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Advancing *Leishmania* Research: The Role of Novel Technologies in Unraveling Host-Pathogen Dynamics

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ABSTRACT

Leishmaniasis is a vector-borne parasitic disease caused by *Leishmania* species and is prevalent in many of the world's tropical and subtropical countries. This neglected disease primarily impacts the tropical and subtropical regions of the world; however, climate change could exacerbate this scenario and lead to the wider dissemination of the disease, a threat amplified by the fact that there is no protective vaccine or immunotherapy available. To address this challenge, controlled human infection models (CHIM) have been developed to delineate the early events following infection. These models leverage single-cell multi-omics technologies and artificial intelligence to generate large-scale data, which is then integrated into a system encompassing parasite heterogeneity and the host immune profile. This approach aims to more precisely deconvolute the intricacies of the host-parasite-vector interplay, potentially leading to the development of more effective vaccines or therapies. This mini-review highlights the role of novel technologies in unraveling host-pathogen dynamics.

INTRODUCTION

Leishmaniasis is a vector-borne disease caused by parasites of the genus *Leishmania* and is transmitted through the bite of infected female sand flies. The disease disproportionately affects populations in tropical and subtropical regions, where it is associated with factors such as malnutrition, population displacement, poor housing, immunosuppression, and a lack of financial resources. However, climate change is expected to alter the disease's distribution, further increasing its global impact if it remains neglected [1]. Therefore, a concerted global effort is needed not only to support currently affected regions but also to prevent the further geographical distribution of the disease.

Unfortunately, an effective vaccine remains elusive despite extensive global research. A major impediment is that the complex host-pathogen interaction is not fully elucidated. Traditionally, research has approached the intricacies of this interaction in a reductionistic manner, investigating contributing factors such as the vector [2, 3], parasite [4, 5] and human host [6, 7] in isolation. For example, studies often focus on a single factor in *Leishmania* infection, such as a specific immune response or a particular gene, while overlooking other crucial aspects like the parasite's interactions with different host cells or the roles of other immune cells. Reductionism breaks a complex system into its constituent components and defines the system as the sum of these parts, often disregarding the critical interactions between them. Recognizing that biological systems are more complex than the sum of their individual parts [8], the field of systems biology has emerged to provide a holistic analysis by considering all interactions among these components [9]. This approach uses 'omics' technologies to capture the molecular content of cells. Through computational analysis, it integrates multi-layered data from genomics, transcriptomics, and proteomics to elucidate population heterogeneity, correlates of protection, pathogenesis, and novel biomarkers [10]. This integrated data holds significant promise for accelerating the development of a protective vaccine or effective immunotherapies.

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Recently, significant advances in single-cell omics have revolutionized systems biology approaches, driven by breakthroughs in single-cell isolation technologies [11]. Conventional 'omics' (i.e., bulk analysis) relied on the molecular analysis of an entire cell population, resulting in an averaged molecular profile that obscured the heterogeneity within that population. However, recent advancements in single-cell isolation and analysis have resulted in single-cell omics, a technology that reveals heterogeneity through cellular clustering [12, 13]. This technology holds great promise for advancing our holistic approach to elucidating the host-pathogen interaction.

High-throughput technologies in single-cell omics analysis

Single-cell omics is enabled by several key technological breakthroughs, including microfluidics, molecular barcoding, and microbead-based systems. Microfluidics is the science and technology of systems that process or manipulate very small amounts of fluids (10^{-9} – 10^{-18} liters) in tiny channels of tens to hundreds of micrometers [14]. This technology has led to the fabrication of devices that enable a wide range of experiments on miniaturized platforms, such as microfluidic chips or portable instruments. The rapid progression in this field has enabled the development of 'lab-on-a-chip' systems for point-of-care diagnostics [15], 'human-on-a-chip' models for drug and vaccine development [16], and specialized devices such as the Fluidigm C1 system for single-cell analysis [17]. A second critical technology is molecular barcoding, in which unique nucleic acid sequences are used to tag molecules originating from individual cells. Although various barcode types exist, DNA barcodes are widely used in single-cell omics [18]. The combinatorial potential of a short DNA sequence allows for the generation of millions of unique barcode identifiers. High-throughput sequencing subsequently identifies these barcodes, making it possible to assign each molecule back to its cell of origin. The third core component involves microbeads (micrometers in diameter) [19]. For instance, hydrogel-based microbeads can be surface-functionalized to allow for the attachment of molecules such as DNA barcodes.

Numerous single-cell omics protocols are available to profile the molecular content of single cells. As an example, Drop-seq is a single-cell transcriptomics technology that uses a microfluidics-based system to partition individual cells into droplets and generate barcoded transcripts. Subsequent Illumina sequencing decodes the individual barcodes, allowing the transcripts to be assigned back to their original single cells. Computational analysis then groups the cells into clusters with similar transcriptomic profiles [20]. Recently, spatial transcriptomics has enabled the mapping of cellular clusters within their native tissue context, leading to an understanding of functional compartmentalization based on gene expression profiles [21]. Moreover, a growing number of single-cell multimodal sequencing technologies are now available to simultaneously profile multiple modalities of data in the same cell. One example is CITE-seq, which combines transcriptomic analysis with measurements of cell-surface protein expression. This technique resembles Drop-seq in its protocol, with the key addition of barcoded antibodies. First, DNA-barcoded antibodies are used to bind to surface markers; the subsequent steps then follow a protocol similar to that of Drop-seq. This process generates two distinct barcoded cDNA libraries—one from cellular mRNA and one from the antibody tags—which are then sequenced. The data can be visualized as clusters with a similar gene expression profile linked to a distinct surface protein profile [22]. Similarly, spatial multimodal technologies enable the precise localization of these multi-omic cell clusters in the tissue of origin [23]. Collectively, single-cell multimodal technologies, along with spatial modalities, are foundational to the development of the Human Cell Atlas [24]. The Human Cell Atlas is a worldwide effort to map and characterize every type of cell in the healthy human body—including their types, numbers, locations, relationships, and molecular components—to provide an open-source resource for future studies of human health and disease.

Controlled human infection models: a holistic approach to deconvoluting disease complexity

A complex system like *Leishmania* infection, which is further complicated by the salivary gland proteins and gut microbiota of the transmitting vector, *Leishmania* secretory exosomes, symbiotic RNA viruses, the host's genetic background, and its associated skin/gut microbiota cannot be resolved by reductionist approaches and obviously, holistic systems biology framework is required. Fueled by technological advances in single-cell analysis and advanced computational biology, controlled human infection models (CHIM) are now being developed in clinical trial settings for real-time disease progression follow-up. In these models, healthy volunteers are deliberately infected with the pathogen under tightly controlled and regulated conditions to study disease pathogenesis, evaluate the effectiveness of potential treatments and vaccines, and elucidate the human immune response to infection. These models have substantially contributed to COVID-19, dengue, and malaria vaccine studies, and their application is expanding rapidly [25].

A CHIM for *Leishmania* research has been developed by the Leish-Challenge consortium at the University of York, UK. Healthy, *Leishmania*-naive volunteers were enrolled in this CHIM, where *Leishmania major*-infected *Phlebotomus duboscqi* sand flies were allowed to feed on their arms for up to 30 minutes. Developing lesions (approximately 3 mm in diameter) were then excised, and the resulting biopsies were analyzed by spatial transcriptomics

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transcriptomics and compared to a normal skin reference profile. This analysis identified thirteen different cell clusters, two of which were distinctly associated with the lesion core and the bite/ulcer site, each with unique cellular and gene expression profiles. Further sub-clustering based on highly expressed genes revealed an association between the lesion core and genes such as *CXCL9* and *CHI3L1*, which are linked to the interferon-gamma response and macrophage differentiation. Sub-clustering based on the cytokine and chemokine gene expression profile associated the lesion core with *CCL18*, *CXCL9*, *CXCL10*, and *CXCL11*, while lesion borders correlated with *CCL5*, *CCL19*, *IL-16*, *IL2RG*, and *CXCR3* [26]. This prototypic model demonstrates how single-cell technology can elucidate the functional compartmentalization of the lesion. It serves as a platform to further investigate the early events following sand fly infection in humans in greater detail [27, 28]. The insights gained from this model are intended to guide future studies in the endemic regions of the world [29, 30].

CONCLUSION

For decades, vaccine development and immunotherapy strategies for leishmaniasis have centered on eliciting a robust Th1 memory response. However, a comprehensive understanding of the underlying immunological events that lead to protective immunity in humans remains incomplete, particularly within the context of the complex host-pathogen-sand fly interplay. To bridge this knowledge gap, it is imperative to leverage CHIMs and single-cell multi-omics technologies. In these models, applying single-cell multi-omics to the host response will enable precise immune profiling at the bite and lesion sites. Furthermore, parasite single-cell multi-omics will help to elucidate the epigenetic impact of parasite heterogeneity on the host immune response. Integrating metagenomics to investigate the impact of interacting microbiota (*e.g.*, from human skin, the human gut, and the sand fly gut) would provide another critical layer of data. The integration of large-scale datasets generated by CHIMs into a more comprehensive and predictive model of the human immune response then will benefit only from artificial intelligence and machine learning regarding the huge amount of data to be analyzed. Ultimately, this integrated approach holds the potential to accelerate the rational design of a protective vaccine and/or effective immunotherapies, which remain a critical unmet need in endemic areas around the world.

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CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest associated with this manuscript.

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AI DISCLOSURE

No AI tools were used in the preparation of this work.

DATA AVAILABILITY

All data are included in this published article.

AUTHORS' CONTRIBUTION

NS: conceptualization and writing.

ETHICS STATEMENT

As this manuscript is a mini-review involving the analysis of publicly available literature, it did not require ethical approval.

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