Advances in Understanding Molecular Pathogenesis of Leptospira and Leptospirosis

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Abstract
Leptospirosis is a disease transmitted from animals to humans, by aerobic spirochete of the genus *Leptospira,* one of the re-emerging tropical infectious disease distributed worldwide. The infection is acquired by contamination with urine or reproductive fluids from infected animals. There are more than 200 recognized antigenic serovars of pathogenic leptospires which have complicated our understanding on this genus pathogenicity. The outer membrane proteins (OMPs) and adhesins of the extracellular matrix are expressed by the leptospires, the leptospiral proteins includes: LigA/B, Lsa21, Lsa27, Lsa63, Lsa24 (LfhA/LenA), LenB to F, LipL32, Lp95, TlyC, and LipL53 that have shown affinity to adhere to host ligands in vitro. *Leptospira* infection, regardless of being pathogenic microorganism, on the other hand is influenced by other host proteins belonging to multiple biological classes. The leptospires may damage the endothelial cells *via* multiple cascades or pathways including endothelial barrier damage and inflammation, potentially leading to vascular hyperpermeability and severe illness *in vivo*. This review provides new insights into the molecular mechanisms of pathogenesis of *Leptospira* infection.

Keywords: Leptospirosis, Pathogenicity, Infection, OMPs, Disease, Protein

Introduction

Leptospirosis have been classified as a zoonotic bacterial disease caused by a thin coiled spirochetes with a hook at one or both pointed ends, this gives a unique characteristic of the Spirochaetales, family Leptospiraceae, genus *Leptospira.* The Leptospires measures 0.1µm in diameter by 6-20µm in length. [**1,2**]

This microorganism is unable to be classified by Gram staining because of the morphological pattern of the thin bacterial cell hence difficult for light microscopy to pick up. However, *Leptospira* species have similar characteristics of Gram-negative bacteria because of the presence of the inner membrane (IM) and outer membrane (OM). [**3**]

The outer membrane is enclosed by a transmembrane β-barrel proteins (OMP) which function as a transporter of molecules, the genome of *Leptospira* species consists of abundant lipoproteins which appear to be attached to the outer membrane and is exposed on the outer surface of the bacteria.[**3**]

Two pathogenic species, *L. interrogans* and *L. borgpetersenii* have their genomes determined by DNA sequencing coding majority of the genes (77-81%) show no homologous to other spirochaetes family, recent studies carried out establish that the genetic determinants plays a role in pathogenesis.[**4**] The infectious leptospires of *L. interrogans* and *L. borgpetersenii* their genomes contain a 3400 and 2800 coding regions (excluding transposases and pseudogenes), and 656 are pathogen-specific, most of these genes their function is poorly understood.[**4**] Leptospires have a large genome and a complex outer membrane very different to other bacteria, the surface membranes proteins are integrated into the lipid bilayer by the amino terminal fatty acids.[**5**] The newly discovered serovars of *leptospira* species have antigens that are similar but complicated to understand its taxonomy of leptospires because in some cases it has become difficult to differentiate between cases in an epidemic where antigens are similar but their genes are different. However, the recent molecular technology and other analytical methods have now confirmed the taxonomy of leptospires.[**6,7**] The genome for *Leptospira* have shown not to have inadequate genes to encode both the secretion machinery type III and IV the proteins that exhibit virulence for instance those that secret toxins and effectors.[**8**]

Experiments have identified *Leptospira* species to have genes orthologous that are able to encode the secretion systems type I which are found in *Leptospira* genomes, they are made of the inner membrane ATP that binds to the protein of both the periplasmic and the TolC forming outer membrane protein [**8**] the *Leptospira* genomes have also shown to have genes orthologous that encode type II secretion proteins, the type II secretion machinery have different types of proteins that are found in the inner membrane and a pilus-like structure that are able to move proteins to the extracellular matrix through an outer membrane pore.[**8**]

One study conducted in cattle that have been vaccinated with a monovalent *Leptospira borgpetersenii* serovar Hardjo subtype Hardjobovis vaccine, their findings concluded that recombinant LipL32 stimulates gamma-interferon production.The leptospiral fragments which stimulates this response have not been identified.[**9**] In this experiment 238 recombinant leptospiral proteins were tested for their ability to stimulate IFN-γ production in blood of cattle that were vaccinated with a commercial monovalent Hardjobovis vaccine. Lipoprotein LipL32 demonstrated to have stimulated significant IFN-γ production in blood of vaccinated cattle, there is no