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CYTOKINE RESPONSE IN BRUCELLA ABORTUS BOVINE INFECTION: LITERATURE REVIEW

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Abstrak

Infeksi Brucella Abortus pada sapi merupakan infeksi yang memiliki efek strategis pada masyarakat khususnya sector ekonomi. Penyakit ini disebabkan oleh bakteri gram negative yaitu *Brucella Abortus.* Penanganan *Infeksi Brucella Abortus* pada sapi masih belum efektif. Terapi berdasarkan respon imun yang ditimbulkan dari *Infeksi Brucella Abortus* terutama respon sitokin menjadi pilihan efektif mengingat setiap jenis sapi memiliki respon imun yang berbeda dalam menghadapi *Infeksi Brucella Abortus.* Tujuan penulisan *literature review ini untuk mengidentifikasi sitokin-sitokin yang berperan dalam Infeksi Brucella Abortus* pada sapi. Metode : pencarian otomatis pada data base PUBMED dengan menggunakan kata kunci *"Brucella Abortus Bovine", "Cytokine", dan "Brucellosis"*. Hasil: 11 artikel yang relevan dan sesuai kriteria inklusi untuk menganalisa sitokin yang berperan dalam *Infeksi Brucella Abortus* pada sapi. Kesimpulan : Sitokin yang berperan dalam infeksi *Brucella Abortus* pada sapi umumnya adalah IL-1, IL-6, IL-12, IL-8, TNF-α, dan IFN-γ.

***Kata Kunci**: sitokin, respon imun, brucella abortus, bovine*

Abstract

Brucella Abortus infection in cattle is an infection that has a strategic effect on society, especially the economic sector. This disease is caused by gram-negative bacteria, namely Brucella abortion. Treatment of Brucella Abortus Infection in cattle is still not effective. Therapy based on the immune response caused by Brucella Abortus Infection, especially the cytokine response, is an effective choice considering that each type of cow has a different immune response in dealing with Brucella Abortus Infection. The purpose of writing this literature review is to identify cytokines that play a role in Brucella Abortus Infection in cattle. Method: automated PUBMED database search using keywords "Brucella Abortus Bovine", "Cytokine", and "Brucellosis". Results: 11 articles that are relevant and meet the inclusion criteria to analyze the cytokines that play a role in Brucella Abortus Infection in cattle. Conclusion: Cytokines that play a role in Brucella Abortus infection in cattle are generally IL-1, IL-6, IL-12, IL-8, TNF-α, and IFN-γ.

***Keywords**: cytokine, Immune Responses, Brucella Abortus, bovine*

1. INTRODUCTION

Brucellosis is a disease with significant economic consequences worldwide, especially in low-income countries. In South and Southeast Asia, bovine brucellosis is a common problem. Brucellosis is prevalent in Thailand, Indonesia, Malaysia, and Myanmar at 1%, 2%, 4%, and 5%, respectively. While Brucella melitensis is often seen in sheep and

goats, Brucella abortus is frequently detected in cattle and buffalo (Riyadh 2022).

Brucellosis is the only disease on the radar of the government in Indonesia. This disease is classified as a zoonotic and causes losses in the livestock world and is associated with miscarriage or reproductive problems, especially during the third trimester, which can cause placental, orchitis, and infertility. Abortions due to brucellosis are common during the seventh month of pregnancy. The economic damage caused by Brucellosis to Indonesian big business is estimated at IDR 3.6 trillion per year, or 1.8% of the country's total livestock assets (Handayani, Priyoatmojo, and Trinugraha 2022).

Brucellosis originates from a facultative intracellular Gram-negative bacterium of the genus Brucella. The main causative agents of brucellosis in cattle are especially Brucella abortus and Brucella melitensis, but B. abortus has a stronger association with cattle. The movement of sick livestock is a simple way of spreading disease, and close contact with sick animals increases the risk of transmission to humans (Mabe 2022).

Important factors in the effective management and elimination of brucellosis include immunization of livestock, serological testing, and culling of affected livestock. By employing the test-slaughter and compensation method, some nations have been able to completely eradicate brucellosis in cattle and claim the status of brucellosis-free territory. This cannot be applied in developing countries due to economic factors and cultural restrictions on slaughtering cattle that make it difficult to destroy sick cattle. As a result, brucellosis is fairly widespread in underdeveloped nations. Consequently, immunization is the cornerstone of brucellosis prevention in animals in this area. Because there is presently no vaccine for brucellosis that can be administered to humans, vaccination of animals is crucial to managing and reducing the incidence of the illness in humans (Chaudhuri et al. 2021).

The economic impact of brucellosis on the livestock sector is usually caused by infertility in both sexes of livestock in the long term abortion, decreased milk yield, decreased productivity, lack of animal market value, lack of labor, lack of reproductive cycles, cattle born with a weak condition, this condition results in a period recurrent infertility and infections that can persist throughout the livestock's life (Maryam et al. 2021).

In general, Brucella infection of trophoblastic cells can lead to increased inflammatory cytokine output by placental tissue, resulting in phenomena of phagocyte colonization and aggregation, resulting in clinical signs of inflammation and miscarriage. The involvement of several cell types results in the emergence of an inflammatory response. Compared to other infection events, it is more complex. Although there are some similarities between pro-inflammatory processes, not all infectious states may require them. According to the models used to describe how one species infects a host, the specific physiological changes that result from Brucella infection in trophoblast cells can be different. Consequently, a comprehensive analysis of the proinflammatory mechanisms of systemic Brucella is still needed (Xiao et al. 2022a).

All components of immunology, from innate immunity to adaptive immunity, are involved in the response to Brucella. Through the use of CD4+ and CD8+ T lymphocytes, passive immune cell transfer in the murine model induces a potent anti-Brucella defense response. For the efficiency of the protective anti-Brucella immune response, it is also believed that the pattern of T lymphocyte cytokine production is significant. According to one theory, while Th2 cytokines promote the spread of brucellosis, Th1 cytokines confer resistance (Rodríguez-zapata et al. 2010).

Brucella must pass via specialized trophoblast cells on the fetal side of the placenta, in between the villi bases of the placental cotyledons, in order to be able to

phagocytize macromolecules. Therefore, Brucella use physiologically significant channels for trans-placental transfer of iron, which the developing fetus needs for erythropoiesis to infiltrate its duplicitous targets. Brucella spread and replicate to the nearest chorioallantoic trophoblast from this phagocytic trophoblast. Massive intracellular multiplication results in trophoblast mortality because it stresses the endoplasmic reticulum and causes a large number of microorganisms to be released into the uterine lumen. While the cycles of endocytosis, intracellular replication, and cell death persist, brucellae invade the cotyledons of the placenta, causing bacteremia and invasion of the fetus (Rossetti, Maurizio, and Rossi 2022).

The main method of treating brucellosis is a mixture of drugs, which may come with various side effects, high recurrence rates, and patient toxicity. New strategies are now being researched to enhance the immune response against brucellosis because live attenuated bacterial vaccines prepared with antibiotic treatment have been shown to have negative effects. Therefore, the focus of current research is disease control by Brucella vaccination (Tarrahimofrad et al. 2022).

Vaccinating young cattle is an effective way to limit disease. The 45/20 adjuvant vaccine, the RB51 vaccine, and the attenuated strain 19 (S19) vaccine are the three most popular vaccines. S19 vaccination is no longer recommended because it can cause problems including latent infection and prolonged antibody. The B. Abortus RB51 vaccine has received official approval in Indonesia for the treatment of bovine brucellosis. The RB51 vaccine provides the same level of protection as the S19 vaccine, causing the same infections, namely latent infections and prolonged antibodies. Therefore, the creation of a reliable and safe vaccination is very important (Khusnia, Suwarno, and Yunus 2021)

The ideal vaccine should provide long-lasting protection, be stable, and be easy to manufacture and store. Vaccines also must not cause an immune response that hinders diagnostic procedures and are not harmful to the immunized animal and those handling it. Vaccines that have specific humoral and cellular immune responses can function against pathogens (Al-Mariri et al. 2022). Therefore vaccination against Brucella Abortus infection in cattle is mediated by the host immune response to increase the host immune response. Similar to simvastatin, it strengthens the host's immune response and controls Mycobacterium Tuberculosis infection by boosting IL-1, IL-12p70, and IL-10 production and inducing apoptosis and autophagy (Nguyen et al. 2022).

By knowing the immune response, Brucella's new strategy to damage the response using T cells is the induction of apoptosis that depends on TNF-α in human T cells, inhibition of CD4+ T cell-mediated immunity by B cells through increased production of IL-10 which is dependent on MHC-II by helper T cells, and neutrophil suppressive effects on Th1 responses during B. abortus infection (Pellegrini 2022).

Writing this Literature Review aims to determine the cytokines that play a role in Brucella Abortus infection in cattle so that it can be used as a reference in creating vaccines or drugs to fight Brucella Abortus infection.

2. METHOD

This research design is an identification of research journals within a period of 2 years, namely from January 2021 to December 2022. The research journals reviewed are those that contain cytokines that play a role in Brucella Abortus Bovine infection.

2.1 Article Selection Method

Several inclusion criteria in this study were 1) articles reviewed in this study related to cytokines that play a role in Brucella Abortus Bovine infection. 2) The

population in the review article is cattle and mice (Mus musculus) or rats (Rattus novergicus) which were infected with Brucella Abortus Bovine. 3) using interleukin intervention which plays a role in Brucella Abortus Bovine infection. Exclusion criteria in this study were cytokines that play a role other than in Brucella Abortus Bovine infection, do not include the results obtained, and journals published before 2021.

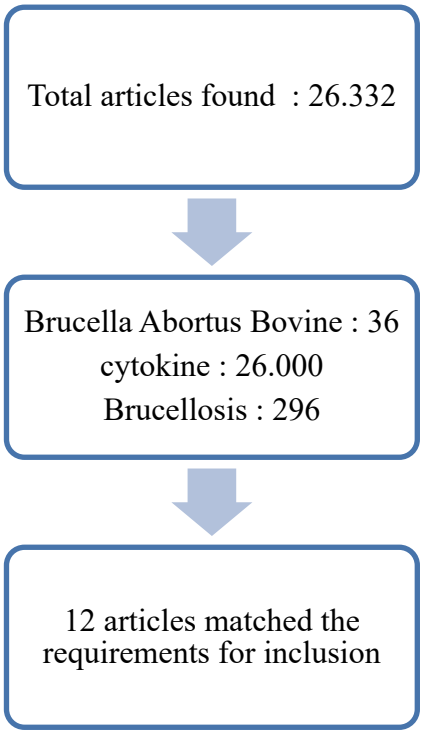

Figure 1. Literature search process

2.2 Article Search Methods

How to find articles in this study is examined methodically, starting with selecting research topics and generating English keywords for journal searches. The database used is PUBMED to search for articles throughout the year, from January 2021 to December 2022. The keywords in English used are"Brucella Abortus Bovine", "Cytokine", and "Brucellosis". The next step is to identify the title of the article that best fits the research we want. Then, abstract identification and overall content analysis were completed to provide study findings that match the researcher's objectives.

Search results using the keywords "Brucella Abortus Bovine" found 36 articles, "Cytokine" got 26,000 articles, and "Brucellosis" got 296 articles. Then the researchers filtered the relevant article titles and inclusion criteria, in order to obtain 11 appropriate articles.

2.3 Analysis Studies

According to the research's goals, pertinent literature, and data gathered utilizing the method of random controlled trial (RCT)

3. RESEARCH RESULTS

Based on research that has been conducted by looking at various populations, there are 11 articles that meet the inclusion criteria. There are 6 cytokines that play a role in Brucella Abortus Bovine infection, namely IL-1, IL-6, IL-12, IL-8, TNF-α, and IFN-γ.

Each cytokine produces a different immune response against Brucella Abortus Bovine infection. Local cattle, purebred cattle and cross-breed cattle give the same cytokine response but with different amounts in dealing with Brucella Abortus Bovine infection. Differences in the immune response in the form of cytokines in each type of cattle indicate the need for different treatment needs based on the type of cattle in dealing with Brucella Abortus Bovine infection (Al-Mariri et al. 2022; He et al. 2022; Heidary et al. 2022; Hussain et al. 2022; Kumar et al. 2020; Riyadh 2022; Saidu et al. 2022; Stranahan and Arenas-gamboa 2021; Tsai et al. 2022; Xiao et al. 2022b; Yang et al. 2021).

Based on the above data, the six cytokines have anti-inflammatory and pro-inflammatory roles. After further analysis, the six cytokines were differentiated based on the response of Th1 cells and Th2 cells. This difference in Th1 and Th2 cell

responses helps in finding therapies both vaccines and drugs to determine the desired mechanism of action of the immune response so that the therapy can be on target, namely attacking intracellular bacteria.

4. DISCUSSION

Brucellosis is a global disease

The globally transmitted zoonotic disease brucellosis poses a significant threat to developing countries. All types of cattle have the potential to be infected with Brucella, both purebred, native and cross breed cattle. Brucella infection mostly affects the reproductive system. In cattle, Brucella Abortus is a major cause of miscarriage, retained placenta, orchitis and burchitis (Oliveira 2021; Tulu 2022). Brucella infection in cows causes weak birth calves, abortion, stillbirth, retained placenta, endometritis and other complications. In bulls, Brucella infection is lower and controlled more quickly (Tulu 2022).

Virulence Factor

Brucella possesses five virulence factors, including cyclic glucan, virB T4SS, pathogen-associated molecular patterns (PAMPs), two-component BvrS/BvrR sensory and regulatory systems, and lipopolysaccharide (LPBS). In addition, four steps of viability, invasion, establishment, and dispersal have been reported to be required for successful Brucella infection of the host. Brucella can proliferate in a wide variety of mammalian cell types, including endothelial cells, fibroblasts, epithelial cells, and microglia, although they usually infect and replicate within phagocytic cells such as macrophages and dendritic cells (Reyes et al. 2022).

Brucella Antigenic Components

LPS, T4SS, BvrR/BvrS, Omp, prpA, and Btp1 are some specific antigenic components of Brucella that control their different antigenic tactics to evade the immune system. These mechanisms include bactericidal action, delayed phagocytosis, intracellular survival, and TNF-α production (Elrashedy et al. 2021).

LPS in Brucella exhibits unusual biological features, such as low endotoxicity, increased resistance to macrophage damage, and low induction of immune responses, in contrast to LPS enterobacteria, such as Escherichia coli or Salmonella spp. The classic E. coli LPS is completely different from this one, and has a different O-chain, central core, and lipid A. Brucella LPS-specific O-chains allow bacteria to penetrate host cells through interactions with lipid rafts on them. surface and to block lysosome fusion in murine macrophages (with the exception of B. ovis and B. canis, which produce crude LPS lacking O-chain). In addition, activation of the complement lectin pathway and complement deposition are also inhibited by the Brucella O-chain(Pellegrini 2022).

Given that LPS composition controls the phenotypic differences between these two Brucella species but does not appear to change virulence, this is the component that has been studied the most. The overall lipid A and core oligosaccharide structures of the two LPS species are considered to be comparable, but the absence or presence of the terminal O-polysaccharide (O-PS) is associated with a coarse or smooth B. Ovis or B. melitensis phenotype, respectively. Despite these significant differences, both LPS are involved in reduced endotoxic activity, low proinflammatory cytokine production, immune system evasion, cell invasion, and resistance to complement and destruction of antimicrobial peptides, although some of these characteristics in B. ovis are related to pattern expression. outer membrane proteins (OMPs) (Rossetti, Maurizio, and Rossi 2022).

OMPs are well-known additional virulence factors that play a role in the integrity of the Brucella outer membrane as well as the initial pathogen-host contact and regulation of host cell function. Omp25d and Omp22 are critical for entry of B. ovis into mammalian cells, but there is no evidence

that this is the case for B. melitensis. More differences between B. ovis and B. melitensis OMPs, as well as how they contribute to differential pathogenicity and host choice, have been predicted in silico or tested in vitro but not by in vivo challenge of the preferred host (Rossetti, Maurizio, and Rossi 2022).

The two-component BvrR/BvrS (TCS) system is a virulence factor that has been demonstrated experimentally in B. abortus. This affects Brucella metabolism and its ability to adapt to the intracellular environment in addition to modulating outer membrane homeostasis. The bvrR and bvrS genes are thought to be present in the B. Ovis genome and to have a high degree of homology to the B. abortus gene, sharing only four different amino acids in each sequence. A BvrR/S mutant B. ovis could not be produced, indicating that in addition to its dual-function property for TCS in smooth Brucella strains, it is also required for Brucella ovis-independent in vitro survival. In contrast, the B. melitensis BvrR mutant was ineffective in Hela cell invasion (Rossetti, Maurizio, and Rossi 2022).

VjbR is a universal transcriptional activator of virulence factors. Both B. melitensis and B. ovis vjbR mutants have been shown to have a similar amount of internalization, but they may be less able to survive in macrophages and human trophoblast cell lines than the WT strain. Both vjbR mutants were consistently eliminated from the spleens of infected mice several weeks after infection, and B. melitensis 1vjbR was harmless in its native host. During vegetative development and intracellular survival in B. melitensis, VjbR positively controls transcription of two key virulence factors, the type four secretion system (T4SS) encoded by the virB operon, and flagellar genes. It appears that VjbR also controls virB expression in B. ovis, but not flagella genes. The flagella locus also appears to be unnecessary for B. Ovis virulence in mice (Rossetti, Maurizio, and Rossi 2022).

Brucella can survive intracellularly and create replicas thanks to T4SS, which transports effector chemicals. Experimental evidence for important functions in Brucella ovis and Brucella melitensis has been found, despite the fact that different regulatory mechanisms are shown in each case. The VirB operon was expressed strongly in B. ovis and B. melitensis 16M under neutral pH culture conditions and was further increased in B. melitensis but not in B. ovis under acidic culture conditions. Furthermore, further studies are needed to determine the quantity and understand the effector of T4SS translocation, how its expression is controlled, and how it affects the development of infection in both Brucella species (Rossetti, Maurizio, and Rossi 2022).

The chronic stage of infection increases the peroxisome proliferator-activated receptor (PPARγ) pathway in splenic myeloid cells of mice infected with B. abortus, resulting in increased intracellular glucose availability. The macrophages that predominate at this stage are alternatively activated macrophages or M2-like macrophages, which are responsible for the PPARγ-mediated switch from oxidative metabolism of glucose to -oxidation of fatty acids. Through a process that depends on the capacity of B. abortus to digest glucose through the gluP transporter, increased intracellular glucose availability allows Brucella to multiply within these cells (Pellegrini 2022).

The Brucella spp. infect the placenta

Inflammation and extracellular replication increase when Brucella infects the placenta. When Brucella is present in phagocytes, it has to circumvent cell-killing mechanisms so that the infection becomes chronic and persistent within the cells. Different studies have shown that Brucella use trophoblastic cells as their target cells and successfully replicate in their Endoplasmic Reticulum (ER) to create ER stress. The exact mechanism by which Brucella causes inflammation of the placental tissue is currently unknown.

According to the findings, Brucella replicated in the ER trophoblast-associated rough cell compartment of the placenta. Placental tissue inflammation, inflammatory cell infiltration, trophoblastic cell necrosis, and ulceration of the chorionic alanine membrane are consequences of the high efficiency of replication brought about by this unique environment (Xiao et al. 2022a).

After entering the trophoblast cell, Brucella does not grow rapidly. One of the best organs for Brucella growth is the placenta. The abundance of placental erythritol can be used by Brucella as its preferred carbon source, which will stimulate it to go there. Brucella reproduces in large numbers once they have sufficient energy reserves and stable habitat. In venomous ruminants, Brucella begin to reproduce widely during the third trimester of pregnancy, and colonies can be seen in the placenta. Within these host cells, Brucella multiply and replicate rapidly, impairing the integrity of the placenta and infecting the developing fetus, which can result in miscarriage (Xiao et al. 2022b).

Immune Response to Brucella spp.

The T-cell-dependent immune response is triggered by the intracellular pathogen Brucella and is intended to terminate intracellular survival and proliferation. Consequently, the essential elements of the immune response are selected based on their compatibility with MHC-II molecules, according to studies of the immune system. By releasing IFN-γ, CD4 cells can promote neutrophil infiltration in infected areas and assist T cells in producing CXC chemokines. The protective response against Brucella is enhanced by stimulation of CD4+ and CD8+ T cells, DCs, macrophages (M), and inflammatory cytokines (IFN-γ and IFN) (Tarrahimofrad et al. 2022).

When fighting intracellular infections such as Brucella, macrophages are considered as important components of the innate immune response. Macrophages destroy most pathogens during the early stages of infection, but some of them still manage to find replicative habitats. Despite the fact that a number of protein antigens have been discovered that can induce a protective immune response in mouse models, the function of some of these immunogenic proteins is still unknown. Various cytokines and chemokines are released during inflammation, a well-known host response to microbial threats. Due to their function as soluble mediators of cell-cell contact and their ability to amplify or coordinate proinflammatory signals to promote the production of effector molecules, cytokines are essential for the innate defense against infection (Zhang et al. 2022).

To prevent the baby from being rejected and attacked by the immune system during pregnancy, the placenta offers a special immunological environment for the developing fetus. The local inflammatory environment that can cause pregnancy difficulties is triggered when the placental cells are infected by bacteria. In a recent study, human Swan-71 cytotrophoblast cells infected with B. abortus showed increased production of IL-6, IL-8, and MCP-1. IL-6 and TNF-α levels in JEG-3 or BeWo cells did not increase in response to B. melitensis or B. papionis infection. This variation may be due to variations in the differentiation state between trophoblast cell lines or by species-dependent reactions of Brucella to trophoblast cells. There should be further investigation (Xiao et al. 2022b).

In the early stages of Brucella infection controlled by TNF-α, IFN-γ, IL-1, and IL-12(Heidary et al. 2022).Brucella infection that causes abortion in cattle is a chronic infection with a dynamic immune response, during the course of the disease there is a change from a mostly Th1-like to a Th2-like pattern. This significant change is still in doubt, the possibility that what happened is the slowing down of Th1 – Th2 through the classical pathway (Priyanka et al. 2021). In mice infected with B.Ovis, B.Melitensis, and B.abortus, the responses of Th1 and Th2 cells were different. The

response of Th1 cells secreting IFN-γ, IL-2, and TNF-β can increase immunity against intracellular pathogens. Response Th2 cells secrete IL-4, IL-6,IL-9, IL-5,IL-10, and IL-13 when infected with B. Ovis, B.Melitensis, and B. Abortus (Al-Mariri et al. 2022).

Cytokines - cytokines that play a role in Brucella Abortus Bovine infection.

Two cytokines important for the ability of the host to suppress Brucella infection are IFN-γ and TNF-α. IFN-γ can stimulate MHC-II production on the surface of macrophages, which in turn stimulates antigen presentation to CD4+ T cells. It has been shown that after infection with B. abortus 2308, mice with monoclonal neutralizing IFN-γ or IFN-γ gene knockout are more susceptible and die more quickly than the control group. TNF is an important proinflammatory cytokine required for the host to fight microbial infections. It has been shown that TNF can induce the production of chemokines and adhesion molecules, which in turn can attract neutrophils to the site of infection. Due to their inability to make NO and IL-12, macrophages from TNF receptor knock-out mice are more susceptible to Brucella pathogens (Zhang et al. 2022).

Expression of the proinflammatory TNF-α had high levels in cross-breeding cattle after being infected with the Brucella S19 strain (Kumar et al. 2020). The high levels of TNF-α in the bovine trophoblast resulted in the cow's placenta becoming inflamed (Tsai et al. 2022). Trophoblastic inflammation in cattle due to Brucella Abortus utilizes the effector proteins BtpA and BtpB to reduce total NAD levels in host cells thereby disrupting immune metabolism and cellular signaling. Elevated NAD levels have been associated with activation and modulation of the inflammatory response in macrophages, particularly in relation to transcriptional regulation of TNF-α in normally activated pro-inflammatory (M1) macrophages (Xiao et al. 2022b). In cattle that are positive for brucella infection, their erythrocytes experience obstacles in TNF-α secretion due to the low inflammatory response. This occurs due to the low concentration of various antioxidant enzymes in erythrocytes, thereby increasing free radical turnover and antioxidant depletion in disease prevention (Hussain et al. 2022).

Two cytokines of the Th2 subtype, IL-10, and IL-4, have potent inhibitory effects on the Th1 immune response. IL-10 is essential for the survival of intracellular pathogens and persistent infections, according to several studies. Antigen-presenting cell (APC) activation is suppressed by Brucella via influencing TLR signaling and inducing IL-10, which is a key mechanism. The development of M0 macrophages into M2 macrophages is driven by the key IL-4 cytokine. IL-4 levels in the peripheral blood of people with chronic brucellosis were greater than those with acute brucellosis, they report, and they are related to IL-10-mediated M2 polarization. Therefore Brucella uses IL-4 to control the activity of immune cells in order to survive (Zhang et al. 2022).

Interleukin-10 expressed by macrophages can function as an anti-inflammatory against bacterial infections. IL-10 levels of each type of cattle differ in the face of Brucella Abortus infection, Holstein macrophages express more IL-10 compared to Nellore zebu cattle, and low levels of IL-10 expression are also found in cattle in Sahiwal (Kumar et al. 2020). Protection against Brucella spp infection may come from IL-10 induction (Al-Mariri et al. 2022).

Fine and rough colony morphology are two characteristics of Brucella. Brucella LPS differs from other Gram-negative lipopolysaccharides (LPS), such as those from the Enterobacteriaceae family, in that it is one of its key pathogenic components. Neither macrophage activity nor pro-inflammatory cytokine formation is stimulated by B. abortus LPS. However, macrophages and DC antigen-presenting capacity appear to be downregulated by LPS Brucella spp., which prevents T lymphocyte

activation and proliferation (Elrashedy et al. 2021).

Brucella infection can result in placental inflammation, fetal deat,h and an increase in neutrophils and monocytes due to the activity of inflammatory factors. Increased levels of IL-6 result in placental inflammation and induce neutrophils and monocytes in trophoblast cells affected by Brucella infection. In addition, increased levels of IL-6 also cause inflammation of the placenta and death of ruminant, human, and rat fetuses (Xiao et al. 2022b). The inflammation is also due to stimulation of Lipopolysaccharide (LPS) in secreting IL-6 in sufficient quantities when infected with Brucella and other gram-negative bacteria (Saidu et al. 2022).

According to some studies, IL-12 is the main cytokine that fights against Brucella infection. IL12, a cytokine that promotes Th1 cell development, inhibits cytokines required for Th2 cell growth and proliferation (Zhang et al. 2022). Increased levels of IL-12p40 have a role in the occurrence of inflammation of the placenta and death of ruminant, huma,n and rat fetuses (Xiao et al. 2022b). Gram-negative bacteria, including Brucell,a can increase IL-12 levels as a pro-inflammatory due to encouragement from Lipopolysaccharide (LPS) (Saidu et al. 2022). The results of bovine peripheral blood mononuclear cells (PBMC) analysis with recombinant protein showed induction of IL-12p40 expression (Priyanka et al. 2019).

All Brucella spp. which is located in the lungs causes considerable production of IFN-γ by CD8+ and CD4+ T cells in both primary and secondary infections. During secondary infection with Brucella abortus, CD4+ and CD8+ T cells were found to significantly induce IFN-γ in the mouse spleen.(Stranahan et al. 2022). Brucella DNA can induce splenic apoptosis by inducing IFN-γ, and Ifn-αβR KO mice are more resistant to infection. As a result, Brucella can use IFN-γ to block the immune response in order to survive inside the cell (Zhang et al. 2022).

IFN-γ levels originating from lipopolysaccharide stimulation can result in inflammation of the placenta up to fetal death (Saidu et al. 2022; Xiao et al. 2022b). Administration of Brucella combination immunization triggers bactericidal activity of macrophages by IFN-γ, high levels of IFN-γ are evidence of protection against infection (He et al. 2022). IFN-γ is essential for brucellosis resistance and is directly related to Brucella eradication (Yang et al. 2021). Studies show that the development of recombinant RB51 by emphasizing IFN-γ secretion develops a Th1 cell immune response thereby increasing protection against Brucella (Sarmadi et al. 2022).

Brucella's ability to reproduce within the cell is very important and vital to ensure that the host cell will not die from infection for a long time. When Brucella infects pregnant animals, it will proactively choose to infiltrate placental trophoblastic colonies to create high-density bacterial colonies, which can quickly cause placental and even miscarriage in affected animals (Xiao et al. 2022a).

Brucella abortus infection resulted in the production of IL-8 in bovine placenta explants. IL-8 secretion is possible due to the production of phagocytes by TNF-α as occurs in humans (Stranahan and Arenas-gamboa 2021). Increased levels of IL-8 result in placental inflammation and induce neutrophils and monocytes in trophoblast cells affected by Brucella infection (Xiao et al. 2022b). Various harmful fetal developments such as miscarriage and apoptotic cell death in the placenta are also due to the expression of IL-8 (Riyadh 2022).

In the early stages of Brucella infection, IL-1 has a contribution in controlling the infection (Heidary et al. 2022). The release of IL-1β in a significant amount functions as a pro-inflammatory mediator that produces inflammation (Saidu et al. 2022). Studies have shown that cattle infected with Brucella that have had abortions have quite high levels of IL-1β expression (Riyadh 2022). In brucella-infected bovine erythrocytes, there is an

inhibition in secreting IL-1, causing an increase in antioxidant turnover and physiological disturbances (Hussain et al. 2022).

Table 1. Cytokines that play a role in the brucella abortus infection process

Cytokines	Role	Reference
TNF-α	Pro-inflammatory	(Heidary et al. 2022; Hussain et al. 2022; Kumar et al. 2020; Tsai et al. 2022; Xiao et al. 2022b)
IL-10	Anti-inflammatory	(Al-Mariri et al. 2022; Kumar et al. 2020)
IFN-γ	pro-inflammatory	(He et al. 2022; Heidary et al. 2022; Saidu et al. 2022; Xiao et al. 2022b; Yang et al. 2021)(Sarmadi et al. 2022)
IL-6	Pro-inflammatory	(Saidu et al. 2022)(Xiao et al. 2022b)
IL-8	Pro-inflammatory	(Stranahan and Arenas-gamboa 2021; Xiao et al. 2022b)
IL-12/IL-12p40	Pro-inflammatory	(Heidary et al. 2022; Saidu et al. 2022; Xiao et al. 2022b)
IL-1	Pro-inflammatory	(Heidary et al. 2022; Hussain et al. 2022; Riyadh 2022; Saidu et al. 2022)

Cytokines that act as pro-inflammatory such as IL-1, IL-12, IL-8, TNF-α, and IFN-γ in the course of Brucella Abortus infection in cattle contribute to fetal death, placental inflammation,n and various dangerous developments for the fetus. By knowing the cytokines that play a role in the occurrence of Brucella infection in cattle, it can determine the development of protective and non-curative immune responses (Riyadh 2022). First, the specific humoral and cellular immune responses that are successfully created from vaccines against pathogen-associated immunogens are a measure of vaccine success. Vaccines for Brucella bacterial infections are expected to have a Th1 type of response tendency because they are able to provide protection against intracellular bacterial infections. TNF-α and IFN-γ are protective cytokines that are important for the management of brucellosis and other diseases caused by intracellular infections. Vaccines that induce the production of Th2 profile cytokines such as IL-6 and IL-10 may increase susceptibility to Brucella infection (Al-Mariri et al. 2022).

Identification of the cytokine profile in Brucella Abortus infection in each type of cattle still requires further research. Given that in some cases, several types of cattle do not produce cytokines at the same level during the course of the infection. Differences in cytokine responses will produce different responses in fighting infection. Therefore, the treatment of Brucella Abortus infection in cattle, both vaccines, and drugs, cannot be compared to the treatment of infections in B. ovis, B. melitensis, and B. Abortus Humans because the resulting immune response is different.

5. CONCLUSION

Cytokines that play a role in Brucella Abortus infection in cattle generally are IL-1, IL-6, IL-12, IL-8, TNF-α, and IFN-γ. Each cytokine will produce a different immune response against pathogens so that in making therapy both vaccines and drugs for Brucella Abortus infection in cattle take this into account.

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