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The therapeutic potential of immune cross-talk in leishmaniasis

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Abstract

Veterans of infection, *Leishmania* parasites have been plaguing mammals for centuries, causing a morbidity toll second only to that of malaria as the most devastating protozoan parasitic disease in the world. Cutaneous leishmaniasis (CL) is, by far, the most prevalent form of the disease, with symptoms ranging from a single self-healing lesion to chronic metastatic leishmaniasis (ML). In an increasingly immunocompromised population, complicated CL is becoming a more likely outcome, characterized by severely inflamed, destructive lesions that are often refractory to current treatment. This is perhaps because our ageing arsenal of variably effective antileishmanial drugs may be directly or indirectly immunomodulatory and may thus have variable effects in each type and stage of CL. Indeed, widely differing immune biases are created by the various species of *Leishmania*, and these immunological watersheds are further shifted by extrinsic disturbances in immune homeostasis. For example, we recently showed that a naturally occurring RNA virus (*Leishmania* RNA virus (LRV)) within some *Leishmania* parasites creates hyperinflammatory cross-talk, which can predispose to ML: a case of immunological misfire that may require a different approach to immunotherapy, whereby treatments are tailored to underlying immune biases. Understanding the intersecting immune pathways of leishmaniasis and its co-infections will enable us to identify new drug targets, and thereby design therapeutic strategies that work by untangling the immunological cross-wires of pathogenic cross-talk.

Keywords: HIV co-infection, hyperpathogenesis, immune cross-talk, immunomodulatory antileishmanial agents, immunophenotyping, *Leishmania* RNA virus, *Leishmania Viannia*, leishmaniasis, metastatic leishmaniasis, nested co-infection

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This review evaluates the possible incidence and effects of pathogenic cross-talk in cutaneous leishmaniasis, as well as its potential in antileishmanial therapy.

Introduction

Veterans of infection, *Leishmania* parasites have been plaguing mammals for centuries. After malaria, leishmaniasis is the most important protozoan parasitic disease in the world, with 350 million people being at risk on five continents in 98 countries, and is steadfastly listed in the top ten most debilitating infectious diseases in the world (according to disability-adjusted life-years) [1–3]. Despite its staggering prevalence and morbidity, it has been categorized as a 'neglected disease', with little clinical research interest, no vaccine, and a vastly inadequate therapeutic arsenal. Thus, the missing noses, drooping lips and agonizingly disfigured faces depicted on pre-Inca pottery are, astonishingly, still relevant today as current prognoses (Fig. 1, inset).

Leishmania parasites are vectored as promastigotes in a haematophagous sand fly and regurgitated into the human epidermis during a blood meal. Host macrophages are quick to innately quarantine parasites into phagolysosomes, which kill intracellular pathogens by compartmentalized oxidative stress. Often, however, the parasites not only survive in this hostile territory, but thrive, employing intricate immune evasion tactics to complete their life cycle as replicating

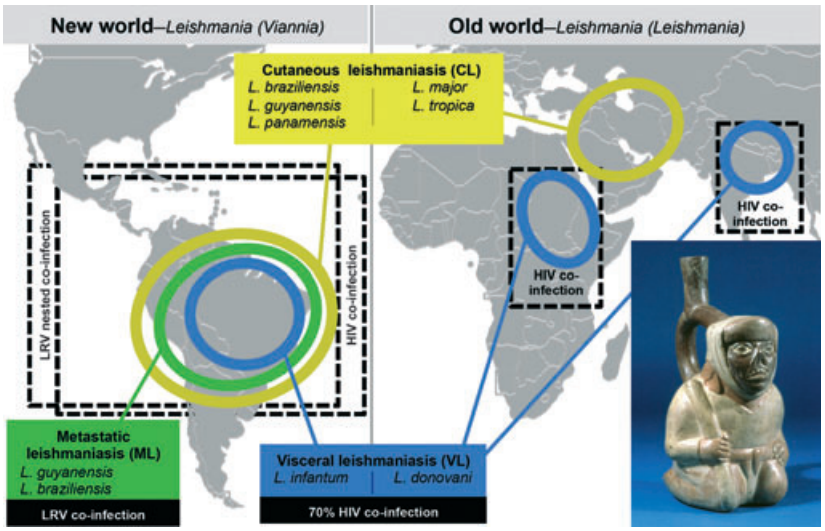

FIG. 1. Distribution of 90% of the global leishmaniasis burden and its association with co-infection. Ninety per cent of the world's leishmaniasis burden occurs in some of the poorest developing nations. The major symptomatic outcomes are geographically isolated, owing to intrinsic virulence factors of the infecting parasite and other endemic co-infections such as *Leishmania* RNA virus (LRV) and human immunodeficiency virus (HIV) (dotted boxes). Complicated cutaneous leishmaniasis, metastatic leishmaniasis and visceral leishmaniasis tend to occur in regions of co-infection. Nested LRV co-infection is found in some isolates of New World *Leishmania Viannia*. *Inset*. Pre-Inca pottery depicting the presence of metastatic leishmaniasis in Peru in 200–600 CE [75].

amastigotes. The disease has various symptomatic outcomes, ranging from a single self-healing cutaneous lesion at the site of inoculation (cutaneous leishmaniasis (CL)) to a metastasizing dissemination of chronic, disfiguring inflammation (metastatic leishmaniasis (ML)). Furthermore, one-quarter of all infections are potentially fatal, disseminating to non-dermal, vital tissues, such as the liver, spleen, and bone marrow (visceral leishmaniasis (VL), which is responsible for at least 50 000 deaths per year). These vastly different outcomes follow geographical patterns, branching with the speciation of *Leishmania* (Fig. 1).

This phylogenetic clustering supports the idea that symptomatic tropism is determined by species-specific parasite factors. For example, parasites causing VL are thought to harbour a 'visceralizing factor'. The A2 gene was proposed as such a candidate, enabling parasites to withstand the heat shock of visceral fever [4,5]. Indeed, genetic introduction of A2 into the non-visceralizing parasite *Leishmania major* supported visceral colonization and heat tolerance [6]. Interestingly, a functional A2 protein is also found in the non-visceralizing exception of *Leishmania mexicana*, indicating that visceralization is a multifactorial process and could be different between Old World and New World species [7]. Interestingly, although the *Leishmania Viannia* subgroup in South America is almost exclusively responsible for mucocutaneous metastasis, no obvious or common 'metastatic factors' have been found within the group. Recently, we were able to correlate disease severity in members of *L. Viannia* with the presence of an endosymbiotic RNA virus in their cytoplasm (*Leishmania* RNA virus (LRV)) [8–11]. Here, the viral nucleic acid triggered a destructive inflammatory cascade through Toll-like receptor (TLR)3, increasing parasite survival, and perhaps even predisposing to infectious metastasis. This finding was yet another demonstration of how potently immunological cross-talk is able to alter the pathogenesis of disease. Indeed, many pathogens are known to exploit innate cross-talk to evade clearance; for example, some pathogens produce foreign pathogen-associated molecular patterns (PAMPs) that mimic a different pathogen. These duplicitous molecules initiate immunological misfiring, down-regulating or misguiding the immune attack, and thereby allowing the pathogen to evade destruction (reviewed in [12]). This interference, however, need not come from the same pathogen, and may be caused by a conveniently timed co-infection, or, indeed, from one nested within the pathogen itself [8]. Cross-talk is a common and under-appreciated mechanism underlying opportunistic disease, whereby secondary pathogens do not just benefit from the resulting immunodeficiency, but also undergo intricate interactions with intersecting immune pathways. Similarly, metastatic and virulent leishmaniases have been linked to extrinsic co-infection as well as to other local immune disturbances. Predictably, human immunodeficiency virus (HIV) infection predisposes to VL by over 1000-fold (Fig. 1). Although the major contributor to this correlation is probably the CD4-