem Rev. 2014 Nov 26;114(22):11305-47.doi 10.1021/cr500365f. http://www.ncbi.nlm.nih.gov/pubmed/25365529 PMID:25365529
2. Peña I, Pilar Manzano M, Cantizani J, Kessler A, Alonso-Padilla J, Bardera AI, et al. New compound sets identified from high throughput phenotypic screening against

three kinetoplastid parasites: an open resource. Sci Rep. 2015;5:8771.doi: 10.1038/srep08771. http://www.ncbi.nlm.nih.gov/pubmed/25740547

3. Khare S, Nagle AS, Biggart A, Lai YH, Liang F, Davis LC, et al. Proteasome inhibition for treatment of leishmaniasis, Chagas disease and sleeping sickness. Nature. 2016 Aug 8.doi: 10.1038/nature19339. http://www.ncbi.nlm.nih.gov/pubmed/27501246
4. Leprohon P, Fernandez-Prada C, Gazanion E, Monte-Neto R, Ouellette M. Drug resistance analysis by next generation sequencing in Leishmania. Int J Parasitol Drugs Drug Resist. 2015 Apr;5(1):26-35.doi: 10.1016/j.ijpddr.2014.09.005. http://www.ncbi.nlm.nih.gov/pubmed/25941624
5. Marr AK, MacIsaac JL, Jiang R, Airo AM, Kobor MS, McMaster WR. Leishmania donovani infection causes distinct epigenetic DNA methylation changes in host macrophages. PLoS Pathog. 2014 Oct;10(10):e1004419.doi: 10.1371/journal.ppat.1004419. http://www.ncbi.nlm.nih.gov/pubmed/25299267

Supporting information

S1 Table. Potential drug targets expressed by *Leishmania*.
(PDF)

S2 Table. Potential drug targets expressed by the host cell or secreted by *Leishmania*.
(PDF)

References

1. Leishmaniasis in high-burden countries: an epidemiological update based on data reported in 2014. Wkly Epidemiol Rec. 2016; 91(22):287–96. Epub 2016/06/07. PMID: 27263128.
2. Alvar J, Velez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. PLoS ONE. 2012; 7(5):e35671. Epub 2012/06/14. https://doi.org/10.1371/journal.pone.0035671 PMID: 22693548;
3. Al-Salem W, Herricks JR, Hotez PJ. A review of visceral leishmaniasis during the conflict in South Sudan and the consequences for East African countries. Parasit Vectors. 2016; 9:460. Epub 2016/08/24. https://doi.org/10.1186/s13071-016-1743-7 PMID: 27549162;
4. Du R, Hotez PJ, Al-Salem WS, Acosta-Serrano A. Old World Cutaneous Leishmaniasis and Refugee Crises in the Middle East and North Africa. PLoS Negl Trop Dis. 2016; 10(5):e0004545. Epub 2016/05/27. https://doi.org/10.1371/journal.pntd.0004545 PMID: 27227772;
5. Berry I, Berrang-Ford L. Leishmaniasis, conflict, and political terror: A spatio-temporal analysis. Soc Sci Med. 2016; 167:140–9. Epub 2016/05/20. https://doi.org/10.1016/j.socscimed.2016.04.038 PMID: 27194448.
6. Liu D, Uzonna JE. The early interaction of *Leishmania* with macrophages and dendritic cells and its influence on the host immune response. Front Cell Infect Microbiol. 2012; 2:83. Epub 2012/08/25. https://doi.org/10.3389/fcimb.2012.00083 PMID: 22919674;
7. Srivastava S, Shankar P, Mishra J, Singh S. Possibilities and challenges for developing a successful vaccine for leishmaniasis. Parasit Vectors. 2016; 9(1):277. Epub 2016/05/14. https://doi.org/10.1186/s13071-016-1553-y PMID: 27175732;
8. Geiger A, Bossard G, Sereno D, Pissarra J, Lemesre JL, Vincendeau P, et al. Escaping Deleterious Immune Response in Their Hosts: Lessons from Trypanosomatids. Front Immunol. 2016; 7:212. Epub 2016/06/16. https://doi.org/10.3389/fimmu.2016.00212 PMID: 27303406;
9. Shio MT, Hassani K, Isnard A, Ralph B, Contreras I, Gomez MA, et al. Host cell signalling and *Leishmania* mechanisms of evasion. Journal of tropical medicine. 2012; 2012:819512. Epub 2011/12/02. https://doi.org/10.1155/2012/819512 PMID: 22131998;
10. Olivier M, Gregory DJ, Forget G. Subversion mechanisms by which *Leishmania* parasites can escape the host immune response: a signaling point of view. Clin Microbiol Rev. 2005; 18(2):293–305. Epub 2005/04/16. https://doi.org/10.1128/CMR.18.2.293-305.2005 PMID: 15831826;

11. Rabhi I, Rabhi S, Ben-Othman R, Rasche A, Daskalaki A, Trentin B, et al. Transcriptomic signature of *Leishmania* infected mice macrophages: a metabolic point of view. PLoS Negl Trop Dis. 2012; 6(8): e1763. Epub 2012/08/29. https://doi.org/10.1371/journal.pntd.0001763 PMID: 22928052;

12. Osorio y Fortea J, de La Llave E, Regnault B, Coppee JY, Milon G, Lang T, et al. Transcriptional signatures of BALB/c mouse macrophages housing multiplying *Leishmania amazonensis* amastigotes. BMC Genomics. 2009; 10:119. Epub 2009/03/24. https://doi.org/10.1186/1471-2164-10-119 PMID: 19302708;

13. Sundar S, Chakravarty J. Antimony toxicity. Int J Environ Res Public Health. 2010; 7(12):4267–77. Epub 2011/02/15. https://doi.org/10.3390/ijerph7124267 PMID: 21318007;

14. Croft SL, Sundar S, Fairlamb AH. Drug resistance in leishmaniasis. Clin Microbiol Rev. 2006; 19 (1):111–26. Epub 2006/01/19. https://doi.org/10.1128/CMR.19.1.111-126.2006 PMID: 16418526;

15. Shakya N, Bajpai P, Gupta S. Therapeutic switching in Leishmania chemotherapy: a distinct approach towards unsatisfied treatment needs. J Parasit Dis. 2011; 35(2):104–12. Epub 2012/10/02. https://doi.org/10.1007/s12639-011-0040-9 PMID: 23024489;

16. Uranw S, Ostyn B, Dorlo TP, Hasker E, Dujardin B, Dujardin JC, et al. Adherence to miltefosine treatment for visceral leishmaniasis under routine conditions in Nepal. Trop Med Int Health. 2013; 18 (2):179–87. Epub 2012/12/04. https://doi.org/10.1111/tmi.12025 PMID: 23199340.

17. Bern C, Adler-Moore J, Berenguer J, Boelaert M, den Boer M, Davidson RN, et al. Liposomal amphotericin B for the treatment of visceral leishmaniasis. Clin Infect Dis. 2006; 43(7):917–24. Epub 2006/08/31. https://doi.org/10.1086/507530 PMID: 16941377.

18. Sinha PK, Jha TK, Thakur CP, Nath D, Mukherjee S, Aditya AK, et al. Phase 4 pharmacovigilance trial of paromomycin injection for the treatment of visceral leishmaniasis in India. Journal of tropical medicine. 2011; 2011:645203. Epub 2011/12/17. https://doi.org/10.1155/2011/645203 PMID: 22174722;

19. Hailu A, Musa A, Wasunna M, Balasegaram M, Yifru S, Mengistu G, et al. Geographical variation in the response of visceral leishmaniasis to paromomycin in East Africa: a multicentre, open-label, randomized trial. PLoS Negl Trop Dis. 2010; 4(10):e709. Epub 2010/11/05. https://doi.org/10.1371/journal.pntd.0000709 PMID: 21049059;

20. Burza S, Sinha PK, Mahajan R, Sanz MG, Lima MA, Mitra G, et al. Post Kala-Azar dermal leishmaniasis following treatment with 20 mg/kg liposomal amphotericin B (Ambisome) for primary visceral leishmaniasis in Bihar, India. PLoS Negl Trop Dis. 2014; 8(1):e2611. Epub 2014/01/07. https://doi.org/10.1371/journal.pntd.0002611 PMID: 24392171;

21. van Griensven J, Boelaert M. Combination therapy for visceral leishmaniasis. Lancet. 2011; 377 (9764):443–4. Epub 2011/01/25. https://doi.org/10.1016/S0140-6736(10)62237-4 PMID: 21255829.

22. Sundar S. Drug resistance in Indian visceral leishmaniasis. Trop Med Int Health. 2001; 6(11):849–54. Epub 2001/11/13. PMID: 11703838.

23. de Moura TR, Santos ML, Braz JM, Santos LF, Aragao MT, de Oliveira FA, et al. Cross-resistance of *Leishmania infantum* isolates to nitric oxide from patients refractory to antimony treatment, and greater tolerance to antileishmanial responses by macrophages. Parasitol Res. 2016; 115(2):713–21. Epub 2015/10/21. https://doi.org/10.1007/s00436-015-4793-4 PMID: 26481489.

24. Nagle AS, Khare S, Kumar AB, Supek F, Buchynskyy A, Mathison CJ, et al. Recent developments in drug discovery for leishmaniasis and human African trypanosomiasis. Chem Rev. 2014; 114 (22):11305–47. Epub 2014/11/05. https://doi.org/10.1021/cr500365f PMID: 25365529;

25. Khare S, Nagle AS, Biggart A, Lai YH, Liang F, Davis LC, et al. Proteasome inhibition for treatment of leishmaniasis, Chagas disease and sleeping sickness. Nature. 2016. Epub 2016/08/09. https://doi.org/10.1038/nature19339 PMID: 27501246.

26. Leprohon P, Fernandez-Prada C, Gazanion E, Monte-Neto R, Ouellette M. Drug resistance analysis by next generation sequencing in *Leishmania*. Int J Parasitol Drugs Drug Resist. 2015; 5(1):26–35. Epub 2015/05/06. https://doi.org/10.1016/j.ijpddr.2014.09.005 PMID: 25941624;

27. Bringaud F, Rogers M, Ghedin E. Identification and analysis of ingi-related retroposons in the trypanosomatid genomes. Methods Mol Biol. 2015; 1201:109–22. Epub 2014/11/13. https://doi.org/10.1007/978-1-4939-1438-8_6 PMID: 25388110.

28. Monte-Neto R, Laffitte MC, Leprohon P, Reis P, Frezard F, Ouellette M. Intrachromosomal amplification, locus deletion and point mutation in the aquaglyceroporin AQP1 gene in antimony resistant *Leishmania (Viannia) guyanensis*. PLoS Negl Trop Dis. 2015; 9(2):e0003476. Epub 2015/02/14. https://doi.org/10.1371/journal.pntd.0003476 PMID: 25679388;

29. Mukherjee A, Boisvert S, Monte-Neto RL, Coelho AC, Raymond F, Mukhopadhyay R, et al. Telomeric gene deletion and intrachromosomal amplification in antimony-resistant *Leishmania*. Mol Microbiol. 2013; 88(1):189–202. Epub 2013/02/21. https://doi.org/10.1111/mmi.12178 PMID: 23421749.

30. Berg M, Mannaert A, Vanaerschot M, Van Der Auwera G, Dujardin JC. (Post-) Genomic approaches to tackle drug resistance in *Leishmania*. Parasitology. 2013; 140(12):1492–505. Epub 2013/03/14. https://doi.org/10.1017/S0031182013000140 PMID: 23480865.

31. Ubeda JM, Legare D, Raymond F, Ouameur AA, Boisvert S, Rigault P, et al. Modulation of gene expression in drug resistant *Leishmania* is associated with gene amplification, gene deletion and chromosome aneuploidy. Genome Biol. 2008; 9(7):R115. Epub 2008/07/22. https://doi.org/10.1186/gb-2008-9-7-r115 PMID: 18638379;

32. Leprohon P, Legare D, Raymond F, Madore E, Hardiman G, Corbeil J, et al. Gene expression modulation is associated with gene amplification, supernumerary chromosomes and chromosome loss in antimony-resistant *Leishmania infantum*. Nucleic Acids Res. 2009; 37(5):1387–99. Epub 2009/01/09. https://doi.org/10.1093/nar/gkn1069 PMID: 19129236;

33. Decuypere S, Vanaerschot M, Brunker K, Imamura H, Muller S, Khanal B, et al. Molecular mechanisms of drug resistance in natural *Leishmania* populations vary with genetic background. PLoS Negl Trop Dis. 2012; 6(2):e1514. Epub 2012/03/06. https://doi.org/10.1371/journal.pntd.0001514 PMID: 22389733;

34. Mannaert A, Downing T, Imamura H, Dujardin JC. Adaptive mechanisms in pathogens: universal aneuploidy in *Leishmania*. Trends Parasitol. 2012; 28(9):370–6. Epub 2012/07/14. https://doi.org/10.1016/j.pt.2012.06.003 PMID: 22789456.

35. Coelho AC, Boisvert S, Mukherjee A, Leprohon P, Corbeil J, Ouellette M. Multiple mutations in heterogeneous miltefosine-resistant *Leishmania major* population as determined by whole genome sequencing. PLoS Negl Trop Dis. 2012; 6(2):e1512. Epub 2012/02/22. https://doi.org/10.1371/journal.pntd.0001512 PMID: 22348164;

36. Pérez-Victoria FJ, Sanchez-Cañete MP, Castanys S, Gamarro F. Phospholipid translocation and miltefosine potency require both *L. donovani* miltefosine transporter and the new protein LdRos3 in *Leishmania* parasites. J Biol Chem. 2006; 281(33):23766–75. Epub 2006/06/21. https://doi.org/10.1074/jbc.M605214200 PMID: 16785229.

37. Lievin-Le Moal V, Loiseau PM. *Leishmania* hijacking of the macrophage intracellular compartments. The FEBS journal. 2016; 283(4):598–607. Epub 2015/11/21. https://doi.org/10.1111/febs.13601 PMID: 26588037.

38. McConville MJ, Naderer T. Metabolic pathways required for the intracellular survival of *Leishmania*. Annu Rev Microbiol. 2011; 65:543–61. Epub 2011/07/05. https://doi.org/10.1146/annurev-micro-090110-102913 PMID: 21721937.

39. Podinovskaia M, Descoteaux A. *Leishmania* and the macrophage: a multifaceted interaction. Future Microbiol. 2015; 10(1):111–29. Epub 2015/01/20. https://doi.org/10.2217/fmb.14.103 PMID: 25598341.

40. Kaye P, Scott P. Leishmaniasis: complexity at the host-pathogen interface. Nat Rev Microbiol. 2011; 9(8):604–15. Epub 2011/07/13. https://doi.org/10.1038/nrmicro2608 PMID: 21747391.

41. Basu Ball W, Kar S, Mukherjee M, Chande AG, Mukhopadhyaya R, Das PK. Uncoupling protein 2 negatively regulates mitochondrial reactive oxygen species generation and induces phosphatase-mediated anti-inflammatory response in experimental visceral leishmaniasis. J Immunol. 2011; 187(3):1322–32. Epub 2011/06/28. https://doi.org/10.4049/jimmunol.1004237 PMID: 21705615.

42. Antoine JC, Prina E, Courret N, Lang T. *Leishmania* spp.: on the interactions they establish with antigen-presenting cells of their mammalian hosts. Adv Parasitol. 2004; 58:1–68. Epub 2004/12/18. https://doi.org/10.1016/S0065-308X(04)58001-6 PMID: 15603761.

43. Contreras I, Estrada JA, Guak H, Martel C, Borjian A, Ralph B, et al. Impact of *Leishmania mexicana* infection on dendritic cell signaling and functions. PLoS Negl Trop Dis. 2014; 8(9):e3202. Epub 2014/09/26. https://doi.org/10.1371/journal.pntd.0003202 PMID: 25255446;

44. Matheoud D, Moradin N, Bellemare-Pelletier A, Shio MT, Hong WJ, Olivier M, et al. *Leishmania* evades host immunity by inhibiting antigen cross-presentation through direct cleavage of the SNARE VAMP8. Cell Host Microbe. 2013; 14(1):15–25. Epub 2013/07/23. https://doi.org/10.1016/j.chom.2013.06.003 PMID: 23870310.

45. Cortez M, Huynh C, Fernandes MC, Kennedy KA, Aderem A, Andrews NW. *Leishmania* promotes its own virulence by inducing expression of the host immune inhibitory ligand CD200. Cell Host Microbe. 2011; 9(6):463–71. Epub 2011/06/15. https://doi.org/10.1016/j.chom.2011.04.014 PMID: 21669395;

46. Chakraborty D, Banerjee S, Sen A, Banerjee KK, Das P, Roy S. *Leishmania donovani* affects antigen presentation of macrophage by disrupting lipid rafts. J Immunol. 2005; 175(5):3214–24. Epub 2005/08/24. PMID: 16116212.

47. Meier CL, Svensson M, Kaye PM. *Leishmania*-induced inhibition of macrophage antigen presentation analyzed at the single-cell level. J Immunol. 2003; 171(12):6706–13. Epub 2003/12/10. PMID: 14662874.

48. Kima PE, Soong L, Chicharro C, Ruddle NH, McMahon-Pratt D. *Leishmania*-infected macrophages sequester endogenously synthesized parasite antigens from presentation to CD4+ T cells. Eur J Immunol. 1996; 26(12):3163–9. Epub 1996/12/01. https://doi.org/10.1002/eji.1830261249 PMID: 8977318.

49. Linhares-Lacerda L, Morrot A. Role of Small RNAs in Trypanosomatid Infections. Front Microbiol. 2016; 7:367. Epub 2016/04/12. https://doi.org/10.3389/fmicb.2016.00367 PMID: 27065454;

50. Singh OP, Sundar S. Immunotherapy and targeted therapies in treatment of visceral leishmaniasis: current status and future prospects. Front Immunol. 2014; 5:296. Epub 2014/09/04. https://doi.org/10.3389/fimmu.2014.00296 PMID: 25183962;

51. Roatt BM, Aguiar-Soares RD, Coura-Vital W, Ker HG, Moreira N, Vitoriano-Souza J, et al. Immunotherapy and Immunochemotherapy in Visceral Leishmaniasis: Promising Treatments for this Neglected Disease. Front Immunol. 2014; 5:272. Epub 2014/07/02. https://doi.org/10.3389/fimmu.2014.00272 PMID: 24982655;

52. Moore KJ, Matlashewski G. Intracellular infection by *Leishmania donovani* inhibits macrophage apoptosis. J Immunol. 1994; 152(6):2930–7. Epub 1994/03/15. PMID: 8144893.

53. Akarid K, Arnoult D, Micic-Polianski J, Sif J, Estaquier J, Ameisen JC. *Leishmania major*-mediated prevention of programmed cell death induction in infected macrophages is associated with the repression of mitochondrial release of cytochrome c. J Leukoc Biol. 2004; 76(1):95–103. Epub 2004/04/13. https://doi.org/10.1189/jlb.1001877 PMID: 15075349.

54. Getti GT, Cheke RA, Humber DP. Induction of apoptosis in host cells: a survival mechanism for *Leishmania* parasites? Parasitology. 2008; 135(12):1391–9. Epub 2008/09/09. https://doi.org/10.1017/S0031182008004915 PMID: 18775094.

55. Das S, Ghosh AK, Singh S, Saha B, Ganguly A, Das P. Unmethylated CpG motifs in the L. donovani DNA regulate TLR9-dependent delay of programmed cell death in macrophages. J Leukoc Biol. 2015; 97(2):363–78. Epub 2014/12/05. https://doi.org/10.1189/jlb.4A0713-378RR PMID: 25473100.

56. Giri J, Srivastav S, Basu M, Palit S, Gupta P, Ukil A. *Leishmania donovani* Exploits Myeloid Cell Leukemia 1 (MCL-1) Protein to Prevent Mitochondria-dependent Host Cell Apoptosis. J Biol Chem. 2016; 291 (7):3496–507. Epub 2015/12/17. https://doi.org/10.1074/jbc.M115.672873 PMID: 26670606;

57. McConville MJ, Saunders EC, Kloehn J, Dagley MJ. *Leishmania* carbon metabolism in the macrophage phagolysosome- feast or famine? F1000Res. 2015; 4(F1000 Faculty Rev):938. Epub 2015/11/26. https://doi.org/10.12688/f1000research.6724.1 PMID: 26594352;

58. Dillon LA, Suresh R, Okrah K, Corrada Bravo H, Mosser DM, El-Sayed NM. Simultaneous transcriptional profiling of *Leishmania major* and its murine macrophage host cell reveals insights into host-pathogen interactions. BMC Genomics. 2015; 16(1):1108. Epub 2015/12/31. https://doi.org/10.1186/s12864-015-2237-2 PMID: 26715493;

59. Moreira D, Rodrigues V, Abengozar M, Rivas L, Rial E, Laforge M, et al. *Leishmania* infantum modulates host macrophage mitochondrial metabolism by hijacking the SIRT1-AMPK axis. PLoS Pathog. 2015; 11(3):e1004684. Epub 2015/03/05. https://doi.org/10.1371/journal.ppat.1004684 PMID: 25738568;

60. Singh AK, Pandey RK, Siqueira-Neto JL, Kwon YJ, Freitas-Junior LH, Shaha C, et al. Proteomic-based approach to gain insight into reprogramming of THP-1 cells exposed to *Leishmania donovani* over an early temporal window. Infection and immunity. 2015; 83(5):1853–68. Epub 2015/02/19. https://doi.org/10.1128/IAI.02833-14 PMID: 25690103;

61. Menezes JP, Almeida TF, Petersen AL, Guedes CE, Mota MS, Lima JG, et al. Proteomic analysis reveals differentially expressed proteins in macrophages infected with *Leishmania amazonensis* or *Leishmania major*. Microbes and infection / Institut Pasteur. 2013; 15(8–9):579–91. Epub 2013/05/01. https://doi.org/10.1016/j.micinf.2013.04.005 PMID: 23628411.

62. Conteduca V, Sansonno D, Russi S, Pavone F, Dammacco F. Therapy of chronic hepatitis C virus infection in the era of direct-acting and host-targeting antiviral agents. J Infect. 2014; 68(1):1–20. Epub 2013/09/10. https://doi.org/10.1016/j.jinf.2013.08.019 PMID: 24012819.

63. Czyz DM, Potluri LP, Jain-Gupta N, Riley SP, Martinez JJ, Steck TL, et al. Host-directed antimicrobial drugs with broad-spectrum efficacy against intracellular bacterial pathogens. MBio. 2014; 5(4):e01534–14. Epub 2014/07/31. https://doi.org/10.1128/mBio.01534-14 PMID: 25073644;

64. Zumla A, Azhar EI, Arabi Y, Alotaibi B, Rao M, McCloskey B, et al. Host-directed therapies for improving poor treatment outcomes associated with the middle east respiratory syndrome coronavirus infections. Int J Infect Dis. 2015; 40:71–4. Epub 2015/09/15. https://doi.org/10.1016/j.ijid.2015.09.005 PMID: 26365771.

65. Zumla A, Rao M, Wallis RS, Kaufmann SH, Rustomjee R, Mwaba P, et al. Host-directed therapies for infectious diseases: current status, recent progress, and future prospects. Lancet Infect Dis. 2016; 16 (4):e47–63. Epub 2016/04/03. https://doi.org/10.1016/S1473-3099(16)00078-5 PMID: 27036359.

66. Santos PC, Teixeira MM, Souza DG. Opportunities for the development of novel therapies based on host-microbial interactions. Pharmacol Res. 2016; 112:68–83. Epub 2016/04/25. https://doi.org/10.1016/j.phrs.2016.04.005 PMID: 27107789.

67. Buates S, Matlashewski G. Treatment of experimental leishmaniasis with the immunomodulators imiquimod and S-28463: efficacy and mode of action. J Infect Dis. 1999; 179(6):1485–94. Epub 1999/05/06. https://doi.org/10.1086/314782 PMID: 10228071.

68. De Muylder G, Vanhollebeke B, Caljon G, Wolfe AR, McKerrow J, Dujardin JC. Naloxonazine, an Amastigote-Specific Compound, Affects *Leishmania* Parasites through Modulation of Host-Encoded Functions. PLoS Negl Trop Dis. 2016; 10(12):e0005234. Epub 2016/12/31. https://doi.org/10.1371/journal.pntd.0005234 PMID: 28036391.

69. Atayde VD, Hassani K, da Silva Lira Filho A, Borges AR, Adhikari A, Martel C, et al. *Leishmania* exosomes and other virulence factors: Impact on innate immune response and macrophage functions. Cell Immunol. 2016. Epub 2016/08/09. https://doi.org/10.1016/j.cellimm.2016.07.013 PMID: 27499212.

70. Yamamoto M, Standley DM, Takashima S, Saiga H, Okuyama M, Kayama H, et al. A single polymorphic amino acid on *Toxoplasma gondii* kinase ROP16 determines the direct and strain-specific activation of Stat3. J Exp Med. 2009; 206(12):2747–60. Epub 2009/11/11. https://doi.org/10.1084/jem.20091703 PMID: 19901082;

71. Ong YC, Reese ML, Boothroyd JC. *Toxoplasma* rhoptry protein 16 (ROP16) subverts host function by direct tyrosine phosphorylation of STAT6. J Biol Chem. 2010; 285(37):28731–40. Epub 2010/07/14. https://doi.org/10.1074/jbc.M110.112359 PMID: 20624917;

72. Ward P, Equinet L, Packer J, Doerig C. Protein kinases of the human malaria parasite *Plasmodium falciparum*: the kinome of a divergent eukaryote. BMC Genomics. 2004; 5:79. Epub 2004/10/14. https://doi.org/10.1186/1471-2164-5-79 PMID: 15479470;

73. Nunes MC, Okada M, Scheidig-Benatar C, Cooke BM, Scherf A. *Plasmodium falciparum* FIKK kinase members target distinct components of the erythrocyte membrane. PLoS ONE. 2010; 5(7):e11747. Epub 2010/07/30. https://doi.org/10.1371/journal.pone.0011747 PMID: 20668526;

74. Silverman JM, Chan SK, Robinson DP, Dwyer DM, Nandan D, Foster LJ, et al. Proteomic analysis of the secretome of *Leishmania donovani*. Genome Biol. 2008; 9(2):R35. Epub 2008/02/20. https://doi.org/10.1186/gb-2008-9-2-r35 PMID: 18282296;

75. Silverman JM, Clos J, de'Oliveira CC, Shirvani O, Fang Y, Wang C, et al. An exosome-based secretion pathway is responsible for protein export from *Leishmania* and communication with macrophages. J Cell Sci. 2010; 123(Pt 6):842–52. Epub 2010/02/18. https://doi.org/10.1242/jcs.056465 PMID: 20159964.

76. Knockaert M, Gray N, Damiens E, Chang YT, Grellier P, Grant K, et al. Intracellular targets of cyclin-dependent kinase inhibitors: identification by affinity chromatography using immobilised inhibitors. Chem Biol. 2000; 7(6):411–22. Epub 2000/06/30. PMID: 10873834.

77. Durieu E, Prina E, Leclercq O, Oumata N, Gaboriaud-Kolar N, Vougogiannopoulou K, et al. From Drug Screening to Target Deconvolution: a Target-Based Drug Discovery Pipeline Using *Leishmania* Casein Kinase 1 Isoform 2 To Identify Compounds with Antileishmanial Activity. Antimicrobial agents and chemotherapy. 2016; 60(5):2822–33. Epub 2016/02/24. https://doi.org/10.1128/AAC.00021-16 PMID: 26902771;

78. Rachidi N, Taly JF, Durieu E, Leclercq O, Aulner N, Prina E, et al. Pharmacological assessment defines *Leishmania donovani* casein kinase 1 as a drug target and reveals important functions in parasite viability and intracellular infection. Antimicrobial agents and chemotherapy. 2014; 58(3):1501–15. Epub 2013/12/25. https://doi.org/10.1128/AAC.02022-13 PMID: 24366737;

79. Sacerdoti-Sierra N, Jaffe CL. Release of ecto-protein kinases by the protozoan parasite *Leishmania major*. J Biol Chem. 1997; 272(49):30760–5. Epub 1998/01/10. PMID: 9388215.

80. Hermoso T, Fishelson Z, Becker SI, Hirschberg K, Jaffe CL. Leishmanial protein kinases phosphorylate components of the complement system. Embo J. 1991; 10(13):4061–7. Epub 1991/12/01. PMID: 1756717;

81. Liu J, Carvalho LP, Bhattacharya S, Carbone CJ, Kumar KG, Leu NA, et al. Mammalian casein kinase 1alpha and its leishmanial ortholog regulate stability of IFNAR1 and type I interferon signaling. Mol Cell Biol. 2009; 29(24):6401–12. Epub 2009/10/07. https://doi.org/10.1128/MCB.00478-09 PMID: 19805514;

82. Pacis A, Tailleux L, Morin AM, Lambourne J, MacIsaac JL, Yotova V, et al. Bacterial infection remodels the DNA methylation landscape of human dendritic cells. Genome Res. 2015; 25(12):1801–11. Epub 2015/09/24. https://doi.org/10.1101/gr.192005.115 PMID: 26392366;

83. Cizmeci D, Dempster EL, Champion OL, Wagley S, Akman OE, Prior JL, et al. Mapping epigenetic changes to the host cell genome induced by *Burkholderia pseudomallei* reveals pathogen-specific and

pathogen-generic signatures of infection. Sci Rep. 2016; 6:30861. Epub 2016/08/04. https://doi.org/10.1038/srep30861 PMID: 27484700;

84. Hari Dass SA, Vyas A. *Toxoplasma gondii* infection reduces predator aversion in rats through epigenetic modulation in the host medial amygdala. Mol Ecol. 2014; 23(24):6114–22. Epub 2014/08/22. https://doi.org/10.1111/mec.12888 PMID: 25142402.

85. Marr AK, MacIsaac JL, Jiang R, Airo AM, Kobor MS, McMaster WR. *Leishmania donovani* infection causes distinct epigenetic DNA methylation changes in host macrophages. PLoS Pathog. 2014; 10 (10):e1004419. Epub 2014/10/10. https://doi.org/10.1371/journal.ppat.1004419 PMID: 25299267;

86. Leng J, Butcher BA, Egan CE, Abi Abdallah DS, Denkers EY. *Toxoplasma gondii* prevents chromatin remodeling initiated by TLR-triggered macrophage activation. J Immunol. 2009; 182(1):489–97. Epub 2008/12/26. PMID: 19109180;

87. Lang C, Hildebrandt A, Brand F, Opitz L, Dihazi H, Luder CG. Impaired chromatin remodelling at STAT1-regulated promoters leads to global unresponsiveness of *Toxoplasma gondii*-infected macrophages to IFN-gamma. PLoS Pathog. 2012; 8(1):e1002483. Epub 2012/01/26. https://doi.org/10.1371/journal.ppat.1002483 PMID: 22275866;

88. Cock-Rada AM, Medjkane S, Janski N, Yousfi N, Perichon M, Chaussepied M, et al. SMYD3 promotes cancer invasion by epigenetic upregulation of the metalloproteinase MMP-9. Cancer Res. 2012; 72 (3):810–20. Epub 2011/12/24. https://doi.org/10.1158/0008-5472.CAN-11-1052 PMID: 22194464;

89. Marazzi I, Ho JS, Kim J, Manicassamy B, Dewell S, Albrecht RA, et al. Suppression of the antiviral response by an influenza histone mimic. Nature. 2012; 483(7390):428–33. Epub 2012/03/16. https://doi.org/10.1038/nature10892 PMID: 22419161;

90. Eskandarian HA, Impens F, Nahori MA, Soubigou G, Coppee JY, Cossart P, et al. A role for SIRT2-dependent histone H3K18 deacetylation in bacterial infection. Science. 2013; 341(6145):1238858. Epub 2013/08/03. https://doi.org/10.1126/science.1238858 PMID: 23908241.

91. Pennini ME, Perrinet S, Dautry-Varsat A, Subtil A. Histone methylation by NUE, a novel nuclear effector of the intracellular pathogen *Chlamydia trachomatis*. PLoS Pathog. 2010; 6(7):e1000995. Epub 2010/07/27. https://doi.org/10.1371/journal.ppat.1000995 PMID: 20657819;

92. Rolando M, Sanulli S, Rusniok C, Gomez-Valero L, Bertholet C, Sahr T, et al. *Legionella pneumophila* effector RomA uniquely modifies host chromatin to repress gene expression and promote intracellular bacterial replication. Cell Host Microbe. 2013; 13(4):395–405. Epub 2013/04/23. https://doi.org/10.1016/j.chom.2013.03.004 PMID: 23601102.

93. Isnard A, Christian JG, Kodiha M, Stochaj U, McMaster WR, Olivier M. Impact of *Leishmania* infection on host macrophage nuclear physiology and nucleopore complex integrity. PLoS Pathog. 2015; 11(3): e1004776. Epub 2015/04/01. https://doi.org/10.1371/journal.ppat.1004776 PMID: 25826301;

94. Ivens AC, Peacock CS, Worthey EA, Murphy L, Aggarwal G, Berriman M, et al. The genome of the kinetoplastid parasite, *Leishmania major*. Science. 2005; 309(5733):436–42. Epub 2005/07/16. https://doi.org/10.1126/science.1112680 PMID: 16020728;

95. Mukherjee S, Mukherjee B, Mukhopadhyay R, Naskar K, Sundar S, Dujardin JC, et al. Imipramine exploits histone deacetylase 11 to increase the IL-12/IL-10 ratio in macrophages infected with antimony-resistant *Leishmania donovani* and clears organ parasites in experimental infection. J Immunol. 2014; 193(8):4083–94. Epub 2014/09/14. https://doi.org/10.4049/jimmunol.1400710 PMID: 25217162.

96. Peña I, Pilar Manzano M, Cantizani J, Kessler A, Alonso-Padilla J, Bardera AI, et al. New compound sets identified from high throughput phenotypic screening against three kinetoplastid parasites: an open resource. Sci Rep. 2015; 5:8771. Epub 2015/03/06. https://doi.org/10.1038/srep08771 PMID: 25740547;