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Review Article

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Mycobacterium Avium Sub Species Paratuberculosis: Virulence Mechanism and Recent Vaccine Developments: A Review

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Abstract

Mycobacterium avium subsp. Paratuberculosis (MAP) causes chronic inflammation of the intestine known as Johne's disease in domestic and wild ruminants. This bacterium has also been linked to Crohn's disease, an inflammatory bowel illness in humans. Young animals are thought to be the most vulnerable to infection via oral uptake of the bacterium from a polluted environment. Following oral uptake, the bacterium can move through the intestinal wall to the basolateral side of the gut via the M cells. Following their discharge into the extracellular fluid of the lamina propria, these bacteria are picked up by macrophages, which ordinarily digest bacteria by enzymatic activities. Mycobacterium paratuberculosis, on the other hand, is specialized in preventing phagosome-lysosome fusion, allowing it to survive inside macrophages. Furthermore, they send anti-apoptotic signals, allowing their host cell to live longer. By inhibiting IL-12, MAP is able to upregulate interleukin (IL)-10, an immunomodulatory cytokine that reduces macrophage destruction of MAP as well as Th1-type immune responses, which are most desirable to battle intracellular infections. New paratuberculosis vaccines are being developed using live attenuated vaccines or subunits, usually recombinant MAP proteins that have been potentiated with adjuvants. Some Th1 antigens have been found by genomic and proteomic studies, including antigen 85 complex proteins (A, B, and C), superoxide dismutase, and heat shock protein 70 in cattle. However, Research on M. paratuberculosis is hindered by its slow growth rate and complex pathogenesis, leading to a lack of comprehensive information. Therefore, this review aims to provide an in-depth understanding of the pathogenesis of Mycobacterium paratuberculosis and explore recent developments in vaccines against this pathogen.

Keywords: Mycobacterium Paratuberculosis, Pathogenesis, Vaccine, John's Disease

1. Introduction

Mycobacterium paratuberculosis is a causative organism of Johne's disease (JD), a chronic gastroenteritis affecting domestic and free-ranging animals, primates, rabbits, stoats, and foxes. This bacterium has also been linked to Crohn's disease, an inflammatory bowel illness in humans (Chamberlin et al., 2001; Manning and Collins, 2001; Niran, 2020).

Newborn and young animals are primarily infected by the fecal-oral route. Consuming milk and colostrum from infected animals might potentially spread the infection. The risk of infection increases in calves up to the age of 6 months but decreases after that. It has been suggested that M. avium subsp. paratuberculosis may also play a role in the etiology of Crohn's disease in humans due to the similarities between the gross pathology and histology of the disease associated with M. avium subsp. paratuberculosis in animals and humans (Naser et al., 2004).

Crohn's disease is a human chronic inflammatory disease which covers the entire thickness of the colon and, in around 60% of cases, is characterized by granulomas. A recent sharp rise in the disease's prevalence, particularly in poor countries and among children, has sparked new interest in and study into this severe condition (Hye-Soo et al., 2020).

During the infectious process, macrophages use pattern recogni-

tion receptors to recognize MAP and initiate phagocytosis (Martinez and Gordon, 2014). Because phagocytosis by intestinal macrophages does not initially induce cytokine release, resident intestinal macrophages perform host defense activities without inducing an inflammatory response (McClean and Tobin, 2016). Despite the fact that these macrophages phagocytize the pathogen swiftly, phagocytosis does not always result in pathogen death. MAP can interfere with macrophage activities and/or responsiveness in a number of ways, including limiting macrophage activation (Arsenault et al., 2012), inhibiting phagosome maturation, preventing macrophage acidification (Hostetter et al., 2003), and delaying macrophage apoptosis (Weiss et al., 2005).

Although host defense macrophages are important first responders to bacterial infection, a protracted inflammatory response may be damaging to the host. Initial MAP infection in Johne's disease causes a subclinical infection with minimal intestinal inflammation, whereas more advanced stages of infection are marked by significant inflammation and an influx of macrophages to the target tissue (Koets et al., 2015).

It's possible that the polarization of macrophage phenotype, which shifts from a host defense phenotype to a regulatory phenotype to assist regulate the inflammation, is what causes the disease to advance from subclinical to clinical phases. Cytokine secretion and the expression of cell surface markers like macrophage receptors can be used to identify the phenotypes of macrophages. IFN-, IL-1, IL-12, IL-23, and TNF- are pro-inflammatory cytokines that are expressed by host defense macrophages (M1), whereas CD163, CD206, and the cytokines IL-1Ra, IL-10, and TGF- are expressed by resolution/regulatory and repair macrophages (M2) (Martinez and Gordon, 2014).

According to Thirunavukkarasu et al. (2015, MAP increases IL-10 secretion from ovine and bovine monocyte-derived macrophages via activation of p38 mitogen-activated protein kinases (MAPKs). IL-10 is an anti-inflammatory cytokine that reduces antibacterial activity and the Th1 response while also increasing the development and long-term survival of MAP in macrophages by decreasing pro-inflammatory cytokine production (Redford et al., 2011). Furthermore, a study by Jenvey et al. (2019 reveals that the inability of macrophages to clear MAP may be due to the stimulation of macrophages oriented towards resolution and repair, which promotes the maintenance of infection rather than the elimination of the infecting pathogen.

The immunization against paratuberculosis has been suggested as an alternative method of control of diseases when combined with management techniques. The creation of vaccines depends heavily on our understanding of host-pathogen interactions. It has long been understood that cellular immune responses mediated by Th1 are crucial for preventing MAP infections. However, recent evidence indicates that innate immune responses, as opposed to adaptive immunity, are more directly linked to protective advantages. However, Research on M. paratuberculosis is hindered by its slow growth rate and complex pathogenesis, leading to a lack of comprehensive information. Therefore, this review aims to provide an overview of the pathogenesis of M. paratuberculosis and discuss recent advancement in vaccine developments.

2. Literature Review

2.1. Biological Characteristics of Mycobacterium Paratuberculosis

On a genetic basis, *M. paratuberculosis* is virtually identical to *Mycobacterium avium*; however, the phenotypic characteristics of the two organisms are different. *M. paratuberculosis* grows much more slowly, requires an iron-transport chemical known as mycobactin for in vitro growth, forms rough colonies on solid agar media, and infects mammals rather than birds. The most appropriate taxonomic classification and proper name for *M. paratuberculosis* has been under debate. An opinion supported by the International Association for Paratuberculosis is that *M. paratuberculosis* should be reclassified as a subspecies of *M. avium* and thus renamed *M. avium* subspecies paratuberculosis (abbreviated *M. paratuberculosis*). This subspecies designation appears in many recent publications concerning the organism (Thorel et al., 1990). For simplicity, the name M. paratuberculosis is used in this paper.

The DNA of *M. paratuberculosis* is >99% identical with that of *M. avium*. This is the reason that many characteristics of the two bacteria are similar. The genetic feature that distinguishes one from the other is the presence of multiple copies of a short DNA element called an insertion sequence (IS) that is unique to *M. paratuberculosis* and is named IS900. Genetic probes used for detection of M. paratuberculosis in clinical specimens or in cultures are based on detection of IS900. A second insertion sequence, named IS901, that is approximately 60% similar in DNA sequence to IS900, was recently found in some strains of *M. avium*. How these insertion elements affect the biology and pathogenic capacity of M. paratuberculosis or *M. avium* is not understood. There is evidence that they play a major role (Michael, 2003).

2.2. Mycobacterium Paratuberculosis in Animal

In Map infected animals, a variety of granulomatous lesions can be detected, which have been classified according to the intensity, location, cellular types, and number of acid-fast bacilli (AFB) (Gonza´lez et al., 2005). Animals with clinical signs usually show diffuse lesions, characterized by widespread granulomatous enteritis, affecting both the lymphoid tissue and lamina propria causing the thickening of the intestinal wall (Delgado et al., 2013).

Mycobacterium paratuberculosis infection occurs mainly through M cells of the Peyer’s patches and, to a lesser extent, through differentiated epithelial cells. After penetrating the intestinal epithelial barrier, MAP invades the sub epithelial macrophages that play a crucial role in the host–pathogen interaction. Granulomatous lesions, composed mainly of macrophages, are the hallmark of paratuberculosis, constituting a complex environment where mycobac-

teria can inhibit the maturation and acidification of phagosomes and transform the potentially hostile macrophages into protected havens assuring their replication (Sigurdardo´ttir and Valheim, 2004). There is still a lack of information regarding macrophage function or diversity within the granuloma in paratuberculosis. In addition, why some granulomas control bacterial growths while others permit it remains unknown. As a reflection of the complexity of these interactions, the existence of different myeloid cell populations that can interact with antigens and participate in the local immune response has been described in the intestine of cattle, with differences related to age or intestinal location (Fries et al., 2011).

According to Ferna´ndez, et al. (2017, the macrophages composing the granulomas associated with Map infection show differences in the expression of several proteins, reflecting changes in their functionality based on the type of lesion. M1-type macrophages will predominate in focal and multifocal forms, suggesting their latent character and the ability to control MAP infection, and partially in diffuse paucibacillary lesions. M2 are the main type in diffuse multibacillary forms, with an immune-regulatory profile that would permit intracellular growth. The immune-histo-chemical analysis of macrophage subsets within Map infection–associated lesions has contributed to increased knowledge on the pathogenesis of this disease.

2.3. Mycobacterium Paratuberculosis In Humans

Crohns disease is a chronic inflammatory disease of the human gastrointestinal tract that is characterized by weight loss, severe diarrhea, and abdominal pain. The similarities between the gross pathology and histology of *M. avium* subsp. paratuberculosis- related disease in animals and Crohn's disease (CD) in humans have led to the suggestion that *M. avium* subsp. paratuberculosis may also have a role in the etiology of the latter. Several further observations strengthen this hypothesis: the detection of the specific DNA insertion sequence IS900 of *M. avium* subsp. paratuberculosis in relatively high numbers in the blood and tissues of patients with CD, the finding of *M. avium* subsp. paratuberculosis-reactive T cells in CD patients, and the culture of viable M. avium subsp. Paratuberculosis forms from blood of people with CD (Naser et al., 2004).

Granulomas make up about 60% of the symptoms of Crohn's disease. Further interest and research have been sparked by the disease's recent sharp rise in prevalence, particularly in poorer countries and among children. The most frequently discussed and addressed reasons are autoimmune, T-cell-mediated immune responses to the local gut flora, and several infectious pathogens, despite the lack of a definitive etiology at this time. Given the apparent similarities to Johne's disease, According to the observations of the Scottish surgeon TK Dalziel (Dalziel, 1913), and possibly earlier by the Polish surgeon Antoni Leniowski in 1904, it has been believed for the past 120 years that MAP may be the causal agent of Crohn's disease. Although Dr. Burrill Crohn initially remarked on its resemblance to well-known mycobacterial infections of the gut, such as Mycobacterium tuberculosis complex (MTB), especially in that it was of a "granulomatous enteritis" nature (Janowitz et al., 1965), the organism was never found or isolated; as a result, several etiologies emerged over time. Due to the lack of a definitive diagnostic test that links MAP to a current disease, this hypothesis is debatable (Campbell et al.2012).

2.4. Pathogenesis and Immune Subversion Mechanisms of Map

2.4.1. Binding and Spread

Mouse models have shown that, after ingestion, MAP attachment to and translocation through the intestinal mucosa is mediated by both M-cells and enterocytes. Moreover, studies in tissue cultures demonstrated that MAP affects the formation of tight junctions in the intestinal mucosa providing a mechanism for increased permeability (Bannantine et al., 2013). There is significant host–pathogen crosstalk during MAP infection as antigens 85 , 35 kDa, MAP oxidoreductase, MAP fibronectin-binding protein, and the histone HupB play important roles in MAP epithelial cell adhesion and/or invasion (Lefrancois et al., 2011).

Microbial infections are initiated by molecular interactions between the pathogen and receptor molecules on host cells, resulting in microbial adhesion and, sometimes, subsequent internalization (Bermudez et al., 2010). Furthermore, when bacteria adhere to surfaces, they are substantially more resistant to host antimicrobial defenses (Pott et al., 2009). The extracellular matrix (ECM) of the cell consists of a complex mixture of macromolecules, including collagens, fibronectin, fibrinogen, vitronectin, laminin, and heparin sulfate (Pott et al., 2009), all of which function as ligands for bacterial adhesion. Fibronectin plays a pivotal role in bacteria-host interactions by interacting with microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) (Everman et al., 2015), a group of microbial surface proteins that interact with ECMs of host cells and initiate infection.

2.5. Binding and Spread

Macrophages use pattern recognition receptors to recognize MAP during the infectious process and begin phagocytosis (Martinez and Gordon, 2014). Phagocytosis by intestinal macrophages does not initially induce cytokine release, thus, resident intestinal macrophages perform their host defense activities without inducing an inflammatory response (McClean and Tobin, 2016). Although these macrophages readily phagocytize the pathogen, phagocytosis often does not result in killing of the pathogen. The functions and/or responsiveness of the macrophage can be disrupted by MAP through a variety of methods, including preventing macrophage activation (Arsenault et al., 2012), blocking phagosome maturation), preventing macrophage acidification (Hostetter et al., 2003), and delaying macrophage apoptosis (Weiss et al., 2005). Although host defense macrophages are vital first responders to bacterial infection, a prolonged inflammatory response can be harmful to the host. In Johne's disease, initial infection with MAP results in a subclinical infection where little intestinal inflamma-

tion is observed, whereas the more advanced stages of infection are characterized by extensive levels of inflammation with an influx of macrophages to the target tissue (Koets et al., 2015).

The progression from subclinical to clinical stages of disease may be a result of the polarization of macrophage phenotype from a host defense phenotype towards a regulatory phenotype to help control the inflammation. Macrophage phenotypes can be characterized using secretion of cytokines and expression of cell surface markers, such as macrophage receptors. Host defense macrophages (M1) are characterized by expression of pro-inflammatory cytokines such as IFN-γ, IL-1β, IL-12, IL-23, and TNF-α, whereas resolution/regulatory and repair macrophages (M2) are characterized by expression of the surface markers, CD163, CD206, and cytokines IL-1Ra, IL-10, and TGF-β (Martinez and Gordon, 2014).

Moreover, a study by Jenvey et al. (2019, suggests that it is possible that the promotion of macrophages polarized towards resolution and repair, which favors maintenance of infection rather than the destruction of the infecting pathogen, is the cause of inability of macrophages to clear MAP.

2.5.1. Immune Subversion

Tissue macrophages and dendritic cells play a crucial role in the recognition of pathogen-associated molecular patterns in the innate phase via toll-like receptors, as well as in antigen processing and the elicitation of cytokine-mediated cellular interactions. Control of MAP infections are dependent on a T helper cell, Th1, type response and the subsequent activation of macrophages by interferon-gamma (INF-γ) secreted by Th1 T lymphocytes in the acquired immunity phase. The killing mechanism of these activated phagocytic cells involves the generation of nitric oxide by the inducible nitric oxide synthase (Li et al., 2011).

In addition to this, Findings using a co-culture of the bovine mammary epithelial cell line MAC-T (34) and bovine blood-monocyte-derived macrophages (BMDM) suggest that phagosome acidification in MAP-infected epithelial cells leads to interleukin (IL)-1β production, macrophage recruitment, and trans-epithelial migration (Lamont et al., 2012). Bacilli are subsequently phagocytosed by these sub- and intra-epithelial macrophages. Once inside phagocytic cells, the ability of MAP to survive and replicate within these phagocytic cells plays a key role in pathogenesis. Moreover, use of a culture passage model showed that MAP lipid composition changes in macrophages developing a pro-inflammatory phenotype. The ensuing host cellular immune response leads to the typical granulomatous enteritis pathognomonic of JD, characterized by the thick and corrugated appearance of the intestinal wall and inflamed lymph nodes (Everman et al., 2015).

Predominantly, MAP drives T helper cells from infected cattle to undergo a Th2 response with enhanced expression of IL-4, IL-5, IL-10, and inhibitors of tissue remodeling factors. This humoral response was confirmed in a neonatal calf model. Other findings also implicated regulatory T and Th17 cells in the immunopathogenesis of JD in both ruminants and wildlife (Robinson et al., 2011).

2.5.2. Persistent Survival in Macrophages

Similar to other mycobacterial strains, MAP can also survive and grow in mononuclear phagocytic cells, and it can develop a latent infection. Therefore, MAP and its components modulate the protective immune response of the host. However, little is known about the MAP components involved in the regulation of antibacterial immunity. Immune responses with a dominant Th1 type have been observed during the early phase of paratuberculosis, with a shift to a dominant Th2 type with disease progression (Magombedze et al., 2017) induced by increased interleukin (IL)-10 (Hussain et al., 2016). It has been reported that MAP stimulates IL-10 secretion from ovine and bovine monocyte-derived macrophages through activation of p38 mitogen-activated protein kinases (MAPKs) (Thirunavukkarasu et al., 2015). IL-10 is an anti-inflammatory cytokine which inhibits antimicrobial activity and the Th1 response as well increases the growth and persistent survival of MAP in macrophages by suppressing the production of pro-inflammatory cytokines (Redford et al., 2011).

Furthermore, proteins and glycolipids of pathogenic mycobacteria are involved in regulating the production of pro and anti-inflammatory cytokines in phagocytic cells. Mannosylated lipoarabinomannan (Man-LAM) derived from MAP induces rapid and prolonged production of IL-10 and facilitates the survival of MAP in macrophages (Hussain et al., 2016). Map41 of the MAP proline-proline-glutamic acid (PPE) protein family induces significant IL-10 as well as interferon (IFN)-production in peripheral blood mononuclear cells (PBMCs) from cattle infected with MAP (Bannantine et al., 2015). According to a recent study MAP1889c was identified as a sero reactive antigen in Crohn's disease patients. Treatment of MAP1889c in M. avium-infected macrophages promoted intracellular bacterial growth and IL-10 production. Thus, the finding suggested that MAP1889c reduces the host anti-mycobacterial response and may be a potential virulence factor during MAP infection (Hye-Soo et al., 2020). However, little is known about MAP protein stimulation of IL-10 production in macrophages and/or dendritic cells (DCs) and the detailed underlying modulatory mechanism.

2.6. Recent Vaccine Developments Against Map

Vaccination against M. paratuberculosis has been considered as an alternative strategy to control the disease when combined with management interventions. Understanding host-pathogen interactions is extremely important to development of vaccines. It has long been known that Th1-mediated cellular immune responses are playing a crucial role in protection against MAP infection. However, recent studies suggested that innate immune responses are more closely related to protective effects than adaptive immunity. Based on this understanding, several attempts have been made to develop vaccines against paratuberculosis. A variety of ideas for designing novel vaccines have emerged and the tests of the efficacy of these

vaccines are conducted constantly. However, no effective vaccines are commercially available yet (Hong-Tae Park et al., 2016).

2.6. 1. Live Attenuated Vaccines

Recently, many researchers have been interested in development of live attenuated vaccines against MAP. These types of vaccines can elicit protective mucosal and systemic immune responses because the diverse antigens included in this vaccine can stimulate both innate and adaptive immunity (Ghosh et al., 2014). Another advantage of this vaccine is that manufacture of live attenuated vaccine is cost effective and easies than that of other vaccines such as subunit vaccines (Ghosh et al., 2015).

Many vaccine candidates have been produced by mutagenesis to attenuate the virulence of MAP. Mutants of MAP have been made by phage-mediated techniques, transposon mutagenesis and allelic exchange mutagenesis (Park et al., 2008). Many transposon mutant libraries have been created to identify virulence mechanisms thereby finding vaccine candidates (Scandurra et al., 2010). Direct mutagenesis using allelic exchange techniques has also been tried by deletion of genes already known to be pathogenic or essential for intracellular survival in M. tuberculosis or M. bovis (Ghosh et al., 2015). The ΔrelA, Δlsr2, and ΔpknG mutants were generated by Park et al. (Park et al., 2008), and each gene was known to be related to virulence factors in M. tuberculosis and M. bovis (Colangeli et al., 2007). Two of these candidates, ΔrelA and ΔpknG were evaluated for virulence attenuation and efficacy as vaccine candidates using macrophages and ileal cannulation models of natural hosts (cattle) and goats. The result showed that ΔrelA mutant was a better vaccine candidate than ΔpknG mutant based on virulence attenuation and inhibition of MAP challenge in baby goats. The WAg906 (ΔMAP1566), WAg913, and WAg915 (ΔppiA) mutants were evaluated. WAg906 and WAg913 were made by transposon mutagenesis using MAP 989 strain, and WAg915 was made by allelic exchange of the ppiA gene (Scandurra et al., 2010). These live attenuated vaccine candidates were evaluated using monocyte derived macrophages (MDM) apoptosis, IL-10 production and animal models (mouse and goat) (Scandurra et al., 2010).

Another mutant, ΔsigL and ΔsigH mutants had been selected as live attenuated vaccine candidates (Ghosh et al., 2013). And these mutants showed attenuated virulence in mice, and elicited significant protective immune responses against MAP infection in mouse models (Ghosh et al., 2014).

2.6.2. Subunit Vaccines

Subunit vaccines have been developed to overcome the drawbacks of whole-cell based vaccines. Whole-cell based vaccines interfere with the diagnosis of both tuberculosis and paratuberculosis in vaccinated animals. However, subunit vaccines using well defined recombinant MAP proteins or DNA encoding immunogenic antigens can overcome the interference issues (Rosseels and Huygen., 2008). Many attempts have been made to identify MAP antigens to develop subunit vaccines using genomic or proteomic analysis. Because the production of IFN-γ induced by Th1-mediated immune responses is crucial to reducing the number of bacteria in the early stages of MAP infection, identifying antigens that induce strong Th1 responses is essential to the development of subunit vaccines. Finding an antigen is also related to development of immunodiagnostic method as well as development of subunit vaccines. Several proteins have been identified as vaccine candidates. (Rosseels and Huygen, 2008).

Several antigens were tested for their potential for use as vaccine candidates: heat shock protein 70 (Hsp70), antigen 85 complex proteins (Ag85A, Ag85B, and Ag85C) (Shin et al., 2005), lipoproteins (LprG and MAP0261c) (Rigden et al., 2006), PPE family proteins (MAP1518 and MAP3184) (Nagata et al., 2005), superoxide dismutase (Shin et al., 2005), and alkyl hydroperoxide reductases (AhpC, AhpD). Among many antigens, the protein Hsp70 has been widely studied as a subunit vaccine candidate. Cattle vaccinated with Hsp70 containing an adjuvant, dimethyl dodecyl ammonium bromide, showed reduced bacterial load compared with a non-vaccinated group in animals experimentally challenged with MAP (Koets et al., 2006). Furthermore, the cross-reactivity with serologic test of paratuberculosis was not observed when a pre-absorption step with Hsp70 was included, and Hsp70 vaccination did not interfere with the skin test of tuberculosis, despite Hsp70 being a major component of mycobacterial tuberculin (Santema et al., 2009). However, recent study suggested that the protective effects of Hsp70 protein are due to B-cell activation and therefore the production of Hsp70-specific IgG1, instead of Th1-mediated immune response producing IFN-γ (Vrieling et al., 2013). To date, researchers have only focused on cell-mediated immune responses to identify candidate vaccines. However, further studies are needed to understand protective mechanisms to MAP of host animals in greater detail, including humoral immune responses in the early stages of infection.

2.6.3. DNA Vaccines

DNA Vaccination against mycobacteria showed very effective protective immune responses in small rodents (Huygens, 2006). Moreover, DNA vaccines have advantages of storage and delivery because they are very stable. Several candidates were evaluated for their ability to induce protective immune responses; however, they were only evaluated in mouse models. Recently, combination of MAP-specific antigens and viral vectors was attempted to increase the ability of antigenic effects of DNA vaccines (Bull et al., 2014). The advantage of viral vectored vaccines is to provide high delivery of antigens to antigen presenting cells, thereby increasing antigen specific CD4+ and CD8+ immune responses (Reyes-Sandoval et al., 2012).

Sequence analysis and annotation of MAP genomes, prediction of proteins (structure, sub-cellular locations and antigenicity) based on the bioinformatics analysis and subsequent validation with laboratory experiments opened up a new era in the development of vaccines against MAP (Bannantine and Talaat, 2015). A rational

frame model has been proposed recently to test the new generation vaccine against MAP. It consists of three phases such as phase I (screening of candidates in bovine macrophages), phase II (mouse challenge models) and phase III (goat challenge model) to develop MAP vaccines (Bannantine et al., 2014).

3. Conclusion and Recommendation

The bacterium Mycobacterium avium subsp. paratuberculosis causes chronic enteritis in domestic and wild animals. This bacterium is also thought to be responsible for Crohn's disease, a chronic, inflammatory granulomatous disease in humans. To date, there has been limited success in controlling, treating, and curing MAP infection. Because of the insidious nature of the illness and our incapacity to recognize subclinical cases, control and eradication of Johne's disease remains a major challenge for the scientific community. In addition to this, MAP infection prevents both acquired and effector immune responses, making a vaccine development very elusive. MAP is also very effectively shielded from the host immune system once it is established and growing within the macrophage. Hence, the crucial period for intervention in a MAP infection should be before or during bacterial invasion and establishment of infection within the macrophage. This bacterium remains a significant challenge for the livestock industry due to its complex pathogenesis and limited control options. However, recent advancements in vaccine development provide hope for the prevention and control of Johns disease. Sub unit vaccines and live attenuated vaccines have shown promising results in terms of immunogenicity and protection. Therefore, further research should be conducted to better understand the pathogenesis, particularly its mechanism of invasion and persistence within the host. Continued efforts should be made to develop a safe and effective vaccine against the disease. Additionally, implementing effective animal husbandry practices and promoting early detection of infected animals through diagnostic tests can prevent the transmission of the bacterium.

Author Declaration

This manuscript has not been published before and it is not under consideration for publication elsewhere.

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Conflict Of Interest

I declare that there involves no conflict of interest while submitting the document

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