Narrative Relation between Low Milk Somatic Cell Count and Mastitis Susceptibility in Dairy Animals

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Abstract

Background: Somatic cell count in milk is closely associated with the incidences of intramammary infections (IMI) in milch animals, and is regarded as a reliable marker of the mammary gland (MG) infection. The contradicting school of thought exist about the interpretation and consequences of SCC; most authors reported the reduced incidences of IMI in dairy cows with lower milk SCC, but some research findings clearly explained the elevated risks linked with lower SCC, and defended in ground of compromised immune status of the focus cows.
Areas Covered: The question of whether low SCC is correlated to increased susceptibility to IMI has aroused the logical and rational debate. However, to date, SCC is considered a key measure in selecting dairy animals that show reduced susceptibility to IMI. As selection indexes prioritize animals with lower SCC, it could enhance the defense mechanisms of the MG concerns that has arisen about the potential long-term increase in susceptibility to IMI. The debate surrounding this issue persists, despite seemingly contradictory findings from previous studies investigating the relationship between SCC and IMI susceptibility in dairy animals. A comprehensive understanding of the leukocyte- dynamics in milk and immune-physiology of mammary cells, along with their functions in combatting infections, can help reconcile these conflicting results. Recent studies focusing on SCC-based selection of dairy animals also contribute to resolving the matter.
Expert Opinion: It becomes apparent that the long-debated issues of susceptibility to IMI associated with SCC is more likely a phenotypic trait linked to immunomodulation rather than a consequence of selection.

Keywords: Dairy animals, Immunity, Leukocyte, Milk resident cells

1 Introduction

Somatic cell count (SCC) is the measure of leukocytes and alveolar epithelial casts in milk and is used as a biomarker of udder health status in milk producing animals (Matera *et al.*, 2022; Panchal *et al.*, 2016; Shook et al., 2017; Sun *et al.*, 2023). Therefore, it is a proxy index for bio- surveying infected mammary gland (MG) that ensures the milk quality (Rainard *et al.*, 2018; Schukken *et al.*, 2003). The frequent fluctuations in SCC proportion are basically due to the rate of migration of leukocytes to the milk from the bloodstream, often in response to microbial invasion in the MG and desquamation of its epithelium (Rainard *et al.*, 2008). These leukocytes primarily function as an initial line of defense in the MG, as evidenced by development of acute intramammary infection (IMI) when the infiltration of leukocytes is impeded (Prin-Mathieu *et al.*, 2002; Vangroenweghe *et al.*, 2005). Moreover, the SCC, or its different form, log SCC and somatic cell score/SCS (Ali & Shook, 1980), serves as a reliable selection criterion for reducing mastitis susceptibility genetically (Odegard *et al.*, 2003). However, most of the selection based on estimated breeding values for mastitis classically rely on log-SCC, without imposing a lower limit; and uses mean lactation SCC commonly because of its moderate heritability (0.15) and widespread data availability (Rupp & Foucras, 2010). Having significant correlation with subclinical mastitis (SCM), use of SCC has an innate contradiction of being poorly associated with acute clinical mastitis (CM), especially those due to coliforms (Rainard *et al.*, 2018). Nonetheless, a robust genetic correlation, averaging 0.6 to 0.7, exists between SCC and CM, validating SCC's role as a surrogate for CM too (Govignon-Gion *et al.*, 2016; Leitner *et al.*, 2024). However, past literatures had emphasized that these two mastitis indicators represent distinct traits (Mrode and Swanson, 1996).
Consensus aligns on the selection against high SCC, yet ideas diverge regarding the consequence of low SCC (Beaudeau *et al.*, 2002; Rainard *et al.*, 2022a; Sharma *et al.*, 2011). However, the issues regarding the potential risks associated with the selection of animals with extremely low SCC which may predispose them to IMIs, both SCM and CM, is a matter of debate (Beaudeau *et al.*, 2002). Some researchers advocate for maintaining a reasonable concentration of somatic cells in milk to mitigate these risks ((Leitner *et al.*, 2024; Schukken *et al.*, 2003) while others argue that there is no clear lower limit to SCC that is correlated with a lower incidence of IMI (Philipsson *et al.*, 1995; Rainard *et al.*, 2018). Furthermore, the concept has been introduced that SCC

comprises two distinct components: the baseline SCC influenced by physiological and environmental factors, and the next linked to vulnerability to IMI (Odegård *et al.*, 2005). Additionally, Heringstad et al. (2006) reported 0.03 and 0.08 heritability of SCS for infected and healthy dairy cows, with higher correlation (0.78) between these traits and stated that SCC may not be uniform in cows with and without mastitis. Numerous literatures have discussed the relationship between low SCC and mastitis susceptibility, yielding seemingly contradictory results (Rainard *et al.*, 2018; Van den Borne *et al.*, 2011). In spite of these analyses, the question remains unresolved to clarify either lower SCC predisposes the producing dairy animals to IMI or not. To navigate this apparent deadlock, it is crucial to consider other factors and explore the possible mechanisms that immune cells and MG tissue employ to fight infections. By doing so, it becomes apparent that the seemingly conflicting previous works are not necessarily irreconcilable. Furthermore, recent researches on dairy cows selected based on SCS contribute new insights to key aspects of the issue, offering a basis for a compelling resolution (Ezzat Alnakip *et al.*, 2014)

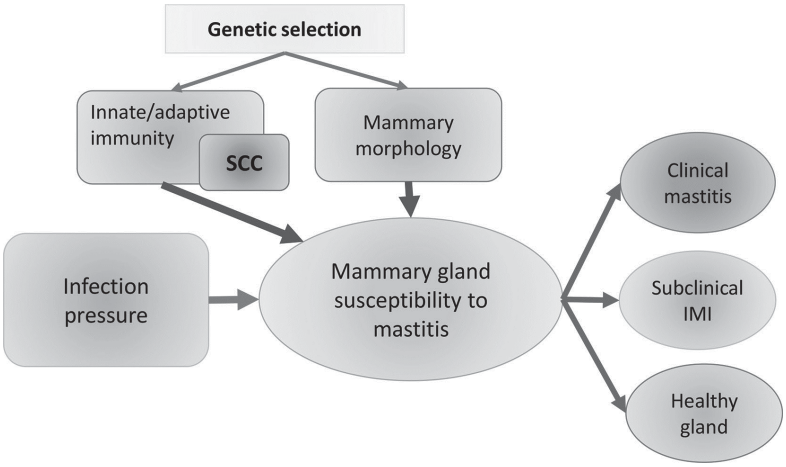

Figure 1: Association of major determinants of the udder health [source: Rainard et al. (2018)].

1.1 Variation on concept, thought and scientific reasoning

Conflicting findings from previous research works have explored the link between SCC levels and mastitis resistance. The challenge in obtaining a clear picture arises from the diverse study methodologies, which involve recording CM or SCM, bulk tank SCC, udder SCC, or teat SCC, often without detailed bacteriological analyses (Rainard *et al.*, 2018). CM is commonly diagnosed and monitored, whereas SCM is estimated through SCC across different levels of lactation and parity (Alhussien et al., 2021; Alhussien & Dang, 2020). The multifaceted nature of various independent and interconnected affecters ultimately determines the UH status (Figure 1). In spite of this complexity, valuable information can be obtained from a diverse collection of statistics and ideas.

The association of incidences of SCC and CM appears to be influenced by the type of infection in the herd (Shook *et al.*, 2017). For instance, Erskine *et al.* (1988) reported a higher incidence of CM in the high SCC cows when comparing the risks of occurrence of IMI in low ($< 150,000 cells/mL$) and high ($> 750,000 cells/mL$) bulk milk SCC producing herds. The high SCC cows experienced higher incidence of CM and showed a strong affinity with *streptococci* and *staphylococci* while *coliforms* were dominant in low SCC herds (Rainard *et al.*, 2018). However, other research results yielded inconsistent results; some of them had reported no association between bulk milk SCC and CM, while others reported a higher incidence in herds with low SCC (Alhussien *et al.*, 2021; Beaudeau *et al.*, 2002; Li *et al.*, 2014). The variation in CM incidence in herds with low SCC may be considerable, and the link between CM and low bulk milk SCC is not well established.
At the cow level, the incidence of CM was observed to increase as SCC decreased in some studies, indicating a higher risk in cows or herds having low SCC, i.e. $< 50-200\times10^3 cells/mL$ (Beaudeau et al., 2002; Suriyasathaporn *et al.*, 2000). Tadich *et al.* (1998) and Barkema et al. (1998) too had suggested that CM tends to be more severe in herds or in cows with low SCC. While various factors, such as a higher incidence of Gm-ve bacterial infections, may contribute to these findings, but may partly be attributed to a reduced immunity of cows to manage infections when their SCC is low. However, a reduced risk of CM in a low SCC cow were reported in contradictory past studies. Steeneveld *et al.* (2008) reported a lower prevalence of CM in low bulk milk SCC herds than in moderately high bulk milk SCC ones, while others reported that cows were at the higher risk of IMI when they have very low SCC in milk. The variations in the study design, population characteristics, and specific SCC thresholds considered may be the cause for these conflicting findings (Petzer *et al.*, 2017; Sumon *et al.*, 2020). But these incompatible and the challenging literatures offer a solid basis in synthesizing the valuable insights into the relationship between SCC levels and mastitis incidence.

2 Milk Somatic Cells as Immune Tool

The MG leukocytes offer a level of cellular defense against microbial invasion by triggering an instant inflammatory response to the IMI (Ezzat Alnakip *et al.*, 2014). In addition, it secretes different immune-mediators like cytokines, chemokines, reactive oxygen species (ROS), and antimicrobial proteins in milk and helps in regulation of the inflammatory processes (Singh *et al.*, 2008). Leukocytes form the majority of somatic cells with a small fractions of epithelial casts from the MG (Concha, 1986). Therefore, lymphocytes, macrophages, and a limited proportion of neutrophil granulocytes are the primary somatic cells in healthy glands (Dosogne *et al.*, 2003). They work as a surveillance line against infective agents and assist in apoptosis of the MG (Barber *et al.*, 1999). Specifically, neutrophils play a crucial role in controlling bacterial proliferation within the MG lumen (Paape *et al.*, 2002) and there is a prominent shift from mononuclear to polymorphonuclear cells in the somatic cell picture during IMI (Table 1) (Sarikaya *et al.*, 2006). As a result, selection against high SCC is essentially a selection against inflammation and neutrophil concentration in milk, while selection against low SCC implies a choice against the concentration of macrophages and lymphocytes. This perspective has led some researchers to propose that high and low SCC could be considered as distinct traits (Madsen *et al.*, 2008). Concerns have been raised about the wisdom of selecting for very low SCC, as it might compromise the mammary gland's ability to combat infection (Kehrli & Shuster, 1994). Therefore, it is important to understand dynamics of milk leukocytes by distinguishing the roles of macrophages and lymphocytes from that of neutrophils, as well as considering the involvement of milk resident cells to evaluate the validity of this concern.

2.1 Role and behavior of Milk Resident Cells

Milk resident cells are immune cells in milk of healthy MGs (Dosogne *et al.*, 2001), and are regularly refilled in milk on each milking, remaining for a short period within the MG lumen (Rainard *et al.*, 2018). More specifically, these cells are evident in the gland cisterns and ducts of the MG where milk flow flushes them out continuously during milking. The composition of the resident cell analyzed in milk evident the continual recruitment of leukocytes from the blood and MG tissue into the lumen (*Ezzat Alnakip et al.*, 2014). It is crucial to recognize that this resident cell mass may not precisely represent the leukocyte residing within the mammary tissue. Despite this, these migrating cells are considered the first line of defense on detecting invading alien agent, operating phagocytosis, and initiating inflammatory processes (Ezzat Alnakip *et al.*, 2014). The concentration of these cells is an important factor in their defensive role, as they rely on encounters facilitated by concentration and convection currents, rather than active movement toward targets (Lengi *et al.*, 2022). The frequency of contact with bacteria and other microbes determines cell activation, chemotaxis, phagocytosis efficiency and dynamics of IMI in the MG.

In-vitro experiments have established that a threshold concentration of phagocytes, approximately $5\times10^5 cells/mL$, is necessary to achieve a significant reduction in bacterial numbers (Li *et al.*, 2002). Given that MG infections are initially detected in cisterns and large ducts (Petzl *et al.*, 2016), these cells become particularly valuable at these sites. However, examinations of the epithelium lining the cisterns and large ducts through histological and immunohistochemical methods have not revealed macrophage-like cells adhering to the epithelium. Therefore, the existence of a substantial population of adhered macrophages in these areas remains to be confirmed (Maxymiv *et al.*, 2012; Rainard *et al.*, 2013).

The bacterial products (metabolites, exotoxins, exosomes, etc.) in milk too can activate milk leukocytes, during the weaker trigger of immune response to infection. Then the activity of these cells is an important point to consider. Milk macrophages have significantly lower phagocytic capacity than blood monocytes or neutrophils (Denis *et al.*, 2006; Dosogne *et al.*, 2001) and are less responsive to IFN-γ and produce less IL-1β, TNF-α, as well as nitric oxide compared to blood monocytes (Denis et al., 2006; Politis et al., 1992). The functions of milk lymphocytes are not well defined, with most displaying the morphometry of T cells, mainly CD8+ T cells (Soltys & Quinn, 1999). Overall, the interaction of lymphocytes with other effector cells relies on random encounter and depend on its concentration in milk. Thus, the lower number of leukocytes in milk in a healthy MG are unlikely to play a significant role in defence.

2.2 Neutrophils and the concept of the leukocyte barrier

At the initiation of inflammation in the MG, there is a profound alteration in the cellular composition of milk (Rainard *et al.*, 2022a; Rainard *et al.*, 2022b). Notably, the MG demonstrates a remarkable ability to rapidly initiate extensive inflammatory responses dominated by neutrophils. This results in a significant increase of neutrophils in the milk, with concentrations often exceeding $100 \times 10^8 cells/mL$ (Schalm & Lasmanis, 1968). Even in cases of persistent Staphylococcus aureus-induced chronic mastitis, neutrophils remain predominant in the milk (Riollet *et al.*, 2001). Neutrophils play an important role in controlling IMI caused by most mastitis pathogens (Paape et al., 2002). As mentioned earlier, maintaining an optimum level of neutrophils is essential for reduction and elimination of bacteria in fluid medium, and this concentration (approximately $3-5\times10^5 cells/mL$) is readily achieved and sustained in the inflamed MG. Schalm *et al.* (1967) suggested that pre-existing leukocytosis

in milk could hinder the establishment of infection following bacterial invasion into the MG lumen, proposing the concept of a leukocyte barrier to infection mediated by neutrophils resulting from local inflammation (Schalm & Lasmanis, 1968). According to the leukocyte barrier concept, a healthy MG is more susceptible to new IMI compared to an already infected and inflamed gland. A logical implication of the leukocyte barrier effect is that herds with low levels of IMI, when exposed to the same infectious pressure, are inherently more vulnerable to new infections than herds with high levels of chronic IMI (Ezzat Alnakip et al., 2014; Farschtschi *et al.*, 2022; Jiang et al., 2022; Lozada-Soto *et al.*, 2020).

Table 1: The differences in distribution of cellular components in mammary gland (MG) between healthy and inflammatory conditions

	Healthy MG	Mastitic MG
SCC	Usually lower than 1×10^5 cells/mL milk. However, a SCC higher than 2×10^5 cells/ mL milk is considered to be a more practical distinguishing threshold for IMI.	SCC is greater than 2×10^5 cells/mL milk according to severity of IMI; with severe IMIs, the SCC may reach 1×10^6 cells/mL references milk or more within a few hours.
Leukocytes	75% of SCC.	Dramatic increase occurs according to severity of IMI at early stages due to recruitment of immune cells from the marginal pool and bone marrow into the MG environment.
Macrophages	35–79% of total leukocytes in milk, constituting the predominant cell type.	9–32% of total leukocytes in milk.
Lymphocytes	10–28% of total leukocytes in milk. The proportions of T- and B-lymphocytes in milk are approximately 40–50% and 20–25%, respectively. $\alpha\beta$ T-cells prevail and are predominantly CD8+ subset with memory characteristics (comprising approximately 50–60% of the T-lymphocyte population).	14–24% of total leukocytes in milk. CD4+ T-cells become the predominant activated phenotype in response to recognition of Ag-MHC class II complexes on Ag-presenting cells, such as B-cells or macrophages. In some circumstances, such as chronic Staph. aureus IMIs, CD8+ are predominantly recruited compared over CD4+ T-lymphocytes.
PMNs	3–26% of total leukocytes in milk.	The predominant cell type, constituting up to 90% of the total milk leukocytes or more. With chronic bacterial IMIs, PMNs also remain as the predominant cells, even for months.

Source: Ezzat Alnakip et al. (2014)

3 The Mammary Epithelium Defense

Numerous studies have confirmed the competence of mammary epithelial cells (MEC) to detect the microorganism and its products (Lahouassa *et al.*, 2007; Rainard *et al.*, 2022a; Yang et al., 2008). The various recognition receptors present in MEC is its identity that read different microbial pattern called microbe-associated molecular patterns (MAMPs) (Jungi *et al.*, 2011). Transmembrane proteins, nucleotide-binding oligomerization domain (NOD)-like receptors (NOD1 and NOD2) as well as toll-like receptors are the major pattern recognition receptors (Porcherie *et al.*, 2012). NOD1 is sensitive to a dipeptide (iE-DAP) of peptidoglycan layer in Gm-ve bacteria, while NOD2 responds to muramyl dipeptide of all peptidoglycans (Rainard *et al.*, 2022a). After detecting these MAMPs, different immune mediators such as antimicrobial peptides, reactive oxygen species, cytokines and chemokines are secreted as a MEC response (Bougarn *et al.*, 2011).

In addition to epithelial cells, the mammary epithelium lining the cisterns and large ducts includes dendritic cells, macrophages, and lymphocytes that closely associated with the epithelial linings (Maxymiv *et al.*, 2012). The cooperation between MEC and these epithelium-associated leukocytes is likely to amplify the response of MEC to bacteria (Bougarn *et al.*, 2010). Notably, the reaction of MEC to *Escherichia coli* and *S. aureus* aligns well with the initial response of the MG, surpassing the response of macrophages to *Streptococcus uberis*

(Gilbert *et al.*, 2013; Günther *et al.*, 2016). This supports the notion that milk leukocytes are not the initiators of MG inflammation; instead, MEC stimulation is essential to initiate the mammary tissue response. The collaboration between MEC and tissue leukocytes is particularly effective near the entry points of pathogens, such as Furstenberg's rosette at the distal end of the teat and the teat sinus. In response to infection, these sentinels of the MG produce chemokines, cytokines, and antimicrobial proteins (Lind *et al.*, 2015; Rinaldi *et al.*, 2010) and combat the existing infection and reduces the risks of evading new ones.
In spite of the prominent role of the mammary epithelium and the presumed low contribution of milk leukocytes to inflammation initiation, observations suggest that low SCC mammary glands may not be less susceptible to IMI than high SCC glands (Jiang *et al.*, 2022; Rainard *et al.*, 2018) and this contradicts common observations. The SCC could potentially serve as an indicator of the reactivity of the MG to bacterial stimuli, not because milk cells trigger the reaction, but due to higher concentrations of migrated cells reflecting higher concentrations of tissue-associated cells. Moreover, beyond a critical concentration, inflammatory milk cells (distinct from "resident cells"in uninflamed glands) might contribute to inflammation initiation (Fromageau *et al.*, 2011; Rainard *et al.*, 2022a; Rainard *et al.*, 2022b).

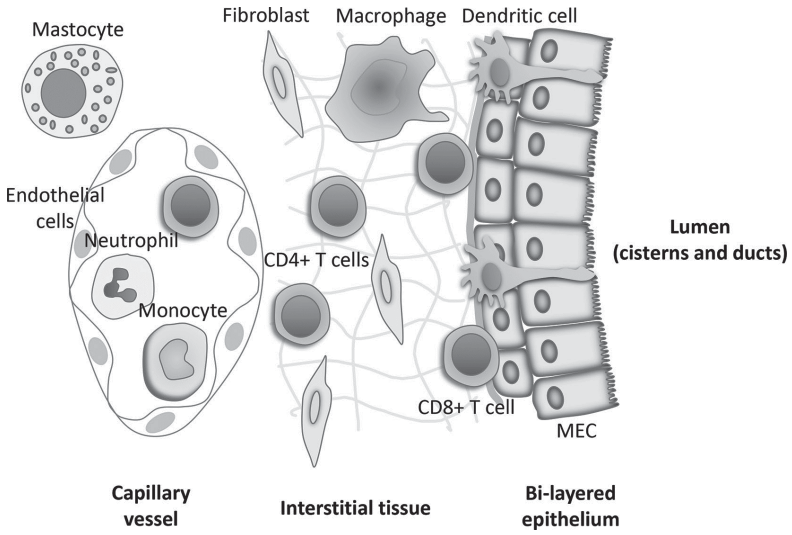

Figure 2: The mammary gland epithelium at the level of cisterns and large ducts. MG epithelium can recognize bacteria and initiate the inflammatory responses. Dendritic cells/macrophages and cluster of differentiation (CD) 8+ T cell is closely associated with the epithelium, adjacent to mammary epithelial cells (MEC) and others in the sub-epithelial tissue. Source: (Rainard et al., 2018)

4 Resistance to Mastitis and Low Scc

Literature exploring the correlation between low SCC and susceptibility to mastitis presents divergent findings (Beaudeau *et al.*, 2002; Rainard *et al.*, 2018). The apparent contradictions in the interpretation of study results can be attributed to the involvement of various mechanisms of underlying IMI:

- The immune barrier formed by milk leukocytosis linked to pre-existing infections
- Infection pressure arising from exposure to diverse pathogens, be they of contagious or environmental origin
- The level of genetic susceptibility of the host to MG infections
- MG reactivity influenced by current or past environmental factors

The dichotomy between resistance and susceptibility to infection is a transient phenotypic trait of the udder, primarily dictated by the physiological state of the animal and its genetic makeup. A crucial factor influencing the susceptibility trait is the presence of prior or concurrent udder infections, inducing persistent innate immunity, termed trained immunity (Netea *et al.*, 2011), as seen with that of the leukocyte barrier. This immunity is largely individual-centric, albeit some effects extend to the entire udder (Bisutti *et al.*, 2023; Rainard *et al.*, 2022b; Vlasova & Saif, 2021).
A significant outcome of the local expression of resistance to infection is that herds with a higher proportion of chronic-infected glands exhibit a lower incidence of new infections. Conversely, herds with a greater percentage of healthy glands face an increased risk of new infections (Rainard *et al.*, 2018). The incidence of CM in a herd with low IMI levels, typically characterized by a low bulk milk SCC, is determined by the prevailing infection pressure. Consequently, low SCC quarters and herds might appear more susceptible to mastitis in epidemiological surveys,

not necessarily indicating an elevated genetic susceptibility in low SCC animals (Beaudeau *et al.*, 2002; Rainard *et al.*, 2018; Rupp *et al.*, 2000).
The primary goal of genetic selection against mastitis is to augment the proportion of animals with low IMI levels and fewer instances of CM. This inadvertently promotes herds with a higher prevalence of phenotypically receptive glands. Consequently, the MG of a low SCC animal is more receptive phenotypically due to its non-inflamed nature, making it less susceptible to mastitis owing to genetic resistance, compared to an infected high SCC cow (Koivula *et al.*, 2005; Leitner *et al.*, 2024).

5 Conclusion

Low SCC is not necessarily an indicator of high susceptibility to mastitis. Previous research reports suggested that increased SCC correlates with heightened MG reactivity due to existing basal inflammation, possibly indicating an alert state in response to local innate immunity. While this heightened reactivity could be advantageous in specific conditions, it entails inflammation and associated drawbacks. In other hand, mastitis susceptibility due to very low SCC may be a phenotypic trait related to immunomodulation, opening area for further well-designed works and not solely a result of selection. Regarding intentional selection for low SCC in dairy animals, researches with divergent selection demonstrate that it does not negatively impact susceptibility to MG infection. Therefore, we can conclude that the SCC of healthy and uninflamed glands does not differ due to SCS- based selection and does not reduce the reactivity to infection but the herds with existing basal bacterial invasions may experience increased risks of mastitis in dairy animals.

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Author Contributions

Conceptualization, methodology investigation writing original draft preparation writing review and editing all works done by DKC.

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