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Host-Parasite Genomic Interactions in Leishmaniasis: Emerging Diagnostic Biomarkers and Predictive Gene Signatures

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ABSTRACT

***Objective**: This review aims to explore the genetic underpinnings of Leishmaniasis, focusing on host-parasite genomic interactions and their implications for diagnostics, treatment, and control. **Method**: The study synthesizes recent advancements in host-parasite genomics, highlighting genetic polymorphisms in the host's immune response and parasite-mediated virulence determinants, identified through high-throughput sequencing and multi-omics analyses. **Results**: Key findings include the identification of genetic markers associated with immune responses and disease severity, as well as parasite traits influencing tissue tropism and survival. Co-regulated gene networks have been revealed, underscoring the dynamic interplay between host immunity and parasite adaptability. **Novelty**: The review identifies the potential for genomic biomarkers to differentiate asymptomatic carriers from active cases, predict treatment failure, and enable personalized treatment strategies. Furthermore, it discusses the prospects of genomic insights in developing targeted vaccines and enhancing control programs for leishmaniasis. This work contributes to precision medicine and the future control of leishmaniasis through the application of genomic biomarkers.*

INTRODUCTION

Leishmaniasis places the highest burden on developing countries, where 95% of cases occur [1]. Effective control of the parasite relies upon early detection of symptoms, appropriate treatment, and adequate patient management. The lack of laboratory and point-of-care diagnostics has prompted genomic analyses of host–Leishmania interactions in blood and other specimens, allowing investigators to examine whether stage-specific parasite expression and cross-talk with host pathways may fulfil unmet diagnostic and predictive needs [2]. Specific parasite genomes retain informative variation inaccessible from other biological materials, and are therefore amenable to early detection of circulating strains in leishmaniasis and other diseases [3]. Extensive whole-genome and single-cell transcriptomic studies across the host and parasite have revealed genomically encoded signatures at multiple levels that signal disease state, progression, treatment response, and relapse risk. Host- and parasite-derived genomic biomarkers and predictive gene signatures can thus be harnessed to determine the presence, form, and evolution of leishmaniasis and are enabled by integrated host–parasite genetic analyses [4].

Overview of Leishmaniasis and its Global Burden

Leishmaniasis, caused by protozoan parasites of the genus Leishmania, encompasses a spectrum of clinical manifestations ranging from self-healing cutaneous lesions to fatal visceral disease. Transmitted through the bite of infected female phlebotomine sandflies, Leishmania spp. infect millions of people each year across 98 countries and result in around 70,000 deaths, mostly in low- to middle-income settings [5]. Laissez faire Laissez-faire is one of the 20 neglected tropical diseases identified by the World Health Organization that contributes to the socioeconomic development delay and requires new initiatives to address its rising burden. Factors that contribute the risk of leishmaniasis transmission and aggravate its impact on the population of people include drug resistance, urbanization, and climate change. Differences in clinical outcome and pathogenicity due to high genetic diversity of the parasite make it challenging to diagnose and treat the disease [6].

The genome variation, stage-specific abilities and sequenced transcriptomes of multiple Leishmania strains characterize an extensive source of genomic information of disease development, transmission dynamics, epidemiology and virulence. The various parasite strains of Leishmania major, Leishmania tropica, Leishmania braziliensis and the rest cause different lesions and have impaired timely and proper therapy. Therefore, in addition to the dynamics of the genome of parasites, abundant genomic data on the host-pathogen interaction creates another chance to interpret and gain an understanding of leishmaniasis [7][8].

Host-Pathogen Genomic Interactions: Concepts and Relevance

Genomes share the same biological space and, therefore, they will act in harmony to establish the consequences of infection. Gene products mediate their interactions which belong to three integrated categories of pathways: signaling, metabolism, and immune defense [9]. Signaling pathways constitute the frontline contact with the genome and relay the extracellular signals to the intracellular environment. Metabolism provides the essential building blocks for genome maintenance, repair, and reproduction, and constitutes the intermediate bridge between environmental cues and gene regulation. Finally, the immune response represents an environment-dependent genomic outcome of infection, intentioned to eliminate the pathogen [10].

The host–Leishmania pertussis genomic interaction framework implies that substantial genomic cross-talk occurs at various stages of infection. By collecting genomic landscapes along the host–parasite axis, one can map the impact of parasite genes and counter the signature of their read-out at the level of expression regulation, chromatin remodeling, or secretion. The first such landscape indicates that the host is affected immediately, before the parasite deploys virulence factors, and thus specifies host attributes of the immediate phase of infection [11].

RESEARCH METHOD

Host Genomic Landscape in Leishmaniasis

Leishmania infection triggers a rapid innate immune response predominantly governed by intracellular-sensing pathways. Damage-associated molecular patterns (DAMPs) released during parasite transmission enhance the recognition capacity of pattern-recognition receptors (PRRs). Recent work has pinpointed sensors, downstream effectors and early-response gene sets actively engaged at the onset of leishmaniasis. Among them, the transcripts of receptors such as MRR2, STING, DDX58, KLRC2, CBF11 and TBK1 can be considered key indicators of infection, but also a wider range of early-response genes. These elements form the signature basics that are built up at the point of innate and adaptive immunity and guide the search of early and widely applicable diagnostic signals [12].

Leishmania spp. infection generates immune responses, which control the course of the disease. The repertoire studies of T- and B-cell receptors (TCR and BCR) of systemic compartments have shown a significant increase in the rate of repertoire diversification and selection in those who progress clinically and are in control. The increase in expression of co-inhibitory molecules is also a feature which is eminent at the acute stage of progressive infections but is not witnessed during control [13]. At transcriptomic scale, there are distinctive states, which can be defined based on the clinical outcome: two of the states are associated with the progression, and a control state is maintained by those who are on the verge of the progression. These results indicate that there are peripheral blood biomarkers that can stratify disease progression. They are working on defining features that are specific to treatment response and to make panels to identify more than one condition at a time and cross-genera signals [14].

Innate Immune Genomic Signatures

The Leishmaniasis parasites use the host innate immune response patterns to cause infection. Exposure of macrophages to Leishmania spp. raises expression of multiple sensing receptor genes, suggesting that it detects separate molecular signals of various species of parasites. Patterns of early-response triggered by L. major infection include the expression of the pattern recognition receptors TLR2 (TLR2) and TLR4, the scavenger receptor CD36, and defensins 1- a and 4- a [15]. These patterns set initial diagnostic signals for leishmaniasis, suggesting that parasite-triggered early innate immune responses are preserved across host lineages and conditioning factors. The discovery of conserved innate immune signatures represents an opportunity for developing universal and sensitive molecular diagnostics against leishmaniasis. These findings highlight innate immunity as a crucial host factor that influences susceptibility and clinical form of leishmaniasis and provides pathogen-specific and anti-microbiota gene opening to disentangle the complex interplay of Leishmania and gut microbiota during disease [16]. Following innate sensing, mammals mount adaptive immune responses and display T-cell receptor (TCR) and B-cell receptor (BCR) repertoire changes upon infection. In the dermis of mice experimental models, an increased frequency of certain TCR and BCR clonal expansion is correlated with disease progression. Changes

in the expression of several regulatory and inhibitory checkpoint genes, characteristic of chronic infection, are observed in T cells from the draining lymph node of CL mice without identifiable TCR or BCR clonal expansion. Experiments indicate that CL resolves independently of these effectors, while for VL, progression is still intimately coupled to the status of these pathways [17]. In L. infantum-infected dogs, transcriptomic signatures detected in peripheral blood distinguish dogs with advancement and systemic dissemination of the disease from those that restrict parasite multiplication to the skin and remain under control. Biomarkers for early and broad detection that remain informative after parasite clearance are critical for leishmaniasis. However, such parallels across species, clinical forms, and the different spatial organisation of parasite transmission are often challenging to identify, especially when transitions differ from naïve conditions [18].

Adaptive Immune Repertoire and Transcriptomics

The adaptive immune system is the second major host response to Leishmania infection. The TCR and BCR repertoires of the adaptive immune system are diversely shaped post-infection and can provide insights into co-infection with other pathogens present, as well as information on the current state of infection. In addition to TCR/BCR repertoire diversity, expression of genes associated with immune checkpoints, such as PDCD1, CTLA-4, LAG-3, and others also associated with Treg functions, distinguishes hosts that can control infection from those that progress. Characteristic transcriptomic states have been described corresponding to control or progression of infection and offer another dimension of exploration and potential biomarker panel increase [19][20].

Parasite Genomics and Its Influence on Disease

Leishmania species exhibit considerable genetic diversity among strains, which directly contributes to the distinct pathogenic profiles observed in different lineages. Each strain-specific Leishmania variant asserts its virulence through distinctive clonal features such as targeted selective sweeps, variations in the cysteine protease cathepsins, surface coat composition, or chemical composition of secreted phospholipases. Clonal genomic polymorphisms generate not only genomic variations in virulence factors that modulate host responses but also strains with markedly different pathogenicity [21]. Ferenczy et al. developed a panel of strain-specific single-nucleotide polymorphisms (SNPs) that afford robust and low-cost differentiation between L. donovani and L. infantum at the species level, as well as the discrimination of relevant subpopulations of L. donovani from India. The panel is applicable directly to human blood samples in combination with low-input host-transcriptome whole-transcriptome amplification and next-generation sequencing, thereby facilitating epidemiological studies of relevant leishmaniasis lineages [22].

Leishmania-specific transcriptomics offers the prospect of assessing parasite infection and multiplication over the course of leishmaniasis infection by interrogating the gene expression profile of the parasite in human biofluids. Depending on the phase of the disease, different Leishmania species cohabitate with macrophages, dendritic cells, or skin fibroblasts in diverse anatomical sites. Stage-specific expression and secretion

profiles of parasite genes remain tightly linked to the interaction between the pathogen and the physiological state of the infected host [23]. The precise time point at which Leishmania species transit from the mosquito vector to the human host, coupled with the genome organization of these agents, allows the identification of appropriate parasite transcripts active at the onset of the infection in humans [24].

Leishmania Genetic Diversity and Strain-Specific Pathogenicity

The genome variation of Leishmania regulates host response, hence, eliciting clinical variability. The availability of aneuploidy provides the knowledge about the ability of the genome to tolerate significant alterations in the number of gene copies in order to ensure strain-specific pathways. In Leishmania donovani, e.g. a study of liver- and spleen-derived lines found tissue-specific variation of aneuploidy with liver-extracted variants with high ploidy at over 300 loci [25]. Variants predicted to enhance virulence also occur in lineage-specific RS-3 genes associated with drug resistance. Genome size and chromosome copy number vary widely among L. panamensis and L. guyanensis strains. Chromosome 14, central to virulence, shows more than 60% variation in strains, and the L. panamensis chromosome 11 analogue exhibits comparable variability. Several virulence-related functional groups, including proteases and lipophosphoglycans, further modulate pathogenicity. Other genomic regions, which remain uncharacterized, also influence the pathogenetic potential of L. panamensis. A portfolio of advanced genome sampling and comparative techniques would elucidate pathway-affecting drug resistance and virulence factors [26].

Parasite Transcriptomics During Different Disease Phases

Leishmania species display characteristic differences in parasite virulence and host pathology, attributed to extensive genetically clonal variants. Although both the presence of Leishmania and the intensity of the immune response determine the clinical outcomes of an infection, the genetic diversity of Leishmania strains influences the rate of disease progression to a significant extent [27].

Leishmania braziliensis, Leishmania donovani and Leishmania infantum species are classified as different species of Leishmania, which have various stages of development laid down in the parasite life cycle. The macrophages of the mammalian host proliferate intracellular promastigotes; the initial step of the illness provokes the significant transcriptional alterations in the parasite. The local innate inflammatory profile is regulated by the differentiable mRNA profile and secreted factors and, therefore, again, the detection of Leishmania in the samples under analysis [28].

Diagnostic Biomarkers Emerging from Genomic Data

Although there exist guidelines on the early detection and treatment of leishmaniasis, lack of effective diagnostics increases chances of misdiagnosis, progression and failure of the disease treatment. Genomic methods are in the process of active investigation in identifying biomarkers of infection, disease progression and susceptibility to treatment. Both the genetics of the host and that of parasite contribute towards the result of infection and provide complex but valuable information that could be used to further improve the knowledge of the disease and related processes [29].

The various forms of the genomic signals based on either the parasite Leishmania or the host give details on the presence of the parasite and on the pathogenic ability of the parasite, the response of the host and its intensity. Next-generation diagnostic assays are being sought after as such genomic signals [30].

Cross-species genomic interactions between host and pathogen are increasingly recognized as critical players in shaping the outcome of the disease. The interactions occur at multiple levels and broadly impact signalling – including immune signalling – and metabolic networks. Understanding the oral–parasite interactions of leishmaniasis is therefore increasingly deemed essential. Beyond the knowledge already acquired on these aspects, further delineating the parasite signals, coupled to the related host responses, has the potential to identify readily monitorable biomarkers indicating the onset and the subsequent severity of the disease [31].

Host-Derived Genomic Biomarkers for Early Detection

The transcriptomic patterns that can be detected in this period, 616 days after infection, indicate the presence of infected hosts; and dominate in Th2-dependent murine models and is reciprocally correlated with the T-cell checkpoint gene Pdcd1. Most of them are associated with generalized interferon and innate immune response triggered by IFN 7, TLR, IL-1 7, and their receptors, and the oldest genes are similar to a conserved signature activated by intracellular pathogens. Comparison with an early-response panel of protein-protein interactions specific to Toxoplasma by cross-species comparison shows that they are highly overlapped, placing these sets in concept space as highly similar and in potential general early-detection systems [32]. The occurrence of conspicuous non-coding RNAs also comes out early as indicators, pointing to the diagnostic strength of this type of markers. There are two other transcriptomic states that later occur during the infection. One is progressive disease in humans and mice, associated with the activity of TGFb, IL-4, and IL-10 and the other is control, associated with Th1 response and increase in the rate of replication of the parasite. The two states hence provide an understanding of the adaptive response and possible stratification in terms of control and progression [33].

Parasite Genomic Signals as Diagnostic Targets

The protozoan Leishmania, the causative organism of leishmaniasis, is waterborne by the bite of a female phlebotomine sand fly and then invaded the macrophage resulting in its establishment. The parasite is complex in its life cycle as it includes differentiation into various stages and a significant metabolic remodelling. Various Leishmania species present visceral, cutaneous and mucocutaneous leishmaniasis and each clinical presentation is having its own range of variation. Genomic and transcriptomic evidence indicates that there are specific Leishmania clonal lineages with unique gene content and variation influenced by virulence and Leishmania capacity to evade host immune response. This genomic and transcriptomic variation of Leishmania strains confers a disease outcome [34]. Moreover, the parasite also experiences a stage-specific transcriptional regulation of major genes associated to pathogenicity during infection in the mammalian hosts. These genes are also known to alter the composition of the secreted

molecules that can further alter the signaling milieu of infected macrophages and detection limits of diagnostic assays that depend on parasite-specific signals [35].

Both parasite-derived DNA and RNA detection would therefore become useful targets of leishmaniasis diagnostic tests to avoid host biomarker dependence issues. These signals may be attacked by identifying the strain-specific concepts in the genome and the stage-specific gene regulatory programs in the transcriptome. Comparison of genomic and transcriptomic data will provide solutions to the parasite cues that are used during the process of establishing various pathogenesis, and other solutions which could be used in designing detection formats that complement host-derived biomarker suggestions made early on [36].

RESULT AND DISCUSSION

Predictive Gene Signatures for Disease Outcome

The appearance of the signs of the cutaneous (CL) or visceral leishmaniasis (VL) could be noticed already at 15 post-infection (p.i.), whereas even a few days later, the genome DNA of the parasite could be detected, both at the skin and even at the bone marrow that enables the active disease detection. The expression signatures of the CD4+ T cell were discovered to differentiate forms of the disease, severity and speed of clinical course. Follow-ups of genes like Slfn14, Tgfbr2 and Irf9 may also reveal response to oral pentavalent antimony therapy and chances of relapse. Notably, time-to-event lagging between the initial therapy and later success or failure were linked with these signatures which highlights their relevance in the customization of timely and effective therapeutic interventions [37].

Gene Signatures Stratifying Clinical Manifestations

Leishmaniasis has a wide range of clinical manifestations that include the cutaneous leishmaniasis (CL) and the visceral leishmaniasis (VL). It has been demonstrated by gene-signature studies that the transcriptional response of the host to infection with Leishmania can differentiate between the two forms of diseases, the severity of CL and the progression rate of VL. The associated biomarkers to detect these such as the derived peripheral blood mononuclear cell (PBMC) gene sets have opportunities to create powerful panels that can further narrow diagnosis and make treatment decisions [38].

Biomarker Panels for Treatment Response and Relapse Risk

Based on genomic profiles of Leishmania parasites determining disease presentation, spread, and outcome to treatment, predictive signatures have been generated to track drug responses as well as gauge the risk of getting recurrence or recurrence after treatment, taking into account the pertinent time-to-event data. It needs to be evaluated in various environments, preferably by using already existing systems that track the response to treatment and the risks of infection through a variety of pathogens, leishmaniasis being among them [39].

Methodologies and Data Integration

The combination of various types of the omics methodologies offers information on the genomic interaction between the host and the parasite in the context of leishmaniasis. The evolutionary profound difference between the genus Leishmania and other closely related organisms has predetermined the niche of intracellular lymphocytes in which they inhabit, which further diversify the possible signalling pathways. Host-pathogen genomic interactions are also complicated by the many host resolutory, tolerant and aggressive responses that different Leishmania species elicit. Therefore, a cross-analysis of different experimental transmission models is crucial to decouple the signalling logic behind it and correctly calibrate transcriptomic-based diagnostic-screening panels. Experimentally generated data of the models of infected organisms by one species of parasites in a broad time frame have been coalesced and inputted into the Algebraic Signature Detector pipeline to specify and rank sets of gene modules that are early-response to specific parasite species or strain-time interaction [40].

Whole-Genome and Exome Sequencing Approaches

Genomic relationships between hosts and parasites determine the formation of specific clinical outcomes during the process of infections. Genomic analysis of leishmaniasis infection by Leishmania strains underscores the interaction between infection-responding signalling, intermediate metabolic and immune defense mechanisms. Attempts to identify the host genomic landscape of leishmaniasis have yielded some major signatures relating to the innate and adaptive immune responses, and this has created new openings to discover effective and convenient biomarkers of diagnosis [41].

Parasite transcripts also influence diagnostics, with genome-wide studies revealing stage-specific patterns of expression and secretion that presumably shape the host milieu and modulate detectability. Host-derived, parasite-derived, and strain-specific signals that remain stable across biological, technical, and geographical perturbations have been harnessed to identify multiple sets of genomic signatures with translational potential. The former include sets of host genes, interferon-stimulated and innate immunity signatures, and non-coding RNAs suitable for early screening of infection in at-risk populations; the latter comprise parasite nucleic acids indicating the presence of Leishmania DNA or RNA, strain-specific markers able to distinguish between the principal Leishmania species affecting humans, and signals associated with copy-number variation that serve as general indicators of parasite replication rate [42].

Whole-genome and exome sequencing allow the assembly of in vivo and uninfluenced leishmanial genomes from different anatomical sites and the recovery of comparable sequences from the infected host. These specifications foster comparative genomics, facilitate cross-target identification, and enable parallel analysis of both parasitic and eukaryotic genomes. When incorporated alongside other modalities, they support the construction of comprehensive host–pathogen interaction networks that clarify the interplay of signals relevant to leishmaniasis [43].

Single-Cell and Spatial Transcriptomics in Leishmaniasis

Single-cell and spatial transcriptomics provide rich insights into cellular heterogeneity, tissue-specific niches, and host–pathogen co-localization during Leishmania major infection. Leishmania progresses between different initial lesions of the skin (cutaneous leishmaniasis, CL) to the spleen (visceral Leishmaniasis, VL), and tissues show characteristic inflammatory transcriptomic patterns. T cell CD4+ and CD8+ analysis demonstrates that Th1 is predominant at the skin stage, which is changed by Th2/Th17 in the spleen. Co-cross-referencing with bulk RNA-Seq datasets of CL and VL allows the identification of direct and indirect host signals of particular parasite stages in multi-organ diffuse CL and different tissue samples of VL [44].

Bioinformatic Pipelines and Cross-Study Meta-Analyses

Experiments that have been done to study immune responses in an infection can be challenged by irrelevant experimental conditions, interpretation problems because of interspecies variation in pathogen/host/environment. The global pattern of the expression of genes can be changed by similar parameters, which makes it difficult to establish a specific pattern of expression closely associated with either the innate or the adaptive stage. The above obstacles require the availability of well-chosen animal models and bioinformatic pipelines, which will be able to combine genomic data across species in a consistent way [45].

To avoid these challenges, meta-analyses of blood and tissue transcriptional profiles that is generated in the models of leishmaniasis, which include excisional, intravenous, and sand-fly needle infection routes, have been conducted. Such analyses combined with animal and human data identified sets of genes that respond to different routes of infection and time. These combined datasets of expression have been used to describe Leishmania- orchestrated macrophage reprogramming, to predict cytotoxic T cell gene signature before clearance and to elicit immune programs between protection and disease progression. To enable the construction of signature-based models, publicly available datasets with a priori gene-ranking data and remote-contamination evaluation have been collected, and pipelines were made available and modified [46].

Clinical Translation and Diagnostic Development

The diagnostic biomarkers and predictive signatures mentioned herein should go through intensive clinical translation in order to achieve their potentials in the management of leishmaniasis. Some of the most important steps are summarized below, and they include assay design, validation of population diversity, regulatory oversight and the ethical considerations. These move towards wide availability as well as convenient functionality which conforms to the point of care demands [47].

The biomarkers and signatures provide the information and direction to the progressive development to the clinically actionable diagnostic tests, which is the basis of the actionable development steps. Signal stability must also be of interest to design and be able to work in crude matrices like blood or tissue homogenates. The length of time that host-derived materials remain viable depends on fundamentally the same principles as the biomimetic parasite-derived counterparts: Late-stage recognition and

developmental studies can be performed on the parasite counterparts due to the ability to maintain viability over a long period. At the same time user-friendly format should be considered in the early development to provide the portability and suitability in the field. These factors enhance the two-way possibility of these biomarkers as screening and follow-up indicators [48].

Leishmaniasis is a complex disease and it requires confirmation in a wide range of population groups to avoid the biases of a narrow genetic background, sociocultural background or pathogenic variants. This need is increased by the unequal distribution of case histories and study data, which helps to promote equitable access to health worldwide as progressive discrimination between groups helps avoid inequitable outcomes. This sensitivity and specificity of candidate biomarkers is of paramount importance hence the need to be able to prove reproducibility in stringent conjunction of literature-validated cross-species entities. The collaboration with the existing surveillance systems facilitates believability and expediency and extends the use of precision medicine to leishmaniasis and related pathogens that use the same innate pathways [49].

7.1. From Biomarkers to Point-of-C care Tests

The transition from biomarker identification to practical diagnostic tools involves several steps. The design of targeted assays must encapsulate the formal signature, ensuring optimal specificity and sensitivity for the anticipated sample type. Target sequences should be monitored for stability, allowing detection of conserved cross-species signals. Additionally, user-friendly formats minimising training requirements and enabling straightforward implementation are essential for high-field applications. Progress on these aspects complements advances in field-deployable extraction and enrichment methods, previously reported [50].

Validation Cohorts and Regulatory Considerations

The diversity of reference populations that are to be validated is required and reproducibility at various levels is to be considered. Regulatory factors are important on assays that will be used on human samples that include adherence to rules regarding the U.S. FDA, EU IVDR and IVDD, and Brazilian ANVISA. It is recommended that developmental processes, analytical goals, and use purposes should be pre-evaluated to evaluate the right regulatory pathways. Dicretive models may be based on frameworks created in different settings, including screens of parasite-specific biomarkers in the blood of malaria, which are also associated with ethical and biological safety [51].

Host-Pathogen Genomic Interaction Networks

Host-pathogen genomic interplay emerges as a key concept to understanding leishmaniasis. Prior research has tended to focus either on the host or the parasite, limiting the identification of common signatures across infection stages, transmission routes, and clinical manifestations. Recent studies that use integrated analyses of both host and parasite genomic data point to the crucial role of such cross-species interactions in determining the overall outcome of the disease . An expanded understanding of these interactions through complementary single-cell and bulk analyses, network

reconstruction, and multi-layer graph integration could help uncover novel, actionable insights for diagnostics and therapeutics [52].

Integrated Network Modeling of Host and Parasite Genes

Leishmaniasis is an endemic disease caused by obligate intracellular protozoan parasites from the Leishmania genus, which are transmitted to vertebrates by female phlebotomine sandflies. The global incidence of leishmaniasis is approximately 1–2 million cases annually. 20 species of Leishmania are known to infect humans and are responsible for a number of diseases ranging from self-limiting cutaneous lesions to potentially fatal visceral infection. Leishmania species exhibit a high virus-like genomic diversity within the host organism. The parasites present multiple strategies to counteract the host immune response along their life cycle. In juxtaposition, the host also deploys an impressively diverse set of weapons (genomic, transcriptomic, epigenomic) to recognize the infecting pathogen and to reprogram cellular pathways to inhibit the parasite's lifecycle. Such host–pathogen interactions drive many clinical outcome variations [53].

Of the utmost importance is to comprehend that the parasite also coordinates certain signals, which it regulates to its benefit, to the responses of its hosts. Thus, the exploration of cross-talk between the parasite and host on the genomic, transcriptomic, epigenomic and proteomic levels is an important concept to elucidate the tools of early diagnostic signatures as well as the distinguishing predictive gene signatures that dictate the outcome of leishmaniasis. The conceptual frameworks facilitate the formation of accurate measures of the disease after infection with Leishmania so as to manage the level of the disease. Besides, they also uncover a large number of diagnostic candidate genes and potential treatment targets [54].

Pathway-Level Insights and Therapeutic Targets

Hostpathogen genomic interactions are other potential directions of undoing leishmaniasis. It is also known that the parasite utilizes secreted proteases, lipid mediators, as well as extracellular vesicles (EVs), which affect host-cell functions, determine cellular reactions, and control the release of cytokines. An analysis of Leishmania RNA-seq data as a co-expression network, revealed many genes co-regulating with pathway components of lipid biology and immune modulation, implying that the candidate signals and biomarkers may be a result of the selective pathogen-host interaction networks. However, the exact chromosomal positions of these candidate signals of the host genome were not identified [55].

Combination of integrated network modeling, host and parasite regulation of co-expressed genes, and transcriptomic data of tissues at different time points helped to understand the pathways that determined the initiation and progression of the disease. The mapping of one such network thus revealed co-regulated units of transcription and signaling pathways that were regulated by long-range interactions between each species during various stages of infection which was compartmentalized. The network-control framework search on candidate hostpathogen interaction signals and pathways then included the pathway-level modelling [56].

Up-to-date knowledge identifies parasite-driven pathways as potential targets of therapy and draws outlines of potential candidates of host genes that can be modified. The integrated models are studied to note the Leishmania-induced circuits that are executed within the host and the species is characterized as a desirable target of pharmacological treatment. The further modeling of putative changes, including the drug administration and genetic editing, to re-establish control of particular Leishmania-modulated circuits, is also identified. Consequently, although not yet formally integrated within the framework, pathogen-directed pathways are anticipated to emerge as pivotal therapeutic nodes warranted deeper exploration. Targeting parasite-directed modules also bears relevance for diagnostic development, as the corresponding time-specific host signals constitute candidate early-readout transcriptional circuits [57].

Future Directions, Gaps, and Ethical Considerations

Current host-parasite genomic studies have yet to reach a variety of geographic regions, with strongly represented areas including Ghana, the Gambia, Brazil, Egypt, and Syria being both well-defined and limited in scope. Efforts to characterize clinical and epidemiological variation, clarify outstanding disease and host questions, and enhance multiscale modeling are encouraged for populations outside the West African-Governorate of Beni-Suef area and throughout the Indian subcontinent. Proposed measures for increasing genomic information and sample availability include collaborations with local researchers, incentivized sharing through, for example, the Global Alliance for Genomic Health and the African and Local Genomic Epidemiology network, and use of tools like the Mosquitos Door-to-Door Community Survey to collect samples and enable retrospective genotyping [58].

High-value datasets in the public domain provably increase local genomic capacity and facilitate long-lasting research growth. A further relevant step is habitat tracking in order to constrain persistence model parameters despite limited population sampling; a candidate parameter set for such tracking remains to be formulated. Current episode-tracking tools lack models of competitive exclusion among circulating strains, and formulations freely accommodating selection distort apparent growth, among other issues in population data [59].

Gaps in Population Diversity and Data Sharing

Leishmaniasis diagnostic biomarker discovery faces important challenges. Current methods are hampered by the absence of robust protocols for parasite tissue sequencing in human samples and genetic bias caused by long-term culture. In situ functional screening enables the identification of clinically relevant genes without extended culture, shedding light on virulence, tropism, and drug resistance. The method provides the ability to analyze large amounts of parasite DNA straight off the infected tissue in order to assist single-cell sequencing and clarify polyclonal methods of adaptation. The structure helps to reduce the ethical issues by concentrating on loci in clinical samples, which can be easily analyzed by qPCR, to bridge the gap between laboratory research and the field-based applications, and to overcome the shortcomings of epidemiological studies that rely on the cultivated parasites [60][61].

Ethical, Legal, and Social Implications of Genomic Diagnostics

Genomic diagnostics of leishmaniasis has significant ethical, legal and social concerns especially when it comes to direct genome sequencing of human tissue samples or biological fluids which are de facto diagnostic in nature. Obligatory consent procedures and samples collected only for further analysis encapsulate such concerns. The continuous improvement of the Pipeline for Leishmania Genomic Biomarkers and the Pipeline for Leishmania Predictive Gene Signatures provides an advantage through the incorporation of functional genomic tools and computational pipelines [62]. The use of cosmid-based functional genetic screening in situ overcomes bottlenecks that limit selection of biomarker for Leshmania species responsible for human pathology, avoids long-term culture biases that obscure the ecological relevance of experimental data, and enables selection of loci that are biologically or biochemically tractable within available model frameworks. Direct parasite sequencing from a relevant biological reservoir permits determination of mechanisms of adaptation, accumulation of resistance-mapping datasets and identification of loci that delineate sub-genomic control over position acquisition or spontaneous mutation that can subsequently be verified using clinical samples obtained from the same or similar biological pool and addressed using simplified q-PCR methodologies [63].

Cohort-appropriate Constitution of Leishmania Genomes, the increasing accessibility of published and proprietary datasets, and the Pipeline for Leishmania Predictive Gene Signatures open up the prospect of combining host pathogen evolutionary and transcriptional information at single-cell resolution. Individual plasticity availability localisation maps can be constructed to investigate leishmaniasis lesion latencies, as a function of cross talk with either epidermal or immune barrier Repair or Widow activities and derive fundamental insights into the pathogenic cross talk at the systemic level as a function of material continuity [64][65]. Individual constitutional leishmanias have been employed to explore polymerase-slippage DNA spectra in conjunction with the accompanying synaptic competition between the nucleoid branching and the ring topology of circular genomes instigated by various mechanism constitutively or transiently induced. Surface rendering of co-localisation information at high-throughput resolution provides critical insights into the host pathogen interaction at the tissue-niche level and addresses the fundamental-ness and the terrain of functional budget trade-off set point and the associated constitutional leishmania variable selection and adaptation across various parts of the world (eating practices, skin-to-skin arrangements, domestic animals, or climatic features) [66][67].

CONCLUSION

Fundamental Finding : Integrated genomic studies of Leishmania and human hosts have provided valuable insights into early detection, treatment prediction, and disease management, enabling the identification of biomarkers well before clinical symptoms emerge. **Implication** : These findings have significant implications for improving diagnostic accuracy, personalizing treatments, and enhancing disease control

strategies, particularly in resource-limited settings. **Limitation** : Despite the advancements, challenges remain in accessing under-studied regions and taxa, and limitations related to the equitable distribution of genomic resources persist, potentially hindering global efforts in genomic epidemiology. **Future Research** : Future research should prioritize the exploration of neglected regions, further develop non-invasive sampling techniques, and address issues surrounding intellectual property governance and environmental impact. Continued efforts to improve species identification through environmental DNA and promote global equity in genomic research are crucial for ensuring broad benefits and addressing bio-safety concerns in the fight against leishmaniasis.

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