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Paratuberculosis: A Potential Zoonosis

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INTRODUCTION

The zoonotic significance of paratuberculosis has been debated for a long time (Dalziel 1913). After the identification and isolation of *Mycobacterium avium paratuberculosis* (MAP) in humans suffering from Crohn's disease in 1986 (Chiodini et al. 1986), the attention of many researchers diverted to finding the zoonotic potential of paratuberculosis (Grant 2005). Furthermore, MAP is considered as an important agent in the pathogenesis of certain human auto-immune diseases. These diseases include human immunodeficiency disease, diabetes mellitus, encephalomyelitis disseminate, chronic autoimmune thyroiditis, Besnier-Boeck-Schaumann disease (Sechi et al. 2008; Paccagnini et al. 2009; Sisto et al. 2010; Cossu et al. 2013). The zoonotic potential of paratuberculosis is based on the analogical relationship of clinical symptoms between Johne's disease in animals (i.e. both ruminants and non-ruminants) and Crohn's disease in human beings (El-Zaatari et al. 2001). The pathogenic role of MAP is associated with several other factors i.e., intrinsic and extrinsic that can influence the onset of chronic disease in humans. The intrinsic factors include the inability of one's immune response to withstand the harms of the pathogen due to genetic problems or injury to lymphoid tissues. On the other hand, extrinsic factors include exposure of humans to the causative agent of disease or disturbance in the microbial flora of the gastro-intestine. All these factors combine to the onset of the pathogenesis of paratuberculosis in humans (Chiodini 1989; Naser et al. 2014). Moreover, antigenic molecular mimicry is also hypothesized to influence the generation of the autoimmune response in humans exposed to the MAP (Cossu et al. 2013).

Paratuberculosis—Animal-based Perspective

Paratuberculosis, also known as John's Disease, is a well-known infectious chronic disease characterized by granulomatous inflammation of the intestines (Eslami et al. 2019). The disease is caused by acid-fast bacteria belonging to the genus *Mycobacterium*, specie *avium*, and sub-specie *paratuberculosis* (Malvisi et al. 2016). The causative agent of this disease is an obligate parasite that is dependent on its host cells and necessarily requires host cellular machinery for division and propagation (Arsenault et al. 2014). The etiological agent was first recognized 100 years ago in large domestic ruminants suffering from intestinal inflammation for a long period by two German researchers (Jöhne and Frothingham 1895). Later on, the disease was recognized as Johne's Disease and the associated pathogen was identified throughout Europe in 1906 (McFadyean 1906) and America in 1908 (Pearson 1908). The *Mycobacterium avium paratuberculosis* (MAP) infects a wide range of animal species. The disease is commonly found in the domestic population of ruminants including cattle, sheep, and goats as well as in wildlife populations e.g., deers, foxes and cotton tail rabbits (Rohde and Shulaw 1990; Whittington and Sergeant 2001; Anderson et al. 2007; Münster et al. 2013). Within the animal herd, the disease may be vertically transmitted from the pregnant dam to the fetus during pregnancy (Whittington and Windsor 2009), or during the neonatal life period of calves through ingestion of infected milk/colostrum (Khol et al. 2013) or other contaminated tamaterial e.g., soil, feces, etc (Aly et al. 2012).The body fluids of infected animals including saliva, semen and blood, etc., may also carry the infectious agent and be transmitted to healthy animals upon exposure to these fluids (Abbas et al. 2011; Sorge et al. 2013). Although MAP is majorly transmitted through the vertical mode of transmission, it may also be transmissible horizontally from infected calves to healthy calves, or from infected calves to wildlife reservoirs and vice versa (Sweeney 1994). On exposure of the animal to the MAP through the oral route, the bacterial organism either settles in the ileum directly or becomes stuck up in the lymphoid organ i.e., tonsils. From tonsil crypts, it gains entry into the blood or lymphatic circulation, and ultimately reaches the ileum and mesenteric lymph nodes (Payne and Rankin 1961; Sweeney et al. 2006). The M-cells in the payer patches of the small intestine assist the movement of MAP across the mucosal epithelium of the small intestine. After crossing the

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epithelial barrier, the MAP reaches the submucosa of the intestine and is phagocytized by the sub-mucosal macrophages (Momotani et al. 1988). The persistent presence of MAP in macrophages leads to the onset of granulomatous inflammatory reaction in the intestine and gut associated lymphoid tissues. This leads to the formation of anti-MPA immunoglobulins due to Th2-lymphocytes activation and release of certain cytokines e.g. IL-4 and IL-10 (Stabel 2000). The MAP starts replicating in the macrophages and then spreads to the uterus, salivary glands, muscles, and other body organs. Thus, the clinical symptoms of disease start appearing and pathogen shed in the faeces and in fluids of infected animals (Sweeney 2011; Arsenault et al. 2014). The appearance of clinical signs in MAP infection is associated with the severe economical losses to the farmers of dairy cows due to prolonged course of disease (Khol et al. 2017). The role of MAP in causing disease in animals is well understood, however, the zoonotic potential of this disease in humans is still debatable.

Paratuberculosis—Human-based Perspective

Zoonotic Transmission

MAP is an environmentally stable pathogenic organism that is viable in the soil and water bodies for approximately 4 months (Garvey 2020). After bacterial shedding in feces, the pathogen resides in the soil of a farm or grazing land. The pathogens may contaminate the soil of pasture due to the utilization of animal manure as fertilizer in fodder crops and reside in the roots and shoot system of plants (Grewal et al. 2006; Kaevska et al. 2014). It may also contaminate the water bodies where municipal water is drained off and resides in biofilms (Botsaris et al. 2016). Therefore, the transmission of MAP from animal reservoirs to humans mainly occurs through direct contact of humans with animal feces, contact with contaminated soil, or consumption of contaminated water (Garvey 2018). The consumption of contaminated milk or milk products is also thought to be a potential source of MAP exposure in humans. Different research studies have confirmed the presence of MAP in the milk of MAP-infected dairy animals and some fermented dairy products e.g., yogurt and cheese (Eltholth et al. 2009; Gill et al. 2011; Van Brandt et al. 2011; Galiero et al. 2016). The presence of MAP in the meat of infected animals has also been previously reported (Alonso-Hearn et al. 2009). Besides oral transmission of MAP, different researches have also suggested the aerosol transmission of the MAP from host animals to humans (Eisenberg et al. 2011; Rhodes et al. 2014). Humans are majorly exposed to the pathogen during the so-called “eclipse phase” of the pathogen in the host animals due to ignorance of the farmers for screening of MAP in their animal herds, trade of infected animals, and inefficiency of the MAP diagnostic tests (Naser et al. 2014; McNees et al. 2015; Dow and Alvarez 2022).

The Global Incidence of Different Human Diseases Associated with Paratuberculosis

The zoonotic potential of MAP was the first time evidenced after the isolation and detection of the pathogen in clinically sick patients suffering from gastro-intestinal inflammation and exhibiting clinical signs similar to that of Johne’s disease in the animal. This disease is known as infectious bowel disease (IBD) or Crohn’s disease and it affects one to two million people around the globe (Molodecky et al. 2012). Later on, MAP was also reported to infect patients suffering from some autoimmune disorders. All these ailments are chronic with no specific treatment and millions of people around the globe suffer from these diseases annually. These diseases include juvenile diabetes, adult-onset diabetes, encephalomyelitis disseminate, chronic auto-immune thyroiditis, and Besnier-BoeckSchaumann disease (Waddell et al. 2015). Juvenile diabetes is a genetic disorder in which the pancreatic cells are unable to produce enough insulin for the regulation of the glucose-glycogen cycle. About 2-5% of people are affected by this type of diabetes in the world annually (Tao et al. 2015). Adult-onset diabetes is a condition seen in adults in which the sugar level of the patient is increased above the normal range due to the inability of the body cells to utilize insulin. Approximately, 90 % of adults in the world suffer from this type of diabetes in the world (Zheng et al. 2018). Encephalomyelitis disseminata is an auto-immune disorder characterized by the injury to the myelin covering of the neurons, thus, creating a hindrance in the transmission of neurological signals to the brain and spinal cord. About 0.3-0.6 individual per one hundred thousand people suffer from this disease in the world each year (Pohl et al. 2016). Chronic auto-immune thyroiditis is an auto-immune inflammatory condition that is characterized by hypothyroidism due to the attack of immune cells on butterfly-shaped thyroid glands in the body. About 3.5-5/1000 females and 0.6-1/1000 males suffer from this condition in the world each year (Ragusa et al. 2019).

Paratuberculosis and Infectious Bowel Disease (IBD)

The term IBD refers to two conditions affecting the gastrointestinal tract in human beings i.e., Crohn’s disease and ulcerative colitis. In both of these conditions, the gross and microscopic inflammatory appearance of the intestinal wall is analogous to that observed in animals suffering from paratuberculosis (Gill et al. 2011). The formation of lesions in the intestines results in the appearance of several clinical signs including loose motions, abdominal pain, and malabsorption of nutrients through villi in the small intestine. Moreover, the condition becomes more severe and chronic after the involvement of the immune system response (Thia et al. 2010). The selective absorptive

capability of the intestine is compromised and the causative agent of paratuberculosis (i.e. MAP) gains access to the different body organs through the circulatory system (Naser et al. 2004). Moreover, similar to the shedding of bacteria from the mammary glands of animals, studies have shown the shedding of MAP in the milk samples from the breast of patients suffering from Crohn's disease (Naser et al. 2000; Bannantine et al. 2014). Another similarity between paratuberculosis and IBD is the mutation of bacterial sensing immunogenic gene i.e., NOD2. The mutation of this gene leads to the defective or no production of NOD2-protein associated with the immune function of certain immune cells e.g. macrophages and paneth cells in the intestinal epithelium (Kuenstner et al. 2015). This genetic relation between Johne's and Crohn's disease suggests that both diseases share a common etiological agent. The MAP is observed in the histopathology of intestinal tissue biopsy samples under 100x objective magnification using acid-fast staining (Jeyanathan et al. 2007). Moreover, the PCR of MAP-specific genes has shown a positive presence in the biopsy samples from intestine (Bull et al. 2003). The doubts regarding etiological resemblance of Johne's disease and Crohn's disease vanished when the successful isolation and culturing of MAP from humans caused active infection in intestine of MAP inoculated goats (Van Kruiningen et al. 1986). All these studies indicate a strong zoonotic relationship between Johne's and Crohn's disease.

Paratuberculosis and Diabetes Mellitus

It is a disease that is characterized by the inability of endocrine cells of the pancreas to produce insulin due to the autoimmunity of T lymphocytes against proteins (heat shock protein and insulinoma-linked proteins) and an enzyme (glutamic acid decarboxylase) in the cells of islets of Langerhans (Kerner and Brückel 2014). Paratuberculosis and insulin-dependent diabetes (also known as diabetes mellitus type-I) are reported to share some genetic similarities (Rani et al. 2010). The mutation of the SLC11A1 gene leads to the protection of MAP from the host's immunity. This gene encodes Natural Resistance Associated Macrophage Protein-1 (MRAMP1) which is a divalent metal ion transporter membrane protein of phagocytic cells and acts by resisting the host cells against several types of microbial pathogens (Hsu et al. 2006). The mutation in the gene of this protein is associated with dysregulation of this protein and the inability of the macrophages to destroy the pathogen (Paccagnini et al. 2009). Researchers have successfully isolated the DNA material of MAP from a patient suffering from insulin-dependent diabetes. This DNA has also been reported to be isolated from patients suffering from adult-onset diabetes (also known as diabetes mellitus type-II). However, the prevalence of MAP is much less (8%) than reported in the case of insulin-dependent diabetes i.e., 63% (Rosu et al. 2009; Manca Bitti et al. 2012). The induction of autoimmunity in insulin-dependent diabetic patients is related to the similarity between the epitopes of glutamine decarboxylase enzyme (GAD65) of humans and heat shock proteins (HP65) of MAP pathogen. The GAD65 is involved in the conversion of gutamine to butyric acid and carbon dioxide, whereas, heat shock proteins are produced in response to the environmental stress. The exposure of MAP to humans and expression of heat shock proteins results in the failure of the immune system to differentiate between self and non-self-antigens i.e., GAD65 and HSP65 respectively. Thus, resulting in the induction of an autoimmune response against these two homologous proteins and leading to the injury of islets of Langerhans in the pancreas. The damaged pancreas results in the inability of endocrine cells to produce insulin and ultimately patient suffers from insulin-dependent diabetes (Dow and Sechi 2011; Dow 2012). Moreover, the research studies have also reported similarities between the other membrane protein (zinc transporter 8) in the beta cells of the pancreas and a MAP protein (i.e. MAP 3865c). The reorganization of antibodies against zinc transporter 8 protein and MAP protein is further evidenced, supporting the role of MAP in the production of an autoimmune response in insulin-dependent diabetes (Masala et al. 2014).

Paratuberculosis and Rheumatoid Arthritis

Rheumatoid arthritis is defined as a chronic autoimmune disease characterized by the painful swelling of mobile joints due to immune-mediated inflammatory reactions (McInnes and Schett 2011). The role of MAP in the pathogenesis of rheumatoid arthritis is similar to that of diabetes mellitus. The research studies have indicated the polymorphic role of the SLC11A1 gene in the dysfunctioning of NRAMP-1 proteins and the production of T-lymphocytes against the body's cells, thus, enabling MAP to manipulate and worsen the inflammatory reaction in joints (Yang et al. 2000).

Paratuberculosis and Chronic Autoimmune Thyroiditis

Chronic autoimmune thyroiditis (also known as Hashimoto's thyroiditis) is an immune system-mediated inflammation of thyroid glands resulting in the decreased production of thyroxin (hypothyroidism). The role of MAP in the pathogenesis of this condition follows the hypothesis of molecular mimicry where the failure of the immune system to recognize the self-body cells leads to the production of antibodies against the ZnT8 membrane proteins in the follicular cells of the thyroid gland (Sisto et al. 2010; Niegowska et al. 2015).

Paratuberculosis and Encephalomyelitis Disseminata

Encephalomyelitis disseminata (also known as multiple sclerosis) is an autoimmune disease affecting the nervous tissues of the brain and spinal cord through injury to the myelin sheaths caused by helper T lymphocytes (Cossu et al. 2017). The myelin sheath acts as a protective shield for neurons and is important in the transmission of nerve impulses from the effector organ toward the CNS (Balice-Gordon et al. 1998). Numerous studies reported the high incidence of encephalomyelitis disseminata in Italy (42%) and identification of MAP from affected patients was associated with the environmental exposure of Italians to the pathogen (Cossu et al. 2011; Cossu et al. 2013). However, some researchers have associated this condition with autoimmunity and related genetic predisposing factors that are further strengthened after the exposure of humans to MAP. The formation of myelin shields on neurons is an important phenomenon and any abnormality or disruption in this procedure causes the onset of neurological symptoms in the affected individual (Stiles and Jernigan 2010). The role of MAP in association with this neuro-behavioral condition is attributed to the reactivity of myelin basic proteins with molecularly similar antigenic proteins of MAP and thus, depleting the myelin from the axons of neurons and resulting in disruption of the transmission of a nervous signal across the CNS (Mameli et al. 2014).

Conclusion

MAP in humans plays an important role in the pathogenesis of Crohn's disease and some autoimmune diseases through the mutation in the genes of certain immune cell membrane proteins, cross-reactivity with cellular proteins, and exhibition of antigenic molecular mimicry. The shedding of bacteria occurs in feces, milk, blood, saliva, semen, etc, and direct contact with these fluids is the very possible root of transmission of pathogens to other animals and human beings. Moreover, the in-utero transmission from infected dams to the fetus in animals, and the consumption of infected meat by humans are also possible routes of transmission of MAP.

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