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A Systematic Review of Virulence Factors in the *Leishmania* Genus

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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

Virulence Factor	Mechanisms of Pathogenesis
HSP23, **HSP60**, **HSP70**, **HSP83**, **HSP90**, **HSP100**, **HSP65**	• Heat shock proteins • Thermotolerance/survival • Chaperones that facilitate the stabilization of proteins in stressful host environments • Significant expression changes in HSPs as parasite is engulfed in host cells • Aid in adapting from poikilothermic insect vector to a homeothermic mammalian host
LPG	• Lipophosphoglycan • Cell surface anchored molecule • Species-specific sugar component • Required to cause infection in the sandfly hindgut
GP63	• Metalloprotease • Cleaves C3b complement • Halts and hinders innate immunity • Protects parasite from cell lysis
CPB	• Lowered virulence in macrophages • Lowered virulence in mice • Required to cause infection
EF-1alpha	• Elongation factor that is part of the parasite exosome • Blocks Nitric Oxide production • Promotes survival
A2	• Exacerbate parasite-derived immunopathogenesis • Significant in visceral leishmaniasis
MPI	• Catalyze the interconversion of F6P and M6P • Required for glycoconjugates • Loss of MPI leads to loss of surface-anchored VF synthesis, such as leishmanolysin

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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