Review

Weil's Disease - from Gut Dysbiosis to Immunopathogenesis and Multiple Organ Failure

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Abstract: Leptospirosis is an important zoonotic disease, causing about 60,000 deaths annually. One of the reasons for the severe course of leptospirosis is a cytokine storm, which develops as a result of an excessive immune response. The gut microbiota that resides in the gastrointestinal tract provides essential health benefits to its host, particularly by regulating immune homeostasis and a bi-directional relationship with many internal organs. A change in the gut microbiota can be caused not only by antibiotics but also by infectious agents such as the coronavirus or the flu virus. It is known that *L. interrogans* can change the microbiota of mice. Thus, gut dysbiosis in leptospirosis can affect the clinical course of the disease, through the gut–organ axis. Modulation of intestinal microbiota by probiotics and/or fecal microbiota transplantation in leptospirosis may become an important area of scientific research.

Keywords: leptospirosis; dysbiosis; Weil's disease

1. Introduction

Leptospirosis is a re-emerging zoonosis, caused by *Leptospira* spp. It is estimated to infect more than a million people with approximately 60,000 deaths annually (1). Disease is usually transmitted by contact with the urine of a host carrying the pathogen in water or soil, causing infection in humans through the skin or the gastrointestinal tract (2). Human leptospirosis has a wide range of clinical manifestations, including mild, asymptomatic infections, as well as serious and life-threatening complications with multi-organ dysfunction, e.g. when kidneys, lungs, and liver are seriously damaged (3, 4). Weil's syndrome (10% of cases), is a severe form of leptospirosis with a high mortality rate; it is characterized by hepatic dysfunctions associated with renal failure and hemorrhages (5). Severe leptospirosis patients should receive early recognition and intensive medical care. The pathology of leptospirosis and the factors that cause severe leptospirosis are currently unclear (6). Because the pathogenesis of leptospirosis is unclear, antibiotic therapy is still the preferred treatment. However, due to the difficulty of early diagnosis of leptospirosis, some patients infected with *L. interrogans* often develop multiorgan dysfunction (7).

Both host factors and pathogens may play an important role in the pathogenesis of leptospirosis (8). Induction of an inflammatory response by a pathogen can initiate destructive immune mechanisms leading to host tissue damage, sepsis, and death (9). The extensive release of cytokines, including interleukin 6 (IL-6), interleukin 1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α), is known as a cytokine storm. Several studies

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have shown how cytokines contribute to pathogenesis and clinical manifestations of leptospirosis (10, 11).

Gut dysbiosis is one potential factor influencing leptospirosis's lethality (12). Gut microbiota interacts with the host immune system in ways that influence the development of different diseases (13). The gut microbiota generates a wide range of metabolites, such as short-chain fatty acids (SCFAs) (14). SCFA has anti-inflammatory effects by inducing apoptosis and preserving the mucosal barriers to endotoxin infiltration (15). There is growing evidence that there is a critical link between the gut microbiome and other organs most affected by leptospirosis, such as the liver, lungs, and kidneys (16, 17). In this review, our objective is to identify the characteristics of innate and acquired immunity in severe leptospirosis and to find the link between gut dysbiosis and cytokine storm as the main immune mechanism that influences the mortality of leptospirosis.

2. Immunopathogenesis

The attachment of bacteria to host cells and the formation of pores are the first steps in Leptospira infection. Leptospira attachment is mediated by virulence factors found on the surface or secreted by bacteria. In Leptospira, several virulence factors involved in pathogenesis have been discovered. These virulence factors are present on the surface of bacteria and help in attachment, formation of pores, and causing damage and lysis to host cells. The surface protein is essential for attachment to host fibroblast, microglia, endothelial, and epithelial cell attachment, as well as laminin, collagen types I and IV, cellular, and plasma fibronectin (18, 19). Leptospiral proteins bind both to ECM components (fibronectin, elastin, laminin, and collagen) and to complement regulators and plasminogen using LigB and LipL32 (Fig.1) (20, 21).

Contact with pathogens during infection activates the innate immune system by initiating an inflammatory response (Fig.2). Microbial Pathogen-Associated Molecular Patterns (PAMPs) are recognized by the Pattern Recognition Receptors (PRRs) expressed at the surface of innate immune cells, mainly the Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (22, 23).

The association initiates an inflammatory cascade by activating multiple intracellular signaling pathways, including the NF-κB and activator protein 1 (AP-1), which in turn regulate the expression of cytokines, Prostaglandins (PGs), and Nitric Oxide (NO) (24-26). PGs and NO are pro-inflammatory molecules that increase arterial dilation and vascular permeability, both being key events required for the influx of immune cells (27, 28). Pro-inflammatory cytokines include interleukins (IL)-1β, IL-6, IL-12, interferons (IFNs), and tumor necrosis factors (TNFs), as well as chemokines, which act as chemoattractants to recruit leucocytes to the site of tissue damage and/or infection (26). Interestingly, AP-1 and NF-κB also modulate the pro-inflammatory response through the induction of immunomodulatory cytokines such as IL-4, IL-10, IL-13, or Transforming Growth Factor-β (TGF-β) acting in concert with cytokines inhibitors to offset the massive induction of pro-inflammatory mediators (29). Interestingly, in contrast to other bacterial lipopolysaccharides (LPS) that classically activate the TLR4 signaling pathway, leptospiral LPS are not recognized by TLR4, but by TLR2 in human cells, while both TLR2 and TLR4 are activated in mice (30).

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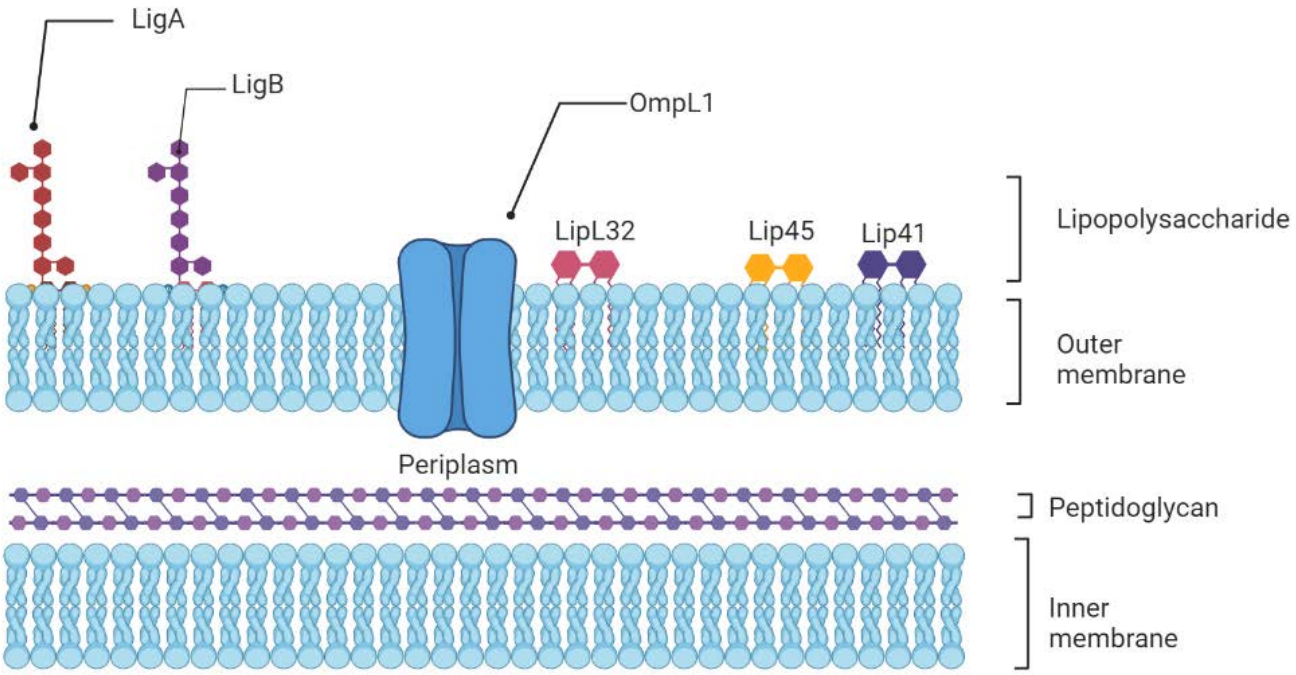

Figure 1. Schematic representation of the architecture of the leptospiral membrane. The inner membrane is closely associated with the peptidoglycan cell wall, which is overlaid by the outer membrane. Surface-exposed lipoproteins (LipL32, LigA, LigB), the transmembrane outer membrane protein porin L1 (OmpL1), and lipopolysaccharide are among the main components of the outer membrane.

An equally important effective mechanism during the first hours of infection is the activation of an alternative complement pathway (31). A clear example of this phenomenon is the observation that saprophytic *L. biflexa* is killed in the presence of normal human serum in a few minutes. Comparatively, pathogenic Leptospira species can persist and are more resistant to the complement system's effects, especially if they are virulent (32).

Because leptospires are extracellular pathogens, the acquired immune response is dependent on antibody production and activation of the complement system classical pathway. Most of the specific antibodies produced in leptospirosis are anti-LPS (8). In many animal models, it became evident that phagocytosis of Leptospira by neutrophils and macrophages is only effective if this pathogen is opsonized by specific IgG (33). In addition to opsonization, these antibodies can agglutinate leptospires and activate the classical path of the complement system (34). Opsonins generated after complement activation may also be important to enhance phagocytosis, as anti-complement receptor type 3 antibodies block the adhesion of Leptospira to leukocytes (20).

The host attempts to kill the leptospira via antibodies and complement, but the pathogen escapes by switching to the complement pathway via its proteins (adhesins, endostatin) (20). Then leptospires attack different tissues where they reside for a while, and when the conditions are not favorable, they initiate apoptosis (35). Although leptospires invade various tissues and move between them, they prefer to colonize the kidney due to the absence of a complement pathway; this is called an immune evasion strategy (4). Even though the host activates a T-cell response to infection, this response appears to be too weak to prevent infection (36).

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3. Immunological aspects of damage to the kidneys, liver, and pulmonary bleeding as the basis of Weil's syndrome

3.1. Immunological aspects of renal damage

The kidneys are the target organs in human leptospirosis pathology. Leptospirosis is associated with an overwhelming activation of inflammasomes and proinflammatory cytokines in the early phases, causing kidney inflammation and subsequent damage. On day 10 of the infection, Leptospira can be found in the proximal tubular cells, and on day 14 of the infection, it can be found in the tubular lumen (37). Its antigens are also found in the proximal tubular cells, macrophages, and the interstitium (38).

Leptospiral outer membrane proteins (OMPs) contain antigenic and virulent compounds, such as lipoproteins, LPS, and peptidoglycan that determine host responses (39). Leptospiral LPS, found in OMPs, appears to be a major antigen affecting leptospiral immunity, and its function is thought to be related to host-pathogen interactions that determine virulence and pathogenesis. Leptospiral OMPs were extracted from cultured mouse renal epithelial cells, which displayed the expression of a variety of genes related to tubular cell injury and inflammation, to elucidate the mechanisms of tubule interstitial injury caused by Leptospira (40). Nuclear transcription factor kappa B (NF-κB), activator protein-1, and several downstream genes expressed in the medullary thick ascending limb cells are all activated by the leptospiral OMPs (40). LipL32, a key virulence lipoprotein on the OMP, induces tubulointerstitial nephritis-mediated gene expression in mouse proximal tubular cells and is a prominent immunogen during human leptospirosis infection (41). Furthermore, LipL32, a hemolysin that causes erythrocyte hemolysis during leptospira infection, has a direct impact on the proximal tubular cells by significantly increased expression of some pro-inflammatory cytokines, such as inducible nitric oxide (iNOS), monocyte chemoattractant protein-1 (MCP-1), and TNF-α (42).

The effects of TLRs as the first line of immune defense mechanisms in the innate immune response were evaluated to determine whether TLRs could mediate the inflammatory response induced by Leptospiral OMP in renal proximal tubular cells. Interestingly, only TLR2 but not TLR4 resulted in increased levels of iNOS and MCP-1 expression. As a result, the findings demonstrate that TLR2 is required for the early inflammatory response that occurs after Leptospiral OMPs, specifically LipL32, stimulate iNOS and MCP-1 in proximal tubular cells (43).

Leptospirosis induces the secretion of IL-1 and IL-18 from human macrophage cells through reactive oxygen species and cathepsin B-mediated activation of the NLRP3 inflammasome, which activates a cascade of inflammation in renal tubular cells (44). Other circulatory cytokines and chemokines, including IL-6, IL-10, MCP-1, and TNF-α, are also produced during leptospirosis infection. An acute increase in cytokines and chemokines in patients with leptospirosis can lead to dangerous sepsis syndrome and severe sepsis due to an imbalance between pro- and anti-inflammatory reactions (45).

Thus, acute kidney injury (AKI) following leptospirosis can arise due to acute tubular necrosis (ATN) from ischemia and poor perfusion of renal tissue as the result of sepsis and septic shock. In addition, sepsis-associated AKI (sepsis-AKI) in leptospirosis is also possible, especially in patients with low blood pressure episodes. Pieces of evidence from both experimental and clinical studies show that septic shock develops into sepsis-induced immunosuppression, leading to the death of the host because of innate and adaptive immunity disturbances (46).

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3.2. Pathogenesis of leptospirosis pulmonary hemorrhage syndrome (LPHS)

The main cause of death in patients with leptospirosis is LPHS. The LPHS-related fatality rates are greater than 50% (47, 48). There are two main hypotheses for the pathogenesis of leptospirosis: a toxin-mediated mechanism and/or host immune responses. The relatively low number of leptospires recovered from lung tissue suggests a possible role of circulating bacterial toxins produced at distant sites, such as the liver (49). Although specific toxins are still unknown, a wide range of predicted proteases and hemolysins that may be involved in lung damage are encoded in the genomes of pathogenic Leptospira (50, 51).

LPHS was established in a guinea pig model (52) using Leptospira interrogans serovar Copenhagen strains isolated from Brazilian patients who died from hemorrhage and acute respiratory failure (53). This study showed that immunoglobulin and complement are deposited along the alveolar septa and that they can be associated with lung bleeding (52). In addition, immunoglobulin deposits were observed in the alveolar septum and the alveolar space in a human case of LPHS (54).

3.3 Pathogenesis of leptospirosis liver injury

It is known that the most serious form of leptospirosis, Weil disease, is also characterized by liver injury. Jaundice is an important manifestation of liver dysfunction, but its mechanism of leptospirosis has not yet been fully elucidated. The presence of jaundice implies a poor prognosis with a mortality rate of 19.1% (55).

Previous findings in patients recovering from leptospirosis, and thus out of the hemorrhagic phase of the disease, revealed non-specific hepatocellular damage affecting the sinusoidal pole, endoplasmic reticulum, mitochondria, and bile secretory apparatus (56, 57). The sinusoidal pole showed altered microvilli and the intercellular spaces were frequently widened with secondary microvilli and bile canaliculi dilated with partially or completely absent. The tight junctions were usually, but not always, preserved (58-60).

The pathogenic leptospires invade the intercellular junctions of host hepatocytes, and this invasion contributes to the disruption of the junction (61). Bile leaks from the biliary capillaries to the blood circulation during the induction of jaundice. This is a novel mechanism of jaundice caused by leptospiral infection, based on previous electron microscopy studies in hamster experimental models of leptospiral infection (61).

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The mechanism of jaundice proposed by Miyhara et al. is supported by the electron microscopy finding for leptospires and/or their remnants in the intercellular spaces of hepatocytes in humans, particularly in guinea pigs experimental disease (62).

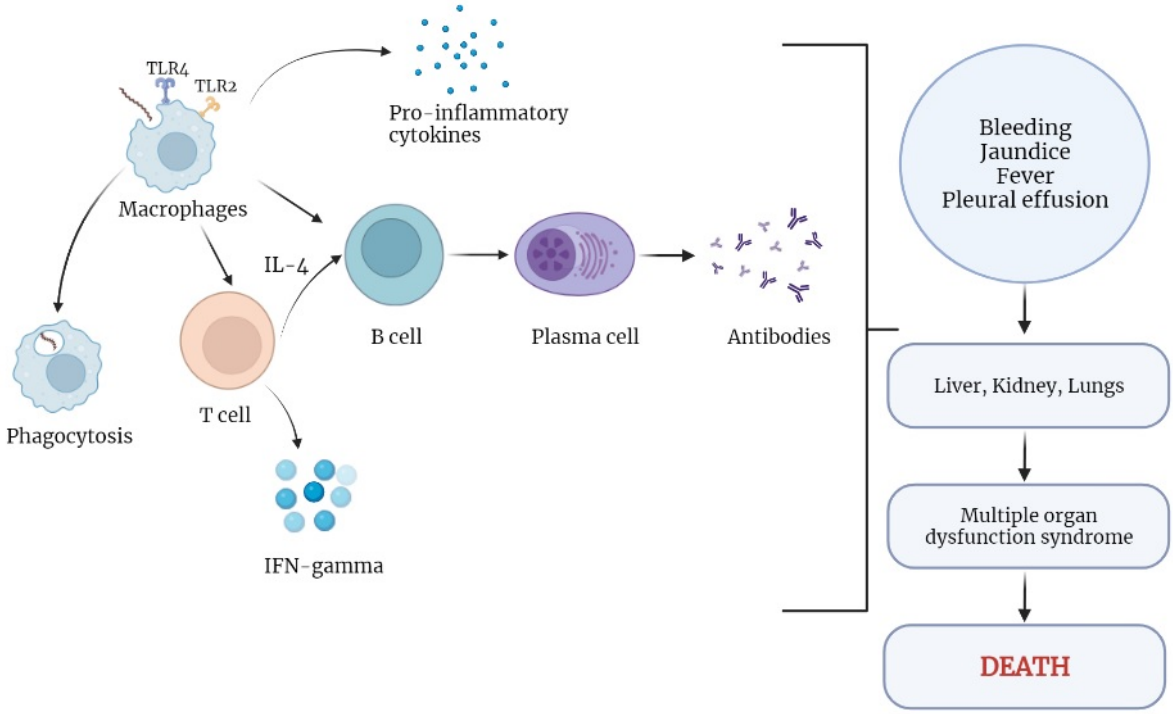

Figure 2. Immune response against Leptospira infection. Innate immune cells, such as macrophages, recognize Leptospira through innate receptors, i.e. TLR2 or TLR2, leading to their activation and thus expression of pro-inflammatory cytokines (IL-6 and TNF-alpha) and expression of surface markers (MHC class II). The activated cells phagocytose the leptospires and mediate killing by ROS. The activated innate immune cells initiate the adaptive immune response by processing and presenting Leptospira antigens to T cells that produce IL-4 stimulating the differentiation of B cells into antibody-producing plasma cells. It may produce IFN-gamma to enhance Leptospira killing by macrophages. Antibodies then mediate the killing and clearing of the bacteria from the organism.

3.4 Pathogenesis of pancreatic involvement in leptospirosis

Acute pancreatitis was previously reported as an uncommon complication of leptospirosis (63). The exact mechanism of acute pancreatitis in leptospirosis is not fully described. An immunological basis for pathogenesis of leptospirosis, including TLR2 activation, is described recently (64). The most consistent pathologic finding in leptospirosis is a vasculitis of capillaries manifested by endothelial oedema, necrosis, and lymphocytic infiltration (65). Small vessel vasculitis and ischemic injury, leading to activation of proteolytic enzymes, and auto-digestion is a possible mechanism (66).

3.5 Pathogenesis of bleeding in leptospirosis

Bleeding is a common symptom of severe leptospirosis. Although the cause of leptospirosis hemorrhages is not completely understood, some studies report ongoing fibrinolysis, activation of coagulation, impaired anticoagulation, and thrombocytopenia, whereas the involvement of disseminated intravascular coagulation is controversial (67-69). Endothelial cell infection and activation have also been implied as a mechanism in leptospirosis hemorrhages, contributing to severe disease manifestations (70, 71).

3.6 Genetic Susceptibility

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Over the last decade, the study of genetic susceptibility to infectious disease has undergone revolutionary change (72). Variations in host genetic makeup may lead to differences in susceptibility toward leptospirosis (73). Human leukocyte antigen (HLA), cytokine genes, and killer-cell immunoglobulin-like receptors (KIR) polymorphisms were investigated by Fialho et al. in patients with a history of leptospirosis and healthy controls (74). According to the scientists, leptospiral infection susceptibility was substantially correlated with alleles in the HLA-A and B loci, as well as various HLA haplotypes. Patients with a prior history of leptospirosis also had significantly higher levels of polymorphisms in the IL-4 and IL-4R genes. Contrarily, Esteves et al. observed that leptospirosis infection was responsive to genetic variation in the IL12RB1, IL1, and CISH genes (75). Recent investigations have also shown that the TLR1 Ile602Ser and TLR2 Arg753Gln gene polymorphisms have a significant impact on the development of severe leptospirosis with jaundice and hepatic insufficiency (76).

4. Gut microbiota involved in leptospirosis

The human gastrointestinal tract (GI) is an extremely diverse and complex microbial ecosystem with more than 10^{14} resident species interacting with the host and actively participating in many physiological processes, particularly in supporting the maintenance and development (77).

An imbalance in our gut microbiome is the cause of many diseases, including metabolic diseases, noncommunicable diseases, and infectious diseases (78, 79). It is well known that the gut microbiome plays a major role in initiating, adapting, and regulating the immune response (80, 81). The gut microbiota produces SCFAs that have anti-inflammatory properties, such as inducing apoptosis, inhibiting the tumor cell cycle, and preserving mucosal barriers to endotoxin infiltration (15). Since most immune cells are located in the intestine, the gut microbiota plays a crucial role in the immune response of the intestine and other organs. Nowadays, there is growing evidence for the important link between the gut microbiome and other organs, such as the liver, the kidney, and the lung, which are most often damaged in leptospirosis (17, 82, 83). The crosstalk between the gut and the lungs, kidneys, and liver is well-established, but the mechanisms by which the gut influences these organs or vice versa are unknown and relevant research is still in its early stages (84).

4.1 Gut–Kidney Axis

The gut microbiota produces many uremic solutes and toxins, such as indoxyl sulfate, and p-cresyl sulfate (PCS) during chronic kidney disease (CKD). However, increasing urea concentration results in a change in the intestinal microbiota. In patients with CKD, uremic toxins can cause renal anemia, pruritus, fatigue, mineral bone disorders, neurological damage, and cardiovascular impairment (85). The pathogenic interconnection between the gut microbiota and kidney diseases is called the gut–kidney axis and appears to be involved in a wide range of clinical manifestations, such as CKD, acute kidney injury (AKI), hypertension, nephrolithiasis, hemodialysis, and peritoneal dialysis (86).

AKI is a prominent feature of leptospirosis, characterized by tubulointerstitial nephritis and tubular dysfunction. The non-oliguric hypokalemic form of AKI is an important sign of leptospiral nephropathy (87). The incidence of AKI in patients with leptospirosis varies between 10% and 88%, depending on the definition of AKI, age, and severity of the disease (88).

AKI triggers immune responses, leading to epithelial disruption by activating macrophages and neutrophils of innate immunity and the T helper type 17 (Th17) cell from

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adaptive immunity (83). These processes result in a leaky gut that causes dysbiosis. Studies have demonstrated that AKI causes gut dysbiosis in 24 hours (89). In contrast, gut dysbiosis also causes an imbalance of different chemicals, specifically uremic toxins, and SCFAs, ultimately altering immune and hormonal homeostasis and causing a worsened AKI (90).

4.2 Gut–Liver Axis

The gut-liver axis refers to the bidirectional relationship between the gut, along with its microbiota, and the liver, arising as a result of interactions between signals generated by dietary, genetic, and environmental factors (91). The interconnection of the gut and the liver explains why disturbances in the intestinal barrier result in an increased portal influx of bacteria or their products to the liver, where they cause or influence a range of hepatic diseases (92).

Gut dysbiosis has been linked to liver diseases with distinct aetiologies, including acute liver injury, viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcohol-related liver disease, autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) (93-95).

The liver is constantly exposed to bacterial components and microbial metabolites via the portal vein. LPS is a component of the cell wall of gram-negative bacteria, and mild release of LPS from the gut can stimulate liver regeneration and tissue repair (96, 97). Furthermore, gut microbial metabolites, such as bile acids, SCFAs, and tryptophan metabolites, affect host metabolism and the immune system, which may indirectly influence liver injury and regeneration (98).

The role of gut-derived LPS as a cofactor in acute liver injury has been shown in models of acute liver injury induced by various hepatotoxic agents (99). Under primary liver damage, gut-derived LPS can activate Kupffer cells to release pro-inflammatory mediators, such as TNF-α, interleukins (IL-1 and IL-10), lysosomal enzymes, and superoxide, which aggravate inflammatory responses and necrosis (95).

Gut-derived LPS is crucial for liver regeneration (96). When the liver is subjected to an experimental physical or chemical injury, gut-derived LPS will pass through the compromised liver and spill into the general circulation, leading to low-grade systemic endotoxemia, which causes the production of hepatotropic factors, such as insulin, glucagon, epidermal growth factor (EGF), vasopressin and triiodothyronine (T3) (100).

SCFAs are important substrates for the integrity of the epithelial barrier, which limits the pro-inflammatory load on the liver. Butyrate enhances gut barrier function by increasing the expression levels of claudin-1 and zonula occludens-1 (ZO-1), decreasing LPS translocation and inhibiting downstream inflammatory responses (101). Thus, SCFAs can indirectly affect liver damage and regeneration by maintaining the function of the intestinal barrier (102).

4.3 Gut–Lung Axis

The microbiota plays an essential role in the education, development, and function of the immune system, both locally and systemically (79). Emerging experimental and epidemiological evidence highlights crucial cross-talk between the intestinal microbiota and the lungs, called the 'gut–lung axis' (103). Changes in the constituents of the gut microbiota, through either diet, the disease is linked with altered immune responses and

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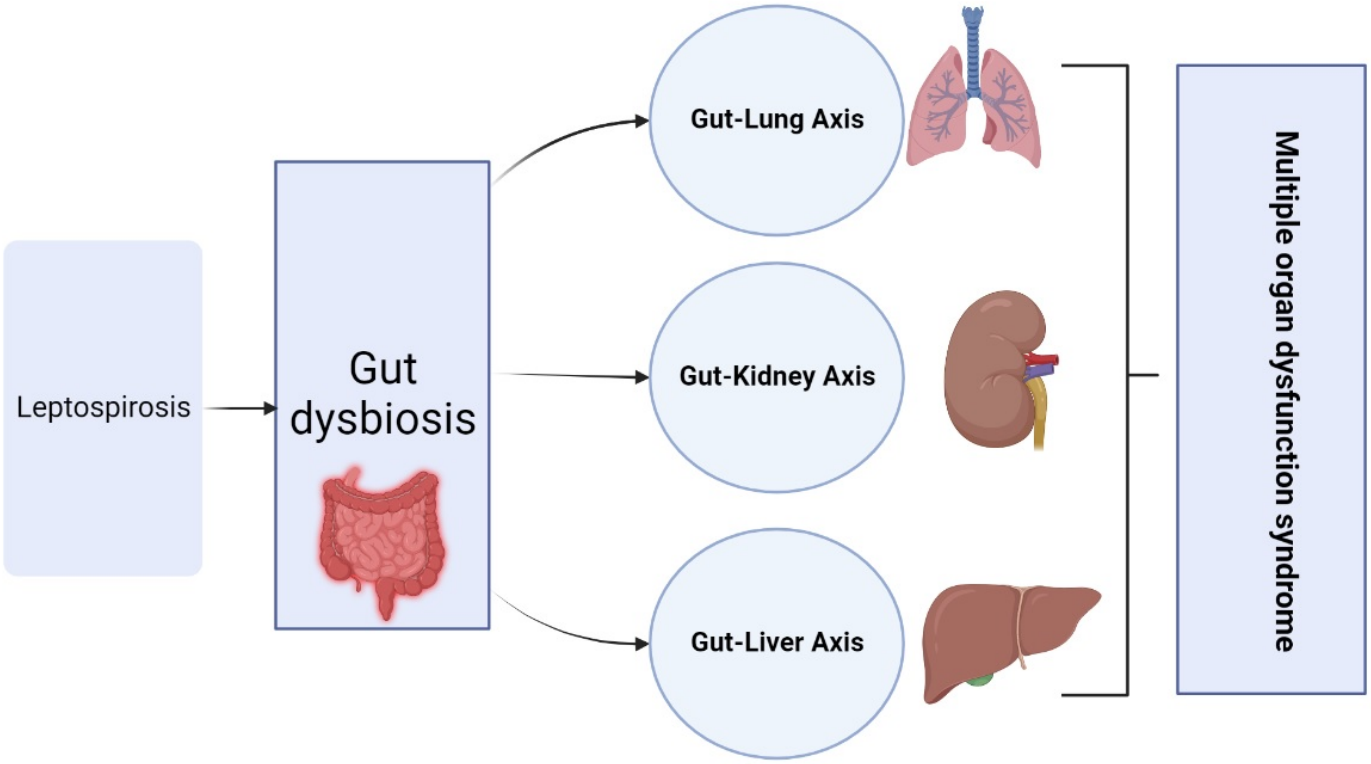
homeostasis in the airways (104). The gut-lung axis is bidirectional, meaning that microbial metabolites and endotoxins from the gut can affect the lungs, while lung tissue inflammation can affect the intestinal microbiota (79).

An example of the influence of microbiota on the gut–lung axis is the relationship between intestinal SFB and pulmonary Th17 response. SFB can stimulate Th17 in the lungs and protect it from *Streptococcus pneumoniae* infection, enhancing lung mucosal immunity (105). Dysbiosis of intestinal flora has been associated with respiratory diseases, such as asthma and cystic fibrosis (106, 107). These studies show that microbes play an essential role in cross-talk between the gut and the lungs and that microbial dysbiosis in the lungs may affect the homeostasis of the gut, and vice versa (108)

Figure 3. The influence of altered gut microbiota on the course of leptospirosis. According



to our hypothesis, leptospirosis-induced gut dysbiosis can lead to a pro-inflammatory immune response, which can be one of the factors resulting in a severe course of leptospirosis.

4.4 Gut microbiota and leptospiral infections

The role of the gut microbiota in leptospirosis infection was investigated using 16S rRNA sequencing, finding that the relative abundance of Firmicutes and Bacteroidetes between uninfected mice and leptospire-infected mice 7 days after infection differed significantly at the level of type and genus. Firmicutes/Bacteroidetes ratio (F/B Ratio) was significantly increased in the group of infected mice (12). The study found that pre-depleting the gut microbiota of mice with antibiotics resulted in a significant increase in the burden of Leptospira in organs, such as the liver, kidneys, and lungs. Reverse effects were obtained with fecal microbiota transplantation (FMT) (12).

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Changes in the gut microbiota may result from activation of intestinal immunity caused by L. interrogans infection. Host immune activation induced rapid transcriptional and metabolic adaptation of intestinal microbes (109).

Disturbance of the gut environment caused by infection results in disruption of the homeostasis between gut immunity and microbiota and eventually leads to an expansion or decrease of certain bacteria (110).

We proposed the hypothesis that gut dysbiosis caused by leptospirosis can lead to a more severe course of the disease, due to connections called axes (Fig.3).

5. Discussion and conclusion

Leptospirosis is one of the most widespread and dangerous zoonoses in the world. The main cause of death in leptospirosis is the development of a severe form of leptospirosis - Weil's disease, which affects the kidneys, lungs, and liver, which are a "triad" of target organs in leptospirosis.

Leptospires are capable of altering gut microbiota. Similar mechanisms, according to which infectious agents change the gut microbiota, have also been revealed for SARS-CoV-2, Influenza, M. tuberculosis, and some other microorganisms (111-114). Most of the current studies emphasize the possible influence of these microbiota changes on the course of diseases (115-117).

The gut microbiota can play a crucial role in directing immune responses outside the local environment, including the lungs, kidneys, and liver. This may be achieved by the systemic dissemination of metabolites, as has been shown for SCFAs (79). These metabolites are produced in the colon but can reach other organs through the bloodstream, where they can exert their anti-inflammatory properties (118). This complex interaction between the gut microbiota and the host's immune system, which affects the body's functions, has led to the formation of an "axis" between them (119). This crosstalk occurs via an array of signaling pathways and direct chemical interactions between the host and the microbes, e.g. through SCFAs.

Therefore, the cross-connection of the gut microbiota with many internal organs of the body plays an important role in the clinical course of many diseases, including leptospirosis. Disturbance of the microbiota, such as antibiotic treatment, could increase susceptibility to *L. interrogans* infection. A whole line of research is being conducted to investigate the influence of gut microbiota on the course of leptospirosis and will expand the field soon.

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