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Leptospira: A Review on Pathogenesis and Host Immune Response

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Abstract

Leptospirosis, the world's most common zoonotic disease and is a growing public health concern, especially in developing countries. The genus Leptospira contains many disease-causing organisms which can cause various clinical symptoms from mild flu disease to severe illness with complications of the multi-organ system which may lead to even death. The mechanisms of Leptospira pathogenesis is largely unknown. This article will focus on leptospira pathogenesis and various virulent factors which are involved in leptospira pathogenesis and how it evade the host immune response and it also shed light on host immune response after infection.

Keywords: epidemiology, leptospirosis, pathogenesis, virulence

Introduction:

The most prevalent zoonotic disease, leptospirosis, is distributed worldwide. Leptospirosis is highly infectious disease cause by gram negative bacteria, leptospira and is becoming a major public health issue (Bharti 2003; Levett 2001). Leptospirosis is common urban and rural areas in the tropics, subtropics, and temperate regions. In developing countries, epidemics often involve occupational exposure, tourism, or sports activities in immediate proximity with animals enhance the possibility of infection spread to people, with 0.5 million cases recorded each year with a death rate of minimum 5-10% (Guerreiro et al 2001).Human leptospirosis is is perhaps the most widely recognized life-threatening diseases, causing considerable mortality and morbidity in endemic areas of tropical and subtropical countries (Vieira et al 2020). Infection may occur as a result of human exposure to a contaminated environment carrying leptospiral or in close contact with infected animals either directly or indirectly. Human leptospirosis has the wide range of clinical manifestations, which includes mild asymptomatic infections to severe and life-threatening complications, including multi-organ dysfunctions, including the kidneys, the lungs, and liver are badly compromised (Latchoumi et al 2020).

Despite extensive research on the pathogenesis of human leptospirosis, it is still unclear to what extent the host factors or the pathogen itself play a role in the pathogenesis of the disease (Coppola et al 2020; Ranjeeth et al 2020). In human leptospirosis, the innate immunity of the host, specifically the polymorphonuclear neutrophils and complement system, are implicated in the first line of protection. Pathogenic leptospira, for its part, has developed a variety of escape tactics to dodge host immunity and infect people (Latchoumi et al 2016).

Therefore, this review focuses on understanding leptospira pathogenesis and escape strategies from immune system of host. In the future, a better understanding of leptospiral immunity and how Leptospira subverts the immune system could lead to new insights into the production of therapeutic regimens against this species

Epidemiology:

The geographical distribution of human leptospira is worldwide. Several factors are responsible which control the infection and rate of transmission. These factors are floods, climatic change, sanitation level and population density (Pappas et al. 2008). Leptospirosis transmission require persistent flow of pathogen among animal reservoir or maintenance host. Leptospira colonizes the kidney and are shed in urine from wide range of animals. They live for many weeks in muggy soil and water by forming biofilms or by aggregating (Ristow et al. 2008; Trueba et al. 2004). Humans get infected by coming in touch with urine of infected animals either direct or indirect. The entry of pathogen in humans is usually via cut or abrasion in skin or through conjunctiva. During the last one decade the pattern of leptospirosis epidemiology has changed, the leptospira infection breakout in sporting events and recreational facilities, primarily due to change in climatic conditions (Victoriano et al. 2009; McCurry et al 2009). In geographical distant countries like Brazil and Israel, epidemiology changes have been observed from rural to urban areas (Ko et al. 1999; Kariv et al. 2001). Leptospirosis turned to be a significant health problem where disease is endemic, but due to tourism and recreational activities leptospirosis become a major infectious disease in non-endemic region.

Pathogenesis:

Leptospirosis, an infection caused by pathogenic Leptospira after environmental exposure, create enduring renal carriage and shedding in urine of reservoir animals. The susceptible hosts experience tissue damage in various organs. The infection from Leptospira involves host cells invasion, colonization of tissues in multiple organs, and host immune evasion. The multiple steps of leptopsira pathogenesis are discussed below.

Invasion:

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The initial step of Leptospira infection is the attachment of bacteria with host cells and form pores. The attachment of Leptospira is arbitrate by several molecules (virulence factors) which are present on surface or secreted by bacteria. Several virulence factors are discovered in leptospira which are involved in pathogenesis. These virulence factors are present on surface of bacteria and help in attachment or are secretory proteins either involve in forming pores or cause lysis/damage of host cells. Leptospira surface protein play major roles in attachment to host Fibroblast, microglia, endothelial and epithelial cells (Cinco et al. 2006)

The host-pathogen interaction is mediated by several Leptospira surface proteins that are involved in binding to numerous parts of extracellular matrix (ECM) (Atzingen et al. 2008; Stevenson et al. 2007 ; Merien et al. 2000). The degree on leptopsira invasion is enhanced by binding of surface protein s to host plasminogen. Pathogenesis of Leptopsira is facilitated by several other proteins such as hemolysins and proteases which are encoded by genome of these organism (Vieira et al. 2009, 2010a). A few virulent factors which are responsible for leptospira pathogenesis and invasion are mentioned in table.

Sn	Virulence Factor	Function
1	LPS (Lipo-polysaccharide)	Structural Integrity of cells
2	Loa22	Lipoprotein
3	LipL32 (hemolysis-associated protein I (Hap I),)	Lipoprotein
4	LenA (Lsa24) family includes LenB, LenC, LenD, LenE, LenF	leptospiral endostatin-like protein
5	Hemolysins (SphA and Sph2)	Responsible for translocation of leptospira in various tissues
6	Leptospiral Immunoglobulin-Like Proteins, Lig (Lig A, LigB, LigC)	adhesins and invasion-mediation
7	HemO	Degrade the heme molecule by disrupting tetrapyrrole ring

Table 1: Virulent factors involved in invasion and pathogenesis of leptospira

Leptospiral Persistence and Immune Evasion

Unlike salmonella or mycobacterium, Leptospira are not intracellular facultative bacteria but they live briefly in host cells and swiftly moved through cell monolayers in vitro (Barocchi et al. 2002; Merien et al. 1997; Liu et al. 2007). They dwell in cytoplasm or phagosomal compartments in non-phagocytotic cells. The intracellular future of these spirochetes, with same efficiency, differ in both human and murine macrophages. In human macrophages, after phagocytosis by macrophage cell they escape from

phagosome to cytoplasm where they multiply and apoptosis of cell occur whereas in murine macrophages these are degraded by lysosome hydrolase (Tu et al. 1982; Li et al. 2010). Thus, Leptospira have developed a phagosomal escape mechanism to evade immune system and rapidly disperse to various host tissues and cause infection.

There are multiple factors that promote leptospiral endurance and dodge host immune system. Leptospira infection are flushed out from all organs except renal tubules where they colonize, multiply and give long term renal carriage in reservoir animals. During acute and chronic infection, kidney is the main target and for survival renal tubule condition are favourable (Yang et al 2007). Kidney is the organ that gave long endurance to leptospira. The mechanism which promote survival of leptopira in kidney is challenging to determine. However, it is assumed that due to absence of complement sytem antoi-leptospira antibodies failed to kill these bacteria (Monahan et al. 2008). Leptospira are immune to complement system, both alternate and classical pathway. They dodge alternate pathway by acquiring compliment factor H through binding by Len surface protein (Verma et al. 2006 ; Stevenson et al. 2007 ; Meri et al. 2005) and escape classical pathway by binding to complement fragment C4b-binding protein alpha chain (C4BPA) through LcpA (leptospiral complement regulator-acquiring protein A) (Barbosa et al. 2009, 2010). In rat kidney, bio-film formation and cell aggregation corresponds to long endurance and high concentration in urine shedding (Ristow et al. 2008). Further it has been observed that expression of LPS O antigen promote the high persistence of bacteria in hamster kidney. However, the mechanism is still not clear and needs further investigation (Nally et al. 2005).

On the basis of proteomic analysis, when comparison is done between leptospira present in urine to that of in-vitro then it shows that antibodies isolated from serum of infected rats reacts with high amount of antigen from in vitro Leptospires as compared to those Leptospires which are isolated from infected host (Monahan et al. 2008). This analysis indicates that specific antigen expression and its down regulation by leptospira promotes renal colonization, long endurance, and immune evasion (Xue et al. 2010). Using microarray technique, various genes are evaluated which are responsible for innate immune response and it was found that various OMP genes are downregulated which might be the strategy to escape host immune response. Thec progression of disease is also depend upon host susceptibility factor, dose of infecting strain, and virulence characteristics of infecting strain. Certain species and serovars of leptospira cause severe disease in humans more often than others (Lingappa et al. 2004). The leptospira pathogenesis and immune invasion is described in Figure 2.

Host Immune Response

It was earlier thought that humoral immune system provide immunity against leptospirosis (Adler et al 1977). The response was targeted against LPS. This conclusion was supported with evidence includes: passive transfer of immunity, correlated to the level of anti-LPS antibodies in transferred sera and immunity to various animals against leptospirosis like guinea pigs, hamsters, dogs, and monkeys by anti-LPS monoclonal antibodies (Adler et al 1978; Jost 1986). However, anti-LPS antibodies was not

able to provide complete immunity against all serovars of leptospira. Hence it was argued that there are other factors apart from LPS which might be responsible for immunity against leptopsira. Previous study indicate that protein extract might provide immunity against both homologous and heterologous challenge (Sonrier 2000). This led to identification of various outer membrane proteins that provide immunity against leptospiral infection in animal models. B-cells plays a major role in providing immunity with help from other factors like IFN- ɣ and iNOS secreted by T-Cells. Despite Leptospires are not tough bacteria, but their ability to invade the host cells and reside in various phagocytotic and non-phagocytotic cells help them to escape agglutinating anti-bodies and thus evade host immune system (Merien 1997 ; Barocchi 2002).

Many studies in cattle have shown a change in pattern of host immune response following leptospiral infection. Generally, vaccine given to cattle are based on killed *L. borgpetersenii* serovar Hardjo, and its defensive ability depends upon its efficiency to stimulate Th1 response and IFN-ɣ release (Bolin 2001; Brown 2003). Vaccine that activate high antibody production but fails to elicit Th1 response, do not provide protection. The need for Th1 response for immunity against infection does not confined to single serovar (hardjo) or host (cattle). In recent years various reports have showed that high level of protection against infection with *L. interrogans* serovar Pomona corelated with high level of Th1 response in hamsters (Faisal et al. 2008, 2009a). Multiple evidence has showed the role of cell mediated immunity, especially CD4 and ɣδT-cells with the release of IFN-ɣ against the infection (Klimpel 2003). Leptospires stimulate the production of ɣδT-cells in leptopsira infected patient. Despite the population of these lymphocyte is very small in blood (1-5%) but they can play important role in host defense in epithelial tissue and mucosal surface where they are present in rich numbers as leptospira enter through cut skin or mucosal route (Bonneville 2010). The differentiation of CD4 T-Cells into phenotype (Th1& Th2) secreting cytokines, play a significant role in host defence by supplementing the immune response. The role of CD8 cells (CTL) have not been seen in providing immunity but few studies have shown increase number of these cells in patients infected with selected serovars. Mice having low level of CD8 cells develop lung and kidney lesions and patients from which CD8 cells are acquired multiply in response to Lig protein peptide (Guo 2010; Van Voorhis 1996).

The latest report focusses on the significance of innate immunity, particularly Toll Like receptors (TLR), in developing early immunity against Leptospira infection (Chassin 2009). For the potent innate immunity against leptospira infection response both TLR2 and TLR4 are essential. In mice, LPS is recognized by both TLR2 and TLR4 whereas TLR2 and TLR1 in human which makes the mice immune and human vulnerable to leptospirosis (Nahori 2005). Effective innate immunity can be conferred to mice against leptospira by improving the recognition of LPS and thus make mice immune against the infection. For example, TLR4-deficient C3H/HeJ newborn mice are prone to leptospiral infection (Viriyakosol 2006). On the contrary, human cells cannot detect LPS of leptospira because TLR4/ MD2 of human cannot recognize Lipid A of LPS and thus weaken innate immunity response against leptospira lead to leptospirosis.

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In reciprocation to bacterial invasion of various tissues, host has adapted a different approach by compartmentalization of tissues with different mechanism of protection in different tissues like B-cells in liver and T-cells in kidney. The difference in developing productive immune response against leptospira infection between mice (maintenance) and human (accidental) might grant early control of infection. Currently, all the available data regarding the mechanism of host immune response against leptospira infection are vague. Despite that host recognized the LPS of leptospira through TLR2 and TLR 4 and consequently produce antibodies against LPS and outer membrane proteins. While host tries to kill Leptospires through antibodies and compliment but pathogen escape this by switching of the compliment pathway through its proteins (adhesins, endostatins). Leptospires then attack various tissues where they reside for a while and when condition become unfavourable, instigate apoptosis. Even though Leptospires invade various tissues and move between them but they prefer to colonize the kidney due to absence of compliment pathway, a immune evasion strategy. Despite the fact host activate the T-cells response against the infection, the response seems to be too weak to prevent the infection. The host immune response against leptospira is described in figure 2.

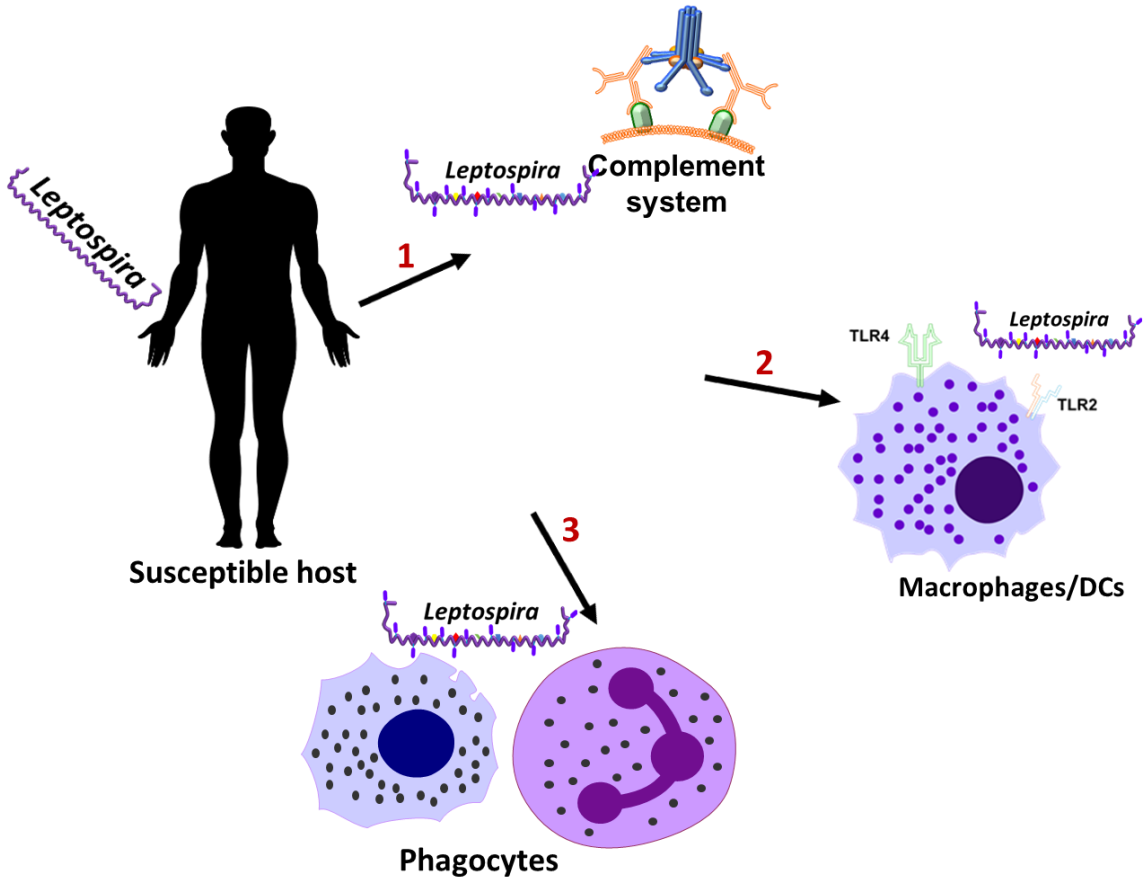

Fig 1: *Leptospira* pathogenesis and immune evasion in susceptible human host. (1) *Leptospira* enters the host through skin aberration or cut. It acquires complement regulators (FH, C4BP) through surface exposed proteins and escapes killing by complement system. (2) It escapes recognition through

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Toll like receptors like TLR2 or TLR4 via downregulating the expression of surface proteins and evades activation of innate response and subsequent adaptive response. (3) It modulates the function of phagocytes like neutrophils and monocytes to evade from phagocytosis and other mechanism of killing.

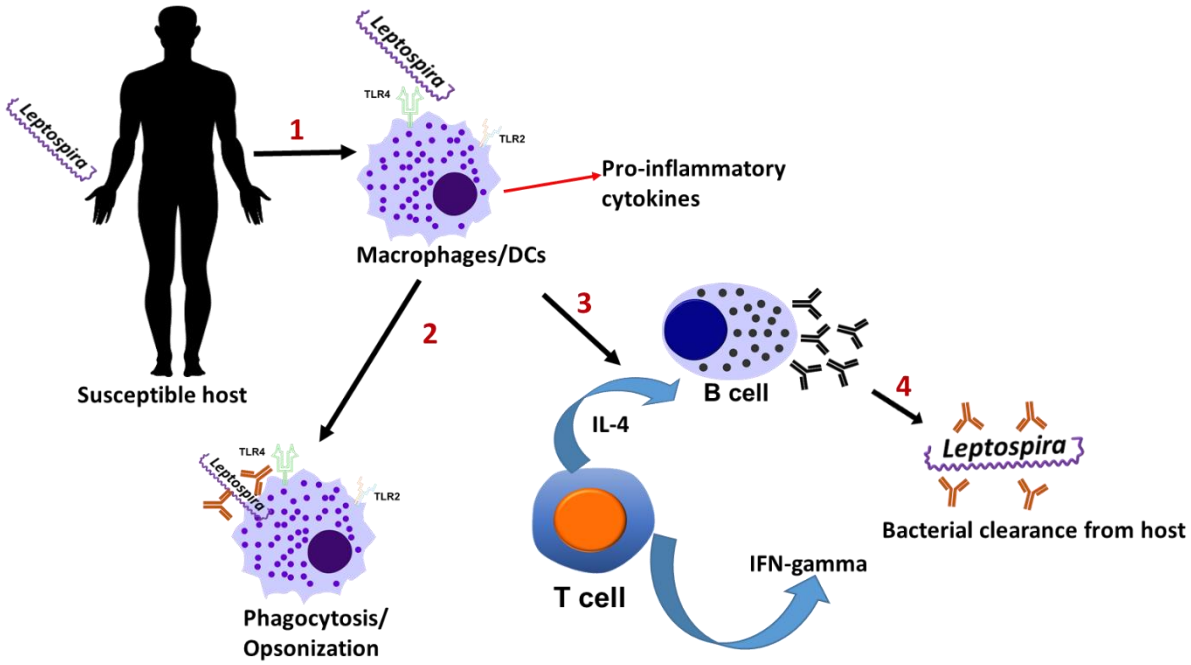

Fig 2: Host Immune response against *Leptospira* infection. (1) Host innate immune cells like macrophages and Dendritic cells recognize *Leptospira* through innate receptors like TLR2 or TLR2 leading to their activation (expression of pro-inflammatory cytokines like IL-6 and TNF-a) and expression of surface markers (CD80, CD86, MHCII). (2) The activated cells then phagocytose the bacteria and mediate killing by ROS. (3) The activated innate immune cells then initiate adaptive immune response by processing and present *Leptospira* antigens to T cells which produces IL-4 to help B cells produce antibodies. It may produce IFN-gamma to enhance *Leptospira* killing by macrophages. Antibodies then mediate killing and clearing the bacteria from the host.

Conclusion

The infection like leptospiral can cause complications in the multi-organ system or even death in unintended hosts (e.g., humans) but infection is mild and asymptomatic in reservoir hosts like rodents.

Differential host immune responses have been proposed as a potential cause of different disease outcomes, but the mechanisms remain unclear. Thanks to the availability of animal models of chronic and acute leptospirosis, as well as genetic studies and knockout mouse models can now be used to be a better understanding of host colonisation and resistance to severe disease in leptospirosis. These approaches helps to identify both host determinants and virulent factors that are responsible for the disease.

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