Chapter 8
Intricate Role of Reactive Oxygen Species and Reactive Nitrogen Species in Leishmaniasis: Mechanisms, Implications, and Therapeutic Potential

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ABSTRACT

Leishmaniasis, caused by protozoan parasite, poses a significant global health challenge, affecting millions worldwide. The immune response to Leishmania involves the generation of ROS and RNS, which are critical for controlling the infection. During Leishmaniasis, phagocytic cells, generate ROS and RNS as part of the immune response, which are critical for killing intracellular pathogens. Leishmania has evolved mechanisms to survive oxidative stress by enhancing its antioxidant defences like superoxide dismutase and trypanothione reductase, which neutralize these reactive species. This ability to counteract ROS and RNS not only aids in the parasite's survival within host cells but also contributes to chronic inflammation

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and tissue damage, ultimately influencing disease progression and severity. This chapter explores the intricate role of ROS and RNS, highlighting their dual function in regulating the parasite and contributing to disease pathology, therapeutic potential of targeting ROS/RNS pathways.

1. INTRODUCTION

1.1. Background on Leishmaniasis:

Leishmaniasis, caused by *Leishmania* parasites and transmitted through the bite of infected sandflies, remains a significant global health burden, affecting millions across more than 90 countries. The disease manifests primarily in three forms: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (ML), the latter being the most severe and often fatal if untreated. About 12 million of the world population is currently infected and over 350 million people are at risk, leishmaniasis disproportionately affects impoverished regions, particularly in South Asia, East Africa, and Latin America (Knight et al., 2023) (Sundar & Chakravarty, 2012). The disease is endemic in areas with warm, humid climates favorable to sandfly vectors, exacerbated by weak health infrastructures and socioeconomic challenges.

Visceral leishmaniasis, also termed as kala-azar, is especially deadly, with mortality rates exceeding 95% if left untreated. It is endemic in countries such as India, Brazil, and Ethiopia, contributing significantly to the global burden of neglected tropical diseases (NTDs) (Scarpini et al., 2022). Conversely, cutaneous leishmaniasis, while less lethal, can lead to severe disfigurement and long-term social stigma, impacting the social well-being of those affected. Both forms of the disease face the challenge of drug resistance, particularly in regions with limited access to effective treatments (Wijnant et al., 2022). Current therapies, such as antimonials, are not only toxic but also costly and increasingly ineffective due to emerging resistance, emphasizing the urgent need for new drugs and treatment strategies.

The co-infection of leishmaniasis with HIV further complicates disease management. In regions like Brazil and Ethiopia, co-infection rates are rising, leading to more severe disease manifestations and higher mortality rates (Wamai et al., 2020). HIV-infected individuals are more susceptible to leishmaniasis due to their weakened immune systems, and conventional treatments are less effective in these populations. This underscores the need for targeted interventions and more robust healthcare systems capable of addressing such complex co-infections.