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Review Article

Cellular Defence in Mammary Gland: An Overview

S H Zalavadiya[1]*, M B Bhesaniya[2]
1MVSc, Department of Veterinary Surgery & Radiology
2Assistant Professor, Department of Veterinary Anatomy
College of Veterinary Science and Animal Husbandry,
Kamdhenu University, Junagadh, Gujarat-362001, India
***Corresponding Author:** drsunny.zalavadiya@gmail.com
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Introduction:

The mammary gland of ruminants is the organ of extremely economic important due to the major role in providing nutrition source for a significant portion of the world's human population. The mammary gland in ruminant is also responsible for providing protective immunity to neonates and for defending itself from invading pathogens (Kehrli & Harp, 2001). 0 which is one of the commonest diseases of milch animals, complex and complicated in nature, keeps us away from milk - the precious 'amrit'.

Antibiotics are an integral part of most mastitis control scheme and growing resistance of many bacterial strains to antibiotics is a rapidly increasing concern (Angulo *et al*., 1999). Current methods for the control and prevention of bovine mastitis have the potential for creating human health hazards both from antibiotics used to treat mastitis and from the chemicals used to sanitize teat and equipment.

So, the time has come for a shift in our approach from treatment and prevention of mastitis to increase natural immunity of mammary gland. The immune response to an incoming infection into the mammary gland is of utmost importance for the health of dairy cow. In general, the vaccination so far is of little value in controlling mastitis due to diversity of bacterial strains and their antigenic properties (Chakrabarty, 2003). One means of decreasing the impact of mastitis on the dairy industry is to increase the natural ability of the cow to resist the infections. This is a consequence of various defence systems collectively referred to as "resistance of the mammary gland to mastitis". Knowledge of these systems is incomplete and their interaction is often unknown. Their effectiveness is subject to anatomical, cellular, histochemical and biochemical influences.

A mammary gland is an exocrine gland that produces milk to feed young offspring It is specific type of apocrine gland, situated in the inguinal region. Mammary gland made up of connective tissue, fat, and tissue that contains the glands that can make milk. The cow has four mammary glands grouped into a

structure called an udder. A strong udder suspensory system provides proper attachments of the gland with the body.

Mammary Gland Immunity:

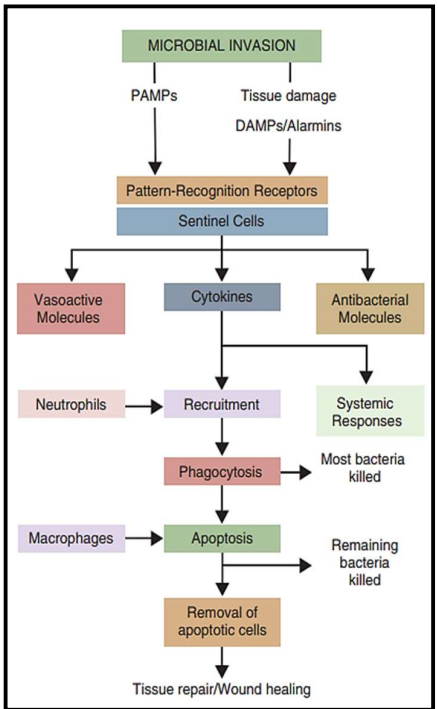
The mammary gland is protected by a variety of defense mechanisms, which can be separated into two distinct categories: innate immunity and specific immunity.

Innate immunity, also known as nonspecific responsiveness, is the predominant defense during the early stages of infection. Nonspecific responses are present or are activated quickly at the site of infection by numerous stimuli; however, they are not augmented by repeated exposure to the same insult. Nonspecific or innate responses of the mammary gland are mediated by the anatomical barrier of the mammary gland, macrophages, neutrophil, natural killer (NK)- like cells, and by certain soluble factors (Sordillo *et al.*, 1997).

The anatomical factors related to the mastitis resistance are teat sphincter muscle, teat keratin, teat cistern lining, teat shape, teat length, teat diameter, furstenberg's rosette, teat pigmentation, teat skin, size of alveoli etc. Cellular factors responsible for mammary gland protection are epithelial lining and immunological cell population like various leukocytes.

The histochemical and biochemical substances related to the protective immunity of the mammary gland against mastitis are protective proteins such as immunoglobulin, lactoferrin etc. and trace minerals namely copper, zinc, iron, manganese etc.

Conversely, **the specific or acquired immune system** recognizes specific determinants of a pathogen that facilitate selective elimination. Recognition of pathogenic factors is mediated by antibody molecules, macrophages, and several lymphoid populations. Because of the "memory" of certain lymphocytes, specific immune responses can be augmented by repeated exposure to a pathogen. In the mammary gland, both innate and acquired protective factors are coordinated to provide optimal protection from disease (Sordillo *et al.*, 1997).



Innate immunity response

Cellular Defence of Mammary Gland:

Through several complementary mechanisms, the teat end can prevent the penetration of mastitis-causing pathogens and inhibit most bacterial growth. There are some circumstances, however, when this important line of defence is compromised. For example, during the early dry period and just prior to calving, the smooth muscles in the teat canal become more relaxed due to the accumulation of intramammary pressure associated with milk retention. There is also

incomplete formation of the keratin lining for up to 2 weeks after the abrupt cessation of lactation that is related directly to increased incidence of mastitis (Sordillo & Streicher, 2002). The teat canal also remains dilated for approximately an hour after milking before muscles can fully contract and may provide another opportunity for bacterial penetration of the teat end. As such, teat antisepsis is an important and widely adopted management practice needed to optimize this initial line of mammary gland defence.

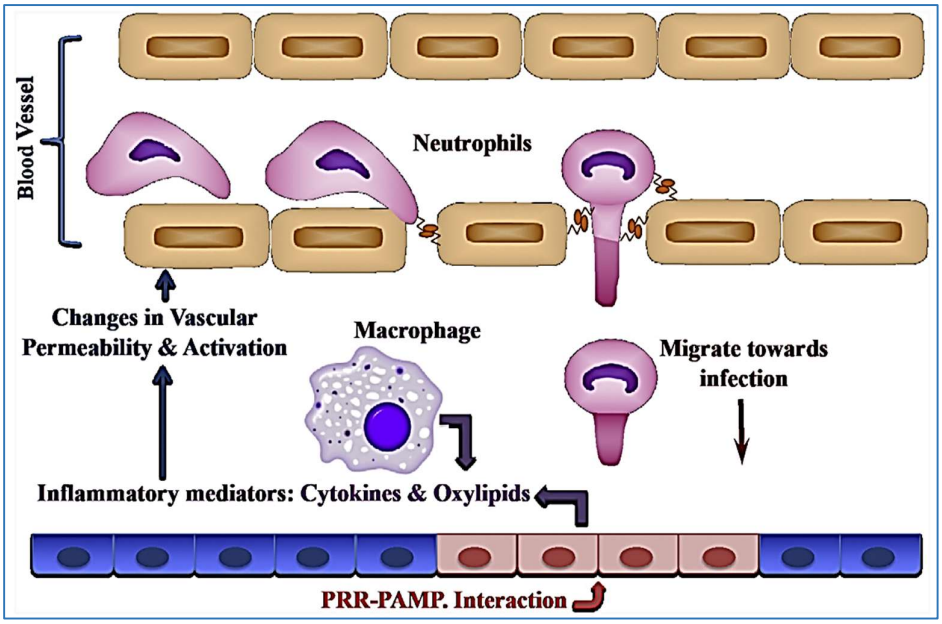
Pathogen Recognition:

When mastitis-causing pathogens successfully penetrate the teat end, the ability to sense the presence of bacteria within the mammary gland is an essential for the onset of the innate immune response. Localized mammary cell populations are capable of facilitating pathogen recognition and can effectively stimulate the several immune processes. Both immune and nonimmune cells in the mammary gland possess pattern recognition receptors (PRRs) that can interact with a diverse array of conserved unique to groups of microbes, termed pathogen-associated molecular patterns (PAMPs). Examples of these PRRs are the Toll-like receptors (TLRs), which are a family of transmembrane proteins expressed on not only leukocyte populations but also endothelial cells, epithelial cells, and fibroblasts that are distributed throughout mammary tissues (Jungi *et al*., 2011 and Kumar *et al*., 2011). Within the TLR family, both TLR-2 and TLR-4 are of particular importance to mammary defense because these receptors recognize PAMPs associated with gram-positive (peptidoglycans) and gram-negative (lipopolysaccharide) mastitis-causing pathogens, including Staphylococcus aureus, Streptococcus uberis, and Escherichia coli (Goldammer *et al*., 2004 and Porcherie *et al*., 2012). After pathogen recognition and binding through PRR-PAMP interactions, intracellular signaling pathways are activated, including nuclear factor (NF)-kB, which control the expression of several soluble mediators that trigger the onset of the inflammatory cascade (Liang *et al*., 2004).

Onset of Inflammation:

Inflammation is a critical component of the innate defense system that should eliminate bacteria within the mammary gland, assist with the repair of any tissue damage that may occur during bacterial invasion, and restore normal tissue structure and function. The inflammatory cascade results not only in the accumulation of antimicrobial factors in the milk but also the increased movement of peripheral blood leukocytes and other plasma components from the blood and into the mammary gland. An efficient mammary gland inflammatory response generally should last less than a week and not cause any noticeable change to milk or mammary tissues. Dysfunctional mammary inflammatory cascades that become exaggerated or protracted, however, can result in extensive tissue damage resulting in uncontrolled acute or chronic mastitis that contribute to significant milk production losses (Akers & Nickerson, 2011 and Halasa *et al*., 2007). Thus, mammary gland inflammatory responses should have a rapid onset to neutralize bacteria during the initial stages of tissue invasion, but a timely resolution to

avoid the immunopathology associated with mastitis.



Recruitment of leukocytes (Onset of imflammation)

The activation of NF-kB is a major signaling pathway by which soluble mediators are produced to drive the onset of the mammary inflammatory cascade (Bannerman, 2009 and Boulanger *et al*., 2003). Cytokines are one of the principal soluble mediators produced during all stages of the inflammatory response. There are several different cytokine categories based on their structure, function, and origin that include interleukins (ILs), interferons (IFNs), chemokines, colony-stimulating factors (CSFs), and tumor necrosis factors (TNFs). Cytokines bind to receptors on target cell membranes and can exert an autocrine, paracrine, or endocrine action. Individual cytokines can interact with other cytokines synergistically, additively, or antagonistically on multiple cellular targets. Cytokines regulate the intensity and duration of the host response to infection by regulating (enhancing or inhibiting) the activation, proliferation, and differentiation of cells involved in the immune response. With respect to the inflammatory response, cytokines are essential to facilitate the extravasation of leukocytes from the blood stream and to the site of bacterial invasion in mammary tissues.

Another important group of inflammatory signaling molecules is a family of potent lipid-derived mediators referred to as oxylipids. These potent lipid mediators capable of regulating essentially every aspect of the initiation and resolution of the inflammatory response (Mattmiller *et al*., 2013 and Serhan & Chiang, 2008). Whereas many immune and nonimmune cell populations are capable of producing oxylipids, macrophages and endothelial cells are a major cellular source within most tissues, including the mammary gland (Ryman *et al*., 2015). Oxylipid biosynthesis is initiated when macrophages or endothelial cells come into contact with PAMPs or other inflammatory stimuli, such as cytokines. A majority of early studies investigating the role of oxylipids in mammary gland inflammatory responses focused solely on

the arachidonic acid– derived eicosanoids derived from the COX pathway, such as the prostaglandins (PGs), thromboxanes (TX), and leukotrienes (LT) (Wheeler *et al*., 2007).

Depending on the type of invading mastitis-causing pathogen, the amount and timing of initial soluble mediator production can vary considerably (Lee *et al*., 2006). The severity of mastitis also may be associated with specific inflammatory mediator profiles. Inflammation is primarily a reaction of the microcirculation where both cytokines and oxylipids have the capacity to interact directly with blood vessels in the mammary gland to alter vascular tone and blood flow within the affected tissues, increase vasodilation of capillaries, and increase vascular permeability needed for the migration of blood leukocytes to the site of injury. The collective responses of the vascular endothelium and infiltration of blood leukocytes into affected tissues as a consequence of cytokine and oxylipid biosynthesis can result in some of the classic signs of inflammation that include heat, swelling, redness, pain, and loss of function.

Innate Cellular Defences:

During inflammation, both resident and newly recruited mammary gland leukocytes play an essential role during the early stages of pathogenesis. Within uninfected mammary tissues, lymphocytes and macrophages are the predominant leukocyte types with relatively low numbers of neutrophils. Total somatic cell counts (SCCs) in healthy mammary glands are often less than 105 cells/mL of milk, and the distribution of leukocytes varies as a function of lactation stage. Total SCCs can increase to greater than 106 cells/mL of milk within just a few hours of bacterial invasion, however, and the major leukocyte type during inflammation are neutrophils. The influx of neutrophil is initiated by cytokines and oxylipids that act directly on the vasculature to cause reductions in blood velocity with a concomitant increase in the expression of adhesion molecules on endothelial cells.15 Adhesion molecules on leukocytes attach to vascular adhesion molecules to facilitate the migration of leukocytes from the blood to the site of injury (Maddox *et al*., 1999). Neutrophils first marginate and then adhere to the local endothelium near the site of infection. Cytokines, oxylipids, and other mediator molecules stimulate adherent neutrophils to move between endothelial cells and pass the basement membrane into the damaged tissue areas. The movement of neutrophils within the tissues is facilitated by chemotactic gradients created by inflammatory mediator molecules at the localized site of infection. Neutrophil migration can occur quickly and accumulate within affected tissues as soon as 30 minutes to 60 minutes after injury (Ezzat *et al*., 2014). The promptness and magnitude of neutrophil migration into mammary gland tissues and milk are considered major determining factors for the establishment of new intramammary infections (Paapeet *et al*., 2002).

An important innate defence mechanism facilitated by mammary gland leukocytes is the ingestion and killing of bacteria, a process referred to as phagocytosis. In the mammary gland, phagocytosis is carried out primarily by neutrophils and macrophages, but dendritic cells are also capable of phagocytosis. The phagocytic process involves the engulfment of bacteria, where it is then encapsulated within a

cytoplasmic vacuole called a phagolysosome. Neutrophils can kill phagocytosed bacterial by either oxygen-dependent or protein-mediated mechanisms. The oxygen-dependent system is operative during the ingestion process in which there is a major burst of oxidative metabolism. The increased oxygen consumption results in the production of reactive oxygen and nitrogen intermediates that are produced through a metabolic process known as respiratory burst. These microbicidal oxidizing agents are located within phagolysosomes and can oxidize bacterial membrane lipids and cause the pathogen's destruction. The primary enzymes involved in catalyzing the oxidation process are myeloperoxidase and superoxide dismutase. (Paapeet *et al*., 2002).

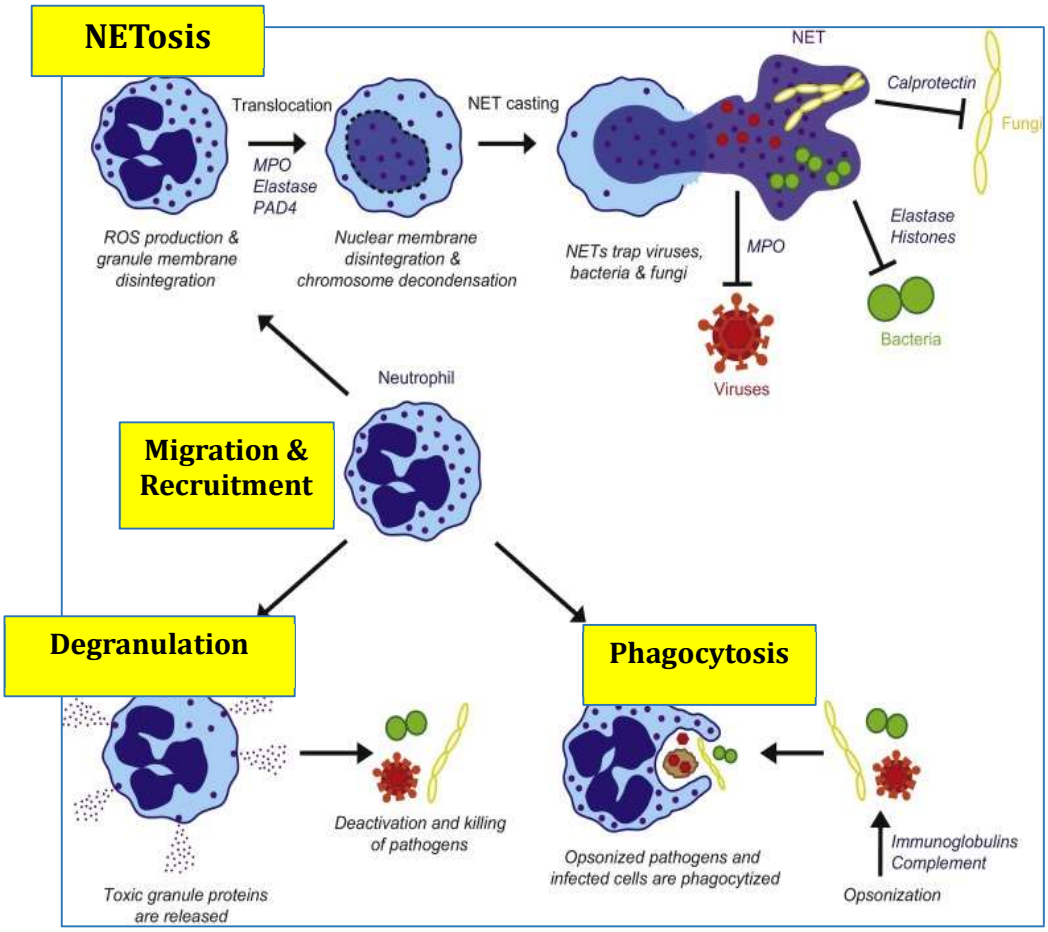
In addition, bacteria may become exposed to and destroyed by several oxygen independent reactants, including lysozyme, a variety of cationic proteins, and lactoferrin. These antimicrobial elements of neutrophils also are stored within large cytoplasmic granules unique to bovine neutrophils. For example, several cationic peptides have been isolated from these large granules of bovine neutrophils and have been studied and described experimentally. Bovine neutrophil cationic proteins are a heterogeneous group including cathelicidin family members and the b-defensins that display antibacterial activity against pathogens associated with mammary gland infection. The degraded bacteria are then exocytosed from the neutrophil with minimal collateral damage to mammary tissues. Mammary gland neutrophils can ingest fat, casein, and other milk components that render them less effective at phagocytosizing bacteria. The phagocytic and bactericidal activities of these cells are especially diminished during the periparturient period and are believed an underlying cause of increased susceptibility to mastitis during this stage of lactation. The phagocytic and bactericidal capabilities of neutrophils, however, can be increased substantially in the presence of opsonic antibody for specific pathogens (Paapeet *et al*., 2002 and Rainard & Riollet, 2006).

Neutrophil extracellular trap (NET) formation is an additional antimicrobial defence mechanism in the innate immune system. Pathogen stimulation of neutrophils triggers the release of nuclear material (DNA and histones) as well as granular proteins and extracellular fibers that function to trap and kill microbes. NETs provide highly concentrated foci of antibacterial substances that bind and kill bacteria independently of phagocytic uptake in the mammary gland (Grinberg *et al*., 2008 and Lippolis *et al*., 2006). NETs also may serve as a physical barrier that prevents further spread of bacteria throughout a cow's tissues. NET formation may be of particular importance to the mammary gland due to their ability to function in the presence of milk in contrast to other neutrophil functions that can be suppressed in that environment (Lippolis *et al*., 2006).

Function of Neutrophil:

Natural killer (NK) cells are a subpopulation of lymphocytes that also may play an important role as part of mammary gland innate immunity. They are characterized as large granular lymphocytes that

have cytotoxic activity independent of the major histocompatibility complex (MHC). A unique aspect of NK cells is their ability to use Fc receptors to participate in antibody-dependent, cell-mediated cytotoxicity. Cytokine-stimulated NK cells also are capable of killing bacteria by releasing bactericidal proteins. NK cells isolated from bovine mammary tissue exhibit bactericidal activity against S aureus and, therefore, these lymphoid populations could be an important aspect of innate defence in preventing mastitis. Changes in this cell population during the periparturient period have not been studied extensively, but the potent bactericidal activity of these cells makes them worthy of future study (Sordillo & Streicher, 2002).



Resolution of Inflammation:

As outlined previously, the onset of inflammation to bacterial invasion is a complex and tightly regulated response. Whereas a rapid and robust inflammatory response is protective, an uncontrolled acute or chronic inflammatory reaction can lead to extensive tissue damage that is associated with diseases pathogenesis. Therefore, a timely and natural resolution of inflammation is fundamental to overall health of the mammary gland. The resolution of inflammation is an active event involving specific proresolving pathways and mediators that expedite the shutdown process by limiting leukocyte infiltration into affected tissues, modifying soluble mediator production, removal of cellular debris, and repairing damaged tissues (Buckley *et al.*, 2014 and Tabas & Glass, 2013). An essential requirement to turn off the inflammatory response is the removal of the mastitis-causing pathogens that initiated the inflammatory cascade. The successful neutralization of the inciting pathogen signals the cessation of proinflammatory mediator synthesis and leads to their catabolism. Alternatively, the production of several anti-inflammatory or pro-

resolving soluble mediators is enhanced. Therefore, if neutrophils are able to migrate rapidly from the blood stream to the mammary gland and effectively eliminate the bacteria, then the recruitment of leukocytes should cease and milk SCCs return to levels found in healthy cows. If bacteria persist, however, then the inflammatory response continues into an acute or chronic state. Prolonged and/or excessive migration of leukocytes from the blood causes considerable damage to mammary parenchymal tissues that result in reduced milk production.

Both cytokines and oxylipids are critical soluble mediators that play a central role in the resolution of the inflammatory cascade. As discussed previously, IL-4, IL-10, and IL-17 are known to actively promote the resolution of inflammation in the mammary gland.11 The expression of these anti-inflammatory cytokines depends on the leukocyte profiles within mammary tissues and the degree of activation based on the infection status of the mammary gland. (Ryman *et al*., 2019). Certain PGs produced during the onset of inflammation, such as PGE2, can serve as negative feedback signals to facilitate the resolution of inflammation (Grinberg *et al*., 2008). The active biosynthesis of proresolving lipid mediators plays an essential role in limiting neutrophil infiltration into affected tissues, enhancing macrophage clearance of apoptotic cells within affected tissues, and facilitates the restoration of tissues to normal function (Tabas & Glass, 2013).

Adaptive Immunity:

Although adaptive immunity takes longer than innate immunity to develop after microbial exposure, it becomes increasingly important if pathogens are able to evade or are not completely eliminated by the innate defence system. In contrast to the generalized nature of innate immunity, adaptive immunity is able to elicit immune responses to specific factors associated with bacterial pathogens, which are referred to as antigens. A fascinating feature of the adaptive immune system is the ability of a cow to recognize and respond to billions of unique antigens they may encounter. When an antigen is encountered more than one time, a heightened state of immune reactivity occurs as a consequence of immunologic memory. As such, a memory response is much faster, considerably stronger, lasts longer, and often is more effective in clearing pathogens compared with the initial exposure to a particular antigen. The ability of the adaptive immune responses to be amplified by repeated exposure to a particular pathogen provides the foundation of mastitis vaccine strategies. It also is important that inappropriate specific immune responses do not occur against a cow's own antigens. For this reason, the immune system is able to distinguish self from nonself and selectively react to only foreign antigens. The ability to recognize only foreign antigens is mediated by genetically diverse, membrane-bound proteins, called MHC molecules. A specific immune response only occurs if antigens are combined with an MHC molecule on the surface of certain cells, a process referred to as antigen presentation. Major components of the innate immune system include immunoglobulin (Ig) molecules, macrophages, dendritic cells, and several different lymphoid

populations that mediate recognition of specific pathogenic factors (Sordillo, 2018).

Factor	Main Functions
MHC	Distinguishes host molecules from foreign molecules
Dendritic cells Macrophages	Antigen presentation Cytokine production
T cells	T_H cells - produce cytokines that regulate adaptive immunity Tc cells - lysis of damaged host cells Produce cytokines capable of down-regulating leukocyte functions
B cells	Mature B cells are antigen-presenting cells and expand into antigen specific memory cells Plasma cells synthesize and secrete antigen-specific antibodies
Ig (antibodies)	IgM is the largest and first produced; role in agglutination and complement activation Enhances bacterial phagocytosis through opsonisation IgA is found at mucosal surfaces and has antiviral function
Cytokines	Immunoregulatory for adaptive immunity Facilitates leukocyte functional capacity

Adaptive Cellular Defences:

Generation of effective specific immunity involves 2 broad cell types, including lymphocytes and antigen-presenting cells. Lymphocytes recognize bacterial antigens through membrane receptors specific to the invading pathogen. These are the cells that mediate the defining attributes of adaptive immunity, including specificity, diversity, memory, and self/nonself recognition. The T cells and B cells are distinct subsets of lymphocytes that differ in function and the expression profiles of protein products. When activated, the variety of immunoregulatory cytokines produced by TH cells play an important role in activating both T cell and B cells, macrophages, neutrophils, and various other cells that participate in the immune response. Differences in the particular pattern of cytokines produced by activated TH cells results in different types of immune responses. For example, IFN-g and IL-2 are believed to enhance some cellular activities associated with innate immunity, such as phagocytosis and intracellular killing. Alternatively, these same cytokines may also enhance the proliferation and differentiation of T cells and B cells during adaptive immune responses (Sordillo & Streicher, 2002).

Conclusion:

The mammary gland possesses a highly coordinated and dynamic immune defense system that plays a crucial role in protecting dairy animals against mastitis. Cellular defenses form the backbone of this protection, involving both innate and adaptive immune mechanisms. Innate immunity provides rapid,

nonspecific protection through epithelial barriers, neutrophils, macrophages, NK cells, and inflammatory mediators, while adaptive immunity ensures pathogen-specific responses and immunological memory through lymphocytes, antibodies, and antigen-presenting cells. Effective pathogen recognition, timely recruitment of leukocytes, efficient phagocytosis, and proper resolution of inflammation are essential for maintaining mammary gland health. An imbalance or failure in these processes can lead to tissue damage, chronic inflammation, and reduced milk production. Therefore, a better understanding of the cellular defense mechanisms of the mammary gland is fundamental for developing alternative strategies to enhance natural immunity, reduce reliance on antibiotics, and achieve sustainable control of mastitis in dairy animals.

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