INTRODUCTION

• Leishmaniasis is a neglected tropical disease divided into three major classifications based on clinical presentation: cutaneous (CL), mucocutaneous (MCL) and visceral (VL)
• Transmitted by the Lutzomyia spp. and Phlebotomus spp. sandflies, there are up to 2 million cases of Leishmaniasis globally, while 350 million people are at risk
• Parasite-determined factors play a complementary role in the pathogenesis of leishmaniasis
• Virulence factors (VFs), or pathogen moieties facilitating disease, can potentiate host cell damage by Leishmania spp. by increased expression, host cell invasion, stress tolerance, and modulation of the host immune system
• Due to large eukaryotic genomes in Leishmania spp., there is a wide array of VFs which contribute to different aspects of pathogenesis; we aim to synthesize this knowledge by systematically mapping the literature

METHODS

• PubMed (NCBI), MEDLINE (OVID), EMBASE (OVID), Web of Science, and LILACS (VHL) were searched from inception to July 2018 using combinations of the search terms “virulence factor”, “Leishmania”, and “Leishmaniasis”, while accounting for unique database syntax
• Iterative inclusion and exclusion of search terms was employed to maximize relevant article extraction
• Primarily, molecular and mechanistic pathogenesis studies in various model systems, observational studies, review studies, cohort studies, as well as clinical trials are included
• Synthesis is done by grouping of similar VFs in similar pathogenesis mechanisms, e.g. heat shock
• 760 MEDLINE, 1942 PubMed, 1314 EMBASE, 438 Web of Science, and 8 LILACS records were retrieved for title and abstract screening; after a multi-step de-duplication pipeline, 2620 remained
• All records undergo double-reviewer screening, with tertiary arbitrators to mitigate any discrepancies

RESULTS

• Some common parasite-derived pathogenesis mechanisms in Leishmania include:
  • Heat shock adaptation to the host environment
  • Evading the immune system
  • Increased expression of survival factors
  • Preventing innate immunity opsonisation
  • Modulation of the host immune system
• Heat shock is mainly directed by heat shock proteins (HSPs):
  • Different HSPs are used preferentially in different species
  • HSP23 can protect against thermal, acidic and oxidative stresses
  • CyP40 is thought to be a co-chaperone that helps the parasite infect macrophages
  • Loss of HSP100 renders L. major and L. donovani non-infective in vitro at physiological temperatures
• Heat shock and resulting thermotolerance is a crucial method by which Leishmania species exert their virulence

DISCUSSION

• The ability to comprehensively synthesize all the known literature around parasite-determined virulence factors can open new doors into network-level pathogenesis
• Connecting the dots between virulence factors (if any) to construct a more complete picture of parasite pathogenesis can help better illuminate the underpinnings of different disease manifestations
• Once all parasite-determined VFs are mapped, it can elucidate how they may tie into host-determined immunopathogenesis mechanisms
• Being able to modulate some of these network-level systems can potentially identify novel targets for therapeutics and diagnostics
• This systematic review has implications for painting a more full picture of parasite-determined Leishmania pathogenesis and hence help tie the ends between different VFs, and maybe shed light into host environmental factors

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