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İÇİNDEKİLER

MOLECULAR VIRULENCE AND IMMUNE EVASION MECHANISMS IN BRUCELLA

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1. INTRODUCTION

Brucellosis is acknowledged by the Food and Agriculture Organization (FAO), the World Health Organization (WHO), and the World Organisation for Animal Health (WOAH) as one of the most critical zoonotic diseases with significant implications for global public health and economic stability. Despite an officially reported annual incidence exceeding 500,000 cases worldwide, the actual burden is presumed to be substantially higher, particularly in endemic regions, where diagnostic limitations and underreporting remain major challenges. Classified as a neglected zoonosis, brucellosis continues to pose a persistent threat in both human and animal populations. (Bosilkovski et al., 2021).

Brucellosis is a zoonotic disease with a global distribution. It remains endemic in Turkey and other Mediterranean countries. The disease is associated with high morbidity in both humans and animals, and represents a significant public health concern as well as a source of substantial economic loss, particularly in developing nations. (Gao et al., 2013a).

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The genus Brucella comprises a dynamic group of bacteria whose genomic diversity and evolutionary adaptations are increasingly being elucidated. While classical species (*B. melitensis, B. abortus, B. suis, B. canis, B. ovis, B. neotomae, B. pinnipedialis,* and *B. ceti*) have been well characterized, the recent identification of atypical strains—such as B. papionis and B. vulpis—has expanded our understanding of host adaptation and evolutionary pathways within this genus. Among these, *B. melitensis* remains the primary etiological agent of human brucellosis, largely due to its high pathogenicity. Transmission predominantly occurs through direct contact with infected sheep and goats or consumption of contaminated unpasteurized dairy products. Recent studies have further elucidated the sophisticated mechanisms by which Brucella evades host immune defenses and establishes intracellular persistence (Rossetti et al., 2022). Additionally, molecular advancements have led to the discovery of novel atypical species, including *B. inopinata* (human isolates), *B. microti* (vole isolates), and *B. papionis* (baboon isolates). These findings underscore the expanding ecological niche and host range of Brucella, suggesting a broader zoonotic potential than previously recognized.. (Scholz et al., 2008; Whatmore et al., 2014; Zheludkov and Tsirelson, 2010).

The genus Brucella is a dynamic group of bacteria that is being increasingly understood through genomic studies. In addition to classical species (*B. melitensis, B. abortus, B. suis, B. canis, B. ovis, B. neotomae, B. pinnipedialis,* and *B. ceti*), atypical species described in recent years—such as *B. ceti, B. papionis,* and *B. vulpis*—have provided new insights into host adaptation and bacterial evolution. Most human cases are caused by B. melitensis, a highly pathogenic species typically transmitted through contact with infected sheep, goats, or their unpasteurized dairy products. Current research highlights the complex mechanisms by which Brucella evades the host immune system

and persists intracellularly (Rossetti et al., 2022). Furthermore, molecular studies have identified additional atypical species, including *B. inopinata* (isolated from humans), *B. microti* (from voles), and *B. papionis* (from baboons). These discoveries suggest that Brucella occupies a broader ecological niche and host range than previously recognized. (Godfroid et al., 2011).

Brucella bacteria are quite resistant to environmental conditions. For example, they are inactivated in 10 minutes at 60 °C, and in 15 minutes in 0.1% phenol. They are also sensitive to disinfectants containing 70% ethanol, iodophors, glutaraldehyde, and formaldehyde (Songer & Post, 2012). However, they can survive for long periods in various food and environmental materials: 17 days in milk, 142 days in butter, 1 month in ice cream, 3 weeks in salted meat products, and up to 1 month in brined cheese (Godfroid et al., 2013).

In Turkey, the consumption of raw animal products such as çiğ köfte, particularly in the Southeastern Anatolia Region poses a significant risk for Brucella transmission. While intact skin is resistant to bacterial entry, exposure through moist or damaged skin can facilitate infection. Additionally, contact with infected animals, especially via the conjunctiva, may lead to transmission. Consequently, veterinarians, veterinary technicians, livestock handlers, laboratory personnel, and workers in the meat-processing industry are classified as high-risk occupational groups (Pappas et al., 2006; Arabacı, 2011).

Brucella species are classified as Biosafety Level 3 (BSL-3) pathogens and must be handled in appropriately equipped laboratories. Given their potential risk, stringent measures are essential for controlling and preventing Brucella infections. Recent advances have enhanced our understanding of pathogen-host interactions, particularly the virulence mechanisms that facilitate intracellular replication. Emerging strategies, combined

with growing genomic and molecular data, are now being employed to dissect these complex processes (Gao et al., 2013a).

Virulence mechanisms and their regulatory systems play a critical role in enabling Brucella species to evade or overcome host immune defenses. As our understanding of these systems expands, they are likely to reveal potential candidates for novel drug targets and identify promising protective antigens for vaccine development.

2. PATHOGENESIS AND HOST IMMUNE RESPONSE OF BRUCELLOSIS

Following host entry, *Brucella* is phagocytosed primarily by polymorphonuclear leukocytes (PMNLs) and macrophages. Unlike other Brucella species, *B. melitensis* demonstrates unique resistance to intracellular killing mechanisms within these phagocytes. Post-infection, the bacteria migrate to regional lymph nodes, where they proliferate during a variable incubation period ranging from 2 weeks to 7 months. Subsequently, they disseminate hematogenously, resulting in bacteremia and preferential colonization of reticuloendothelial system (RES) organs (Moreno and Moriyón, 2001; Tosyalı, 2008).

Brucella exhibits remarkable resistance to phagocytic defense mechanisms. While most bacteria are typically eliminated through oxidative burst and lysosomal degradation following phagocytosis, Brucella survives by neutralizing reactive oxygen species (ROS) via antioxidant enzymes, including copper-zinc superoxide dismutase (SOD) and catalase (CAT) (Tatum et al., 1992).

Brucella demonstrates the ability to infect both phagocytic cells (e.g., macrophages and dendritic cells) and non-phagocytic cells (including trophoblasts and epithelial cells). The pathogen

employs M cells as a portal of entry to traverse mucosal barriers, such as those in the gastrointestinal tract (Xavier et al., 2010). Through inhibition of phagolysosome fusion and resistance to lysosomal enzymes, Brucella establishes a replicative niche within the intracellular compartment. Furthermore, the bacterium modulates host immune responses by activating protein kinase A (PKA) signaling pathways, thereby suppressing inflammatory reactions (Gross et al., 2003).

Brucella resides within vacuolar compartments that exhibit transient interactions with lysosomes during intracellular infection. These interactions induce the expression of key virulence factors, particularly the Type IV secretion system (T4SS) encoded by the virB operon (Guzmán-Verri et al., 2002).

Cellular immunity constitutes the primary defense mechanism against Brucella infection. Professional antigen-presenting cells, particularly macrophages and dendritic cells, activate T-cell responses through MHC-mediated antigen presentation. CD4+ T lymphocytes recognize processed antigens via MHC class II molecules, whereas CD8+ T cells engage antigens presented by MHC class I. Interferon-gamma (IFN-γ) serves as the pivotal cytokine in this cellular immune response, potently enhancing the macrophage bactericidal activity. In contrast, regulatory cytokines including interleukin-10 (IL-10) and IL-4 attenuate this antimicrobial function, thereby promoting intracellular bacterial survival (Madkour, 2008).

During Brucella infection, distinct T-helper cell responses emerge: Th1 cells predominantly secrete interferon-gamma (IFN-γ) and interleukin-2 (IL-2), while Th2 cells primarily produce IL-4, IL-5, and IL-10. Experimental studies in murine models demonstrate that infection with viable Brucella induces a robust Th1-polarized immune response. In contrast, vaccination with

heat-inactivated bacteria preferentially elicits a Th2-type response (Kurar and Splitter, 1997).

In chronic Brucella infections, the persistent host-pathogen interaction between macrophages and bacteria results in granulomatous inflammation. These characteristic granulomas, composed of epithelioid cells and plasma cells, predominantly develop in reticuloendothelial system (RES) organs, including the spleen, liver, and bone marrow The intracellular replication niche of Brucella provides protection from both humoral immunity (antibodies) and antimicrobial agents, thereby contributing to the challenges in clinical treatment of brucellosis. (Chugh et al., 2001).

The antibody response against Brucella begins with the production of IgM, followed by isotype switching that leads to the secretion of IgG and other isotypes. In smooth strains, lipopolysaccharide (LPS) serves as the major immunodominant antigen. The LPS of B. abortus exhibits immunological properties distinct from those of other Gram-negative bacteria, such as Escherichia coli, and can strongly stimulate IgG production through its adjuvant effect (Madkour, 2008).

3. BRUCELLA VİRULENCE MECHANİSMS

3.1. Tip 4 VirB Secretion System

The Type IV secretion system (T4SS) in Brucella species is a multi-subunit protein complex that mediates the transfer of macromolecules and effector proteins into host cells. This system plays a critical role in the bacterium’s intracellular survival and proliferation. In Brucella, the T4SS is encoded by an operon spanning virB1 to virB12 (Cascales and Christie, 2003).

The expression of the virB operon is regulated by VjbR, a LuxR-type transcription factor and a key component of the

quorum sensing (QS) system in Brucella. VjbR is directly associated with the bacterium's intracellular infectivity. Quorum-sensing signals, such as N-dodecanoyl-homoserine lactone (C12-HSL), suppress this regulatory pathway, leading to downregulation of virB genes and impaired intracellular replication (Delrue et al., 2005). Recent studies demonstrate that VjbR acts synergistically with BabR (another LuxR-like regulator) to promote the survival of B. abortus during infection (Zheng et al., 2024).

Following uptake by macrophages, Brucella evades endosomal trafficking pathways and establishes a specialized compartment termed the Brucella-containing vacuole (BCV). These vacuoles avoid lysosomal degradation and instead fuse with the endoplasmic reticulum (ER), creating a replicative niche for the bacterium (Celli et al., 2003). A functional VirB system is critical for this process, mediating interactions with the ER membrane. Notably, virB-mutant strains are unable to hijack the ER and consequently fail to replicate in both HeLa cells and infected mouse spleens (Bellaire et al., 2005).

Brucella delivers various effector proteins to host cells via its Type IV Secretion System (T4SS). Key effectors, including VceA, VceC, BtpA/BtpB, RicA, and SepA, modulate multiple host processes, ranging from autophagy suppression to endoplasmic reticulum (ER) membrane fusion (Ke et al., 2015). A recently identified effector, RS15060 (Yin et al., 2024), was shown to significantly impair bacterial proliferation in macrophages and reduce infectivity in mouse models, further highlighting the crucial role of T4SS effectors in Brucella virulence.

VirB10, a core structural component of the T4SS, spans both the inner and outer bacterial membranes, maintaining the system's structural integrity while facilitating energy

transduction. Its transmembrane domain is particularly crucial for coordinating interactions with other T4SS subunits. Notably, small molecules that disrupt these specific interactions have demonstrated dual effects: reducing VirB10 protein levels while simultaneously downregulating overall virB operon expression. These findings highlight VirB10 as a promising therapeutic target against Brucella infections (Paschos et al., 2011; Wu et al., 2025).

3.2. Base Excision Repair (BER) ve Brucella'da xthA Genlerinin Rolü

DNA molecules are continuously damaged by both endogenous metabolic activities and environmental factors. When this damage involves minor base alterations, cells initiate the Base Excision Repair (BER) pathway. This evolutionarily conserved DNA repair mechanism specifically recognizes and corrects various base lesions, including those induced by oxidative stress, deamination, methylation, and alkylation (Lindahl, 1993).

The BER mechanism proceeds through three major stages. In the initial stage, specific DNA glycosylases recognize and excise damaged or mismatched bases from the DNA strand. These enzymes cleave the N-glycosidic bond between the aberrant base and deoxyribose sugar through hydrolysis, generating an apurinic/apyrimidinic (AP) site (Dianov & Hübscher, 2013). DNA glycosylases achieve substrate specificity by selectively binding to structural distortions in the DNA helix, enabling precise removal of incorrect bases (Jacobs and Schär, 2012).

During the second stage, AP endonuclease (e.g., APE1) introduces a single-strand nick at the 5′ end of the AP site. Certain DNA glycosylases possess intrinsic AP lyase activity, enabling them to cleave the phosphodiester backbone at the 3′ end (Wallace, 2014). In the final stage, DNA polymerase β

incorporates the correct nucleotide at the nick site, followed by DNA ligase-mediated strand sealing, thereby restoring DNA integrity (Dianov & Hübscher, 2013). The BER pathway operates through either short-patch or long-patch repair mechanisms, depending on the lesion size (Jacobs and Schär, 2012).

The Base Excision Repair (BER) system has been identified and functionally characterized in pathogenic bacteria, including Brucella abortus. Genomic analyses have revealed two distinct xthA genes (xthA-1 and xthA-2) encoding key BER pathway components in Brucella species (Sanderson et al., 2006). Among these, *xthA-1* has been shown to encode a functional exonuclease III homolog that plays a direct role in DNA repair processes.

3.3. BvrS/BvrR Çift Bileşenli Düzenleme Sistemi

The intracellular pathogen Brucella requires specialized regulatory systems to establish persistent infection within host cells and evade immune detection. The most extensively studied of these is the BvrS/BvrR two-component system (TCS), a crucial virulence determinant. This system comprises: (i) BvrS, an inner membrane histidine kinase sensor that monitors environmental parameters (including pH, osmolarity, and nutrient availability); and (ii) BvrR, a cytoplasmic response regulator. Upon signal detection, BvrS autophosphorylates and transfers the phosphate group to BvrR, which then modulates expression of virulence-associated genes, enabling Brucella to adapt to the intracellular niche (Altamirano-Silva et al., 2023).

Upon BvrR activation, Brucella significantly upregulates expression of the outer membrane proteins Omp25 and Omp31. These surface proteins confer dual functionality: (1) enhancing bacterial resistance to host immune defenses and (2) facilitating host cell membrane penetration (Guzmán-Verri et al., 2002). Furthermore, the BvrR/BvrS system coordinately regulates

intracellular replication and modulates expression of additional virulence determinants, including the Type IV Secretion System (virB operon) essential for establishing chronic infection (Rivas-Solano et al., 2022). Genetic disruption of this regulatory system renders Brucella incapable of cellular invasion, immune evasion, and subsequent infection establishment. Mutant strains exhibit significant attenuation in laboratory animal models, demonstrating markedly reduced infectivity (Altamirano-Silva et al., 2023).

Notably, this regulatory system exhibits significant homology to conserved two-component systems in plant-associated bacteria (e.g. the ChvG/ChvI system in Agrobacterium tumefaciens). This phylogenetic conservation suggests Brucella evolved these regulatory mechanisms as an adaptive strategy for host-environment interactions (Guzmán-Verri et al., 2002).

3.4. Quorum-Sensing (QS) Regulation System

Brucella species encounter numerous environmental stressors and host defense mechanisms during infection. To overcome these challenges, the bacteria must transition to an intracellular lifestyle and establish persistent infection. This adaptation is mediated in part by a quorum-sensing (QS) system, which enables Brucella to detect environmental signals and regulate gene expression in a cell-density-dependent manner (Gao et al., 2013b; Caudill, Stoyanof and Caswell, 2025).

In Gram-negative bacteria, QS systems predominantly function through LuxI/LuxR-type regulatory proteins. In Brucella melitensis strain 16M, two characterized LuxR-type transcriptional regulators—VjbR and BabR—coordinate multiple physiological processes. These include virulence gene expression, biofilm formation, and intracellular replication (Uzureau et al., 2007, 2010).

Deletion of VjbR significantly impairs Brucella's replicative capacity in infected host cells, while the BabR protein plays a crucial role in virulence maintenance (Caudill et al., 2025). VjbR specifically binds to the promoter region of the virB operon to activate the Type IV secretion system.

3.5. Riboflavin Metabolic Pathway

Riboflavin (vitamin B_2) serves as the precursor for essential coenzymes such as flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). These cofactors are involved in a wide range of cellular processes, including energy metabolism, redox reactions, detoxification, and biosynthesis. For facultative intracellular bacteria such as Brucella, this metabolic pathway is particularly crucial, especially under phagosomal conditions characterized by low oxygen levels and limited nutrient availability (Islam and Kumar, 2023).

In Brucella species, riboflavin biosynthesis involves two lumazine synthase (LS) isoforms encoded by ribH1 and ribH2. These enzymes catalyze the penultimate step of riboflavin biosynthesis, converting the substrate to 6,7-dimethyl-8-ribityllumazine (DMRL). Riboflavin synthase (RS) then mediates the final conversion of DMRL to riboflavin. Comparative enzymatic analysis reveals RibH2 serves as the principal catalyst in this pathway, while RibH1 demonstrates markedly reduced catalytic efficiency (<20% of RibH2 activity) (Bonomi et al., 2010).

3.6. ATP-Binding Cassette (ABC) Sistemleri

ATP-Binding Cassette (ABC) transporters mediate the translocation of a broad range of molecules across the cell membrane by utilizing the energy generated from ATP hydrolysis to ADP. Structurally, these systems typically comprise two transmembrane domains (TMDs) and two nucleotide-binding domains (NBDs) (Van der Does and Tampe, 2005). In bacteria,

ABC transporters are crucial for processes such as nutrient uptake, toxin efflux, and the secretion of virulence factors.

An important example of ABC transporter systems in Brucella species is the Wzm/Wzt complex, which is responsible for the transport of the lipopolysaccharide (LPS) O-antigen. This system mediates the translocation of the full-length O-antigen from the cytoplasm to the periplasm. In this process, Wzm functions as the transmembrane channel, whereas Wzt provides the required energy through ATP hydrolysis (Morrison et al., 2014; Servais et al., 2023).

Mutation of the Wzm/Wzt system results in the loss of O-antigen production, leading to alterations in surface properties and the development of a “rough” phenotype. This change reduces resistance to the host immune system and diminishes virulence (Vassen et al., 2022). Indeed, studies involving wzm/wzt gene deletions in the Brucella abortus S19 strain have demonstrated that these mutants are significantly attenuated in a mouse model (Morrison et al., 2014). Moreover, some studies suggest that such mutants can elicit limited immune stimulation and may hold potential for vaccine development (Vassen et al., 2022).

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CASEOUS LYMPHADENITIS IN SHEEP AND GOATS: ETIOLOGY, PATHOGENESIS, EPIDEMIOLOGY, AND CONTROL STRATEGIES

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1. INTRODUCTION

Caseous lymphadenitis (CLA, pseudotuberculosis) is a chronic infectious disease of sheep and goats caused by *Corynebacterium pseudotuberculosis*, characterized by the development of encapsulated abscesses primarily in lymph nodes and lungs, and occasionally in other internal organs (Batey, 1986; Dorella et al., 2006). In Türkiye, superficial purulent lymph node rupture leads to the colloquial term "Çatlak" ("cracked"), while in sheep, chronic progression and severe weight loss are sometimes referred to as "Thin Ewe Syndrome" (Al-Hababi et al., 2020). The disease typically presents in two chronic forms—external and internal—particularly in small ruminants (Yeruham et al., 2003).

CLA causes substantial economic losses due to reduced reproductive performance, deterioration in skin and wool quality, decreased meat and milk yield, and occasional mortality, especially in young animals (Baird & Fontaine, 2007; Arsenault

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et al., 2003). Although sheep and goats are the primary hosts, *C. pseudotuberculosis* has also been reported in horses, cattle, camels, and humans, highlighting its zoonotic potential (Oreiby, 2015; Ribeiro et al., 2020).

The pathogen possesses strong parasitic capabilities, enabling effective colonization, immune evasion, establishment of chronic infection, and prolonged environmental persistence (Baird & Fontaine, 2007). Among its virulence factors, phospholipase D (PLD) exotoxin is considered the most important, as it disrupts cell membrane sphingomyelin and increases vascular permeability, facilitating dissemination from the entry site to lymph nodes and internal organs (McNamara et al., 1994; Pacheco et al., 2021).

CLA is widespread globally and remains a significant problem in small ruminant production systems, with prevalence rates in some regions exceeding 40% (Oreiby, 2015; Azevedo et al., 2019). In Türkiye, although nationwide prevalence studies are limited, regional investigations indicate that CLA is common, especially in sheep flocks (Parin et al., 2018; Akgül et al., 2018). Due to the intracellular nature of *C. pseudotuberculosis* and the formation of thick-capsulated abscesses, antibiotic treatment is generally ineffective, and the infection often spreads to a substantial proportion of the flock once introduced (Oreiby, 2015; Ribeiro et al., 2020).

2. ETIOLOGY

Corynebacterium pseudotuberculosis is a pleomorphic, Gram-positive, facultative anaerobic bacterium that may appear as coccoid or filamentous rods, often arranged in a characteristic “Chinese letter” pattern (Baird & Fontaine, 2007). It is non-spore-forming, non-capsulated, non-motile, and catalase-positive, measuring approximately 0.5–0.6 μm in width and 1–3 μm in

length. One end of the bacterium is frequently swollen, giving a club-shaped appearance. Dark-staining intracytoplasmic granules, known as metachromatic granules or Babes–Ernst bodies, are commonly observed near the poles and stain intensely with aniline dyes, producing a beaded morphology (Dorella et al., 2006).

Taxonomically, *C. pseudotuberculosis* belongs to the phylum Actinobacteria, order Actinomycetales, family Corynebacteriaceae (Ribeiro et al., 2020). The cell wall contains mycolic acids, peptidoglycan with meso-diaminopimelic acid, arabinose, and galactose, features that contribute to its acid-fastness and resistance to phagocytosis (Pacheco et al., 2021).

On solid culture media, colonies typically appear within 24–48 hours as small (1–2 mm), cream to orange, opaque, and dry with a rough (R-type) morphology (Oreiby, 2015). Isolation requires differentiation from other pyogenic bacteria such as Trueperella pyogenes and Pasteurella multocida, which can be achieved through biochemical profiling or molecular methods such as 16S rRNA sequencing and PCR-based assays (Parin et al., 2018).

Most ovine and caprine isolates share similar biochemical characteristics, typically being positive for catalase, urease, glucose, maltose, and sucrose fermentation, and negative for indole, hydrogen sulfide, and gelatin liquefaction (Azevedo et al., 2019). No major biochemical differences have been reported between sheep and goat isolates (Baird & Fontaine, 2007).

3. VIRULENCE FACTORS

3.1. PLD Enzyme

Among the virulence factors of *C. pseudotuberculosis*, the phospholipase D (PLD) exotoxin is regarded as the most critical.

PLD is a sphingomyelinase that disrupts the phospholipid structure of host cell membranes, increases vascular permeability, and facilitates bacterial dissemination from the infection site to regional lymph nodes and internal organs (McNamara et al., 1994; Dorella et al., 2006; Pacheco et al., 2021).

Produced in the cytoplasm and associated with the cell wall, PLD has been shown to cause endothelial cell necrosis, enter lymphatic circulation, and induce macrophage destruction in experimental infections. Low doses produce dermonecrotic lesions in laboratory animals, while high doses can be lethal to lambs and sheep (Baird & Fontaine, 2007). Antigenically, PLD is conserved among strains, although toxin quantity and lesion severity may vary.

Molecular studies have confirmed PLD as a key target for vaccine development, with recombinant and inactivated PLD formulations demonstrating protective effects in challenge trials (Hodgson et al., 1994; Bastos et al., 2012).

3.2. Serine Protease

A 40 kDa serine protease has been identified as another virulence factor. Although it elicits an immune response and has been tested in subunit vaccine trials, antibodies against this protease alone have not provided sufficient protection in challenge experiments (Walker et al., 1994; Pacheco et al., 2021).

3.3. Mycolic Acid

Despite lacking a capsule, *C. pseudotuberculosis* possesses a mycolic acid-rich outer layer in its cell wall. These long-chain fatty acids are cytotoxic, enhance bacterial survival within macrophages, and contribute to resistance against phagocytosis (Billington et al., 2002; Ribeiro et al., 2020). Experimental administration of mycolic acid extracts in mice

induces local inflammation, congestion, and hemorrhagic necrosis, as well as leukocyte degeneration.

4. EPIDEMIOLOGY

Bacteria of the genus Corynebacterium occur as both commensals and opportunistic pathogens on the skin and mucous membranes of humans and animals. *C. pseudotuberculosis* is primarily transmitted through skin abrasions or wounds, with occasional respiratory spread. Shearing of sheep with abscessed lymph nodes is considered a major route for environmental contamination and flock-to-flock transmission (Baird & Fontaine, 2007). Environmental persistence and stress factors contribute to the maintenance of the infection in herds.

Caseous lymphadenitis (CLA) is typically endemic and often subclinical in small ruminants, making detection challenging due to its long incubation period and the absence of visible lesions in some animals (Oreiby, 2015). The disease is globally distributed, with prevalence rates ranging from <10% to over 50% depending on management practices and geography (Azevedo et al., 2019). In Australia, annual economic losses have been estimated at over USD 17 million due to reduced wool yield (Paton et al., 1994). Similar productivity losses have been reported in North America, Europe, and the Middle East (Ribeiro et al., 2020).

In Türkiye, CLA is not a notifiable disease, and nationwide prevalence data are limited. However, regional studies report frequent isolation of *C. pseudotuberculosis* from slaughtered sheep and goats, with prevalence in some flocks exceeding 15–20% (Parin et al., 2018; Akgül et al., 2018). Molecular and serological studies have confirmed its widespread distribution, particularly in sheep.

The pathogen affects a range of hosts besides sheep and goats, including horses, cattle, camels, deer, and humans, reflecting its zoonotic potential (Bastos et al., 2012; Ribeiro et al., 2020). Human cases are typically occupational and linked to direct contact with infected animals or consumption of raw milk.

Risk factors include age (>2 years), female sex, and poor hygiene during handling and shearing (Magdy et al., 2010). Lesion distribution varies: in sheep, both superficial lymph nodes and internal organs are often affected, whereas in goats, lesions occur more frequently in head and neck lymph nodes (Williamson, 2001).

5. PATHOGENESIS

Corynebacterium pseudotuberculosis typically enters the host through skin wounds, most often during shearing, dipping, or other handling procedures that cause abrasions. Following entry, the pathogen spreads via the lymphatic vessels to regional lymph nodes and subsequently disseminates through the bloodstream to other lymph nodes and internal organs, where it induces caseous granulomatous lesions (Baird & Fontaine, 2007; Ribeiro et al., 2020).

During the early infection phase (1–4 days), neutrophils accumulate at the inoculation site, initiating a local inflammatory response. Between days 5 and 10, bacterial proliferation triggers the formation of pyogranulomas, characterized by a necrotic core surrounded by macrophages, lymphocytes, and a fibrous capsule (Pépin et al., 1997; Pacheco et al., 2021). Lesions are commonly observed in the retropharyngeal and parotid lymph nodes, and in some cases, the lungs.

The phospholipase D (PLD) exotoxin and cytotoxic cell wall lipids are key mediators of local tissue damage and bacterial

dissemination but are not solely responsible for systemic disease progression (Dorella et al., 2006). *C. pseudotuberculosis* is readily phagocytosed by neutrophils and macrophages; however, it can survive and replicate within phagolysosomes, enabling persistence and immune evasion (Baird & Fontaine, 2007). Experimental studies have demonstrated its ability to remain viable in macrophages for extended periods (>48 h), contributing to chronic infection and the formation of encapsulated abscesses (Stefańska et al., 2010; Bastos et al., 2012).

Although significant progress has been made in elucidating the molecular mechanisms of pathogenesis, certain aspects—particularly the detailed interactions with macrophages and the exact mechanisms of host cell death—remain unclear. In experimental goat infections, the pathogen has been shown to preferentially localize within white blood cells, especially macrophages, indicating a strong intracellular adaptation (Pépin et al., 1997; Stefańska et al., 2010).

6. PREVENTION

Due to the intracellular localization of *Corynebacterium pseudotuberculosis* and its ability to form thick-capsulated granulomas, antibiotic therapy is generally ineffective, leading to persistence and spread within affected flocks. This has increased the importance of immunoprophylaxis as the primary control strategy for caseous lymphadenitis (CLA) (Oreiby, 2015).

Vaccination is the cornerstone of CLA prevention, with phospholipase D (PLD) identified as the major virulence factor and primary immunogen. PLD mutants fail to cause disease in experimental models, and recombinant or inactivated PLD-based vaccines have shown significant protective effects in challenge studies (Hodgson et al., 1994; McNamara et al., 1994; Pacheco et al., 2021).

Various vaccine types have been developed, including inactivated bacterins, live attenuated strains, subunit vaccines, and DNA-based formulations (Bastos et al., 2012). Inactivated PLD toxoid vaccines remain the most widely used in small ruminant production. Both monovalent and multivalent preparations exist; the latter often combine inactivated PLD with Clostridium spp. toxoids to broaden protection (Williamson, 2001). While polyvalent vaccines provide herd-level benefits, some studies indicate that monovalent PLD-focused formulations may elicit stronger immunity in goats and sheep (Anderson & Nain, 1984).

Field experience in Türkiye includes the production of an autogenous vaccine by the Sivas Sheep and Goat Breeders' Association (2007–2010) using a local *C. pseudotuberculosis* isolate with aluminum hydroxide adjuvant, with over 90,000 doses administered (Erganiş, 2010; Erganiş et al., 2014). Despite advances, no vaccine has yet achieved complete protection, and control still relies on a combination of vaccination, culling of chronically infected animals, and strict hygiene during shearing and handling.

Recently, in Türkiye, a combined vaccine containing *C. pseudotuberculosis* and *Staphylococcus aureus subsp. anaerobius* antigens has been developed using locally isolated strains and has been made commercially available, representing a significant step toward region-specific CLA control.

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