Milk Somatic Cell Generation and Dairy Quality and Safety: Postprint

Authors: Wang Yue, Su Hanshu, Huang Qingyun, Guo Qi, Jiang Linshu, Wang Bing

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Abstract

Milk somatic cell count is one of the crucial indicators reflecting the mammary health status of dairy cows, and elevated levels of this indicator suggest that cows may be in a subclinical or diseased state. Under normal physiological conditions in dairy cows, the composition and number of milk somatic cells remain essentially stable; however, when mammary trauma or diseases (such as mastitis) occur, milk somatic cell count increases, milk yield decreases, and milk quality deteriorates. Milk quality is directly related to consumer health; therefore, ensuring the quality and safety of raw milk is a primary issue that dairy producers must address. Accordingly, this review examines the relationship between milk somatic cell generation and both milk yield and milk quality, aiming to provide theoretical guidance for improving milk quality and safety.

Full Text

Milk Somatic Cell Formation and Dairy Quality and Safety

WANG Yue, SU Hanshu, HUANG Qingyun, GUO Qi, JIANG Linshu, *WANG Bing*

(Key Laboratory of Dairy Nutrition in Beijing, College of Animal Science and Technology, Beijing Agricultural College, Beijing 102206, China)

Abstract: Milk somatic cell count (SCC) is a crucial indicator of mammary gland health in dairy cows. Elevated SCC suggests that cows may be in suboptimal health or diseased. Under normal physiological conditions, both the composition and quantity of milk somatic cells remain relatively stable. However, when mammary injury or disease occurs (such as mastitis), milk SCC increases, leading to reduced milk yield and deteriorated milk quality. Milk quality directly impacts consumer health, making the assurance of raw milk quality and

safety a primary concern for dairy producers. This review examines the relationship between milk somatic cell formation and both milk production and quality, providing theoretical guidance for improving dairy quality and safety.

Keywords: dairy cow; somatic cell; milk yield; milk quality and safety

Milk somatic cells originate from the cow' s body, primarily comprising mammary alveolar epithelial cells shed from the udder and immune cells involved in host defense. Milk somatic cell count (SCC) represents the total number of somatic cells per milliliter of milk and serves as a key indicator of mammary health. Elevated SCC indicates potential subclinical or clinical health issues in dairy cows, such as mammary trauma, pathogenic bacterial invasion (e.g., mastitis), or metabolic disorders (e.g., acidosis or ketosis), all of which can increase milk SCC while simultaneously reducing milk yield and quality. Safe, reliable, and high-quality raw milk is essential for consumer dietary safety and health. Research has demonstrated that changes in milk SCC correlate closely with milk yield and other milk components [1]. Dos Reis et al. [2] found that milk from cows with high SCC exhibited significantly lower fat, protein, and lactose percentages compared to low-SCC milk, likely due to reduced appetite and insufficient nutrient intake following mastitis infection, resulting in lower blood glucose levels. Ma et al. [3] reported that milk yield gradually declines as SCC increases, with a significant linear negative correlation between production and SCC. For each one-point increase in SCC linear score, milk yield decreases by approximately 0.8 kg. During mastitis, damaged or destroyed mammary cells impair secretory function, leading to elevated SCC and reduced milk production. Therefore, this review aims to summarize the formation of milk somatic cells and their relationship with milk yield and composition, providing theoretical guidance for dairy farm management, health regulation, SCC reduction, and milk quality improvement.

1. Sources, Detection Methods, and Monitoring Significance of Milk Somatic Cells

Somatic cells consist primarily of mammary alveolar epithelial cells and immune cells involved in immune responses, including macrophages, lymphocytes, and polymorphonuclear neutrophils [4]. Under normal conditions, a small number of leukocytes in milk can defend against microbial infections. When exogenous pathogens invade, the body releases large quantities of leukocytes into the mammary gland to exert anti-inflammatory effects, causing a surge in milk SCC [5].

1.2 Detection Methods

Detection methods for milk SCC are based on various physicochemical properties and can be broadly categorized as direct or indirect. Direct methods include manual microscopy and computer vision detection. Manual microscopy involves observing milk samples on glass slides under a microscope with human cell counting, while computer vision detection employs automated image analy-

sis for SCC enumeration [7]. Indirect methods are more numerous and include the California Mastitis Test (CMT), Wisconsin Mastitis Test (WMT), DNA-based assays, ATP assays, electrical conductivity (EC), pH measurement, and viscosity methods [8]. Currently, near-infrared spectroscopy is most commonly used, determining milk components via near-infrared spectra to qualitatively assess SCC.

1.3 Monitoring Significance

Milk SCC typically increases with the severity of inflammation and decreases as inflammation subsides, playing a crucial role in anti-inflammatory responses and tissue repair. Therefore, SCC measurement in milk from various sources can serve as a method to evaluate cow health and the degree of mammary infection [9]. Key applications of SCC monitoring include: (1) tracking the prevalence of subclinical mastitis in herds; (2) assessing infection severity and duration in individual cows; (3) identifying mastitis trends by comparing SCC changes; (4) identifying infected animals through DHI reports highlighting high-SCC individuals, combined with on-site CMT testing to confirm infected quarters; (5) establishing milking order for healthy versus infected cows; (6) preventing high-SCC milk from contaminating bulk tanks to ensure raw milk quality; and (7) establishing culling criteria.

2. Key Factors Influencing Milk Somatic Cell Formation

Jagielski et al. [10] noted that elevated SCC reflects mammary damage and is regulated by inflammatory mediators, with infection being the primary influencing factor. When the mammary gland is uninfected, management, age, season, and other factors have minimal impact on SCC. However, recent studies have found that different dry period lengths can affect SCC during lactation [11]. Additionally, research on protein composition changes in high-SCC milk has revealed associations between prostaglandins and SCC [12].

2.1 Mastitis

Intramammary infection readily induces mastitis, leading to increased milk SCC. The incidence of subclinical mastitis is high, ranging from 46.4% to 85.7% [13]. Although subclinical mastitis lacks clinical symptoms, it can cause dramatic reductions in milk yield [14]. Extensive research has identified mastitis pathogens. Baumert et al. [15] found that *Corynebacterium bovis*, *Streptococcus agalactiae*, and coagulase-negative *Staphylococcus* are primary pathogens causing subclinical mastitis. Mastitis pathogens can be broadly classified into two categories based on transmission characteristics: contagious pathogens that colonize the mammary gland and spread during milking, including *S. agalactiae*, *Streptococcus dysgalactiae*, *Staphylococcus aureus*, and mycoplasma; and environmental pathogens including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Serratia*, *Proteus*, and *Pseudomonas*.

Awale et al. [16] demonstrated that *Streptococcus* infection resulted in the highest milk SCC, followed by coagulase-negative staphylococci. Conversely, Kano et al. [17] found no significant differences in SCC among cows infected with *Streptococcus*, coagulase-negative staphylococci, *S. aureus*, *E. coli*, *Pseudomonas*, or yeast. Aslantaş et al. [18] reported that *E. coli*-induced mammary infection caused sustained rectal temperature elevation, decreased circulating leukocyte levels, increased milk SCC, reduced milk yield, and elevated mRNA expression of Toll-like receptor 2 in somatic cells and cytokines [tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), IL-6, and IL-8] in blood cells. These cytokine and Toll-like receptor mRNA abundance changes, together with milk SCC, can serve as mastitis biomarkers. Cortinhas et al. [19] investigated the effects of *E. coli* lipopolysaccharide (LPS)-induced mastitis on bovine mammary and hepatic transcriptomes, identifying 189 differentially expressed genes in mammary tissue (20 downregulated, 169 upregulated) and 107 differentially expressed genes in liver tissue (42 downregulated, 65 upregulated) between LPS-challenged and control cows. Bioinformatic analysis revealed that LPS challenge activated NOD-like receptor signaling, Toll-like receptor signaling, retinoic acid-inducible gene I (RIG-I)-like receptor signaling, and apoptosis pathways in mammary tissue. Ferreira et al. [20] found that compared to LPS challenge during lactation, early postpartum LPS challenge resulted in fewer, less mature, functionally weaker circulating polymorphonuclear leukocytes with impaired infiltration capacity at infection sites. Jørgensen et al. [21] observed that LPS challenge increased milk SCC within 2.5 hours (local response), while Svensson et al. [22] detected elevated body temperature 2–6 hours post-challenge (systemic response).

Furthermore, studies have identified correlations between milk SCC and the activities of lactate dehydrogenase, β-N-acetylglucosaminidase, and acid phosphatase in mastitic milk. Lactate dehydrogenase originates primarily from damaged epithelial cells and milk leukocytes, with increased activity reflecting inflammatory processes and mammary tissue damage [23]. Research shows significantly elevated lactate dehydrogenase activity following *S. aureus* and *Streptococcus* infections, indicating mammary damage [24-25]. β-N-acetylglucosaminidase, a lysozyme produced in mammary tissue, serves as a marker of epithelial cell destruction. Aitken et al. [26] demonstrated that bacterial infection significantly increases β-N-acetylglucosaminidase activity, enabling prediction of mammary infection. Acid phosphatase, derived from cytoplasm, mitochondria, nucleoplasm, and microsomes, is released into milk through cysteine and dithiothreitol stimulation. Mallard et al. [27] found markedly increased acid phosphatase activity following *S. aureus* infection. Piepers et al. [28] reported significant correlations between lactate dehydrogenase activity and SCC (r=0.7936), as well as between lactate dehydrogenase and both β-N-acetylglucosaminidase and acid phosphatase. β-N-acetylglucosaminidase activity positively correlates with SCC, with varying correlations for different bacterial infections: strong correlations were observed with *S. aureus* (r=0.941), coagulase-negative staphylococci (r=0.761), *Streptococcus* (r=0.808), and *E. coli* (r=0.733). Acid phosphatase activity also

showed highly significant correlations with SCC and the other two enzymes. Collectively, these enzyme activities serve as effective indicators of mammary infection.

2.2 Dry Period

Shortening or omitting the dry period affects energy balance and metabolic status. Van Hoeij et al. [12] investigated the effects of different dry period lengths on mastitis incidence, pre-calving SCC, and post-calving clinical mastitis rates. Cows without a dry period (0 days) exhibited chronic intramammary infections before calving with low cure rates and significantly elevated postpartum SCC compared to cows dried off for 30 or 60 days. The study concluded that dry period length and parity are closely related to postpartum SCC. Additionally, in cows undergoing a 60-day dry period, pre-drying SCC showed strong positive correlation with post-calving clinical mastitis incidence.

2.3 Prostaglandins

Prostaglandin E2 (PGE2) is a crucial lipid metabolite released in response to physiological or pathological stimuli, particularly harmful stimuli, and plays important roles in fever, inflammation, and blood pressure regulation. Guan [29] studied PGE2 regulation of immune cells, finding that under anti-CD3 and anti-CD28 monoclonal antibody stimulation, T cell proliferation inhibition rates increased significantly with PGE2 concentration, showing a strong positive correlation. PGE2 pretreatment reduced macrophage surface IL-12 receptor expression and inhibited TNF-α, IL-1, IL-8, and IL-12 expression. Minuti et al. [30] demonstrated that PGE2 inhibited TNF-α production in zymosan-induced peritoneal macrophages while stimulating IL-10 expression via EP2 and EP4 receptors, indicating PGE2' s capacity to stimulate type 2 immune responses.

Hulbert et al. [31] identified increased prostaglandin-H2 D-isomerase in high-SCC milk, suggesting its upregulation may result from mastitis-induced overexpression or blood-milk barrier damage. Prostaglandins can induce chemokines, leading to infiltration of inflammatory cells including neutrophils, eosinophils, and macrophages [32]. This reflects that epithelial cells can produce prostaglandin-H2 D-isomerase during mastitis, recruiting necessary immune cells by converting prostaglandin H2 to prostaglandin D2 (Figure 1 [Figure 1: see original paper]), thereby increasing milk SCC. While cathelicidins have been reported as mastitis biomarkers, their correlation with SCC is lower than that between prostaglandin-H2 D-isomerase and SCC [33]. Scherpenzeel et al. [34] noted that the stronger correlation between prostaglandin-H2 D-isomerase and SCC suggests it may serve as an SCC indicator in milk. Kuhn et al. [35] proposed that combining prostaglandin-H2 D-isomerase with other mastitis stage-related signals could provide additional information about mammary defense mechanisms during infection, indicating its potential superiority over SCC alone for predicting mastitis.

PTGDS: prostaglandin-H2 D-isomerase; PGH2: prostaglandin H2; PGD2: prostaglandin D2.

Figure 1. The role of prostaglandin-H2 D-isomerase in recruiting SCC in the mammary gland from cows with mastitis inflammation [36].

3. Relationship Between Milk SCC and Milk Yield/Quality

3.1 Milk Yield

Clinical mastitis can cause milk yield losses of 20%–70%, with some cows becoming completely dry [37]. Consequently, milk SCC is inversely related to milk production. However, yield losses from subclinical mastitis vary considerably, ranging from 5% to 28% per quarter or per cow [38].

Gan et al. [39] analyzed DHI records from a Shanghai dairy farm between July 2009 and June 2012 while monitoring subclinical mastitis pathogens. The study examined the relationship between milk yield and SCC from both somatic cell score (SCS) and SCC perspectives, comparing pathogen types with SCC elevation magnitude to assess pathogen virulence. Results showed that SCS effectively reflected milk yield decline with increasing SCC. Herd-level analysis revealed a quadratic relationship between average linear score and milk yield, with each one-point increase in linear score reducing daily yield by 0.56 kg on average. From the SCC perspective, maximum milk yield occurred when SCC was below 50,000 cells/mL, with production declining above this threshold. Between 100,000 and 2,000,000 cells/mL, yield changes were relatively minor, with substantial decreases only occurring beyond 2,000,000 cells/mL. The study also demonstrated that elevated SCC primarily affects milk yield after the peak lactation stage, with minimal differences during late lactation.

3.2 Milk Quality

Compared to healthy cows, milk from subclinical mastitis cows shows no apparent visual differences but exhibits altered composition, including changes in fat, protein, and lactose content that affect quality and flavor [40].

3.2.1 Changes in Conventional Milk Components When SCC reaches 100,000 cells/mL, milk fat percentage decreases by 0.01%, solids-not-fat by 0.019%, protein by 0.001%, and lactose suffers 10%–20% losses [41]. Enhanced vascular permeability during infection increases salt influx from blood, imparting a salty taste [42]. Since lactose constitutes half of solids-not-fat, its reduction decreases total solids-not-fat content [43]. Schrick et al. [44] found significant correlations between SCC and protein/lactose percentages, likely because mastitis increases capillary permeability, raising whey protein content while fibrinolytic enzymes degrade α-casein and β-casein, reducing casein content.

3.2.2 Changes in Other Milk Components Yang et al. [45] studied protein composition changes in high-SCC milk, finding elevated sodium, nitrogen compounds, albumin, and lactate dehydrogenase activity in milk from single-quarter mastitis cows, while immunoglobulin, α-lactalbumin, β-lactoglobulin, calcium, potassium, and inorganic phosphorus decreased. Wiśniewski et al. [46] compared protein profiles between healthy and mastitic milk, revealing reduced hemoglobin, β-casein, -casein, and tryptophanyl-tRNA synthetase activity, but increased cytochrome C oxidase and annexin V in mastitic milk. Following intramammary injection of staphylococcal lipoteichoic acid, elevated SCC was accompanied by detectable proteases including plasmin, cathepsins B and D, and elastase [47].

E. coli-induced mastitis increased SCC and elevated low-abundance inflammatory markers such as serotransferrin, fibrinogen β-chain, S100 calcium-binding protein A12, and antimicrobial peptides [48]. Safi et al. [49] found that during the acute phase of subclinical mastitis, high-SCC milk showed increased haptoglobin and amyloid A, along with elevated serine protease inhibitor A3-1, vitronectin-like protein, and complement factor H. High-SCC milk also exhibited decreased calcium and phosphorus but increased sodium and chloride, causing pH fluctuations and increased electrical conductivity [50]. This principle underlies the conductivity method for SCC detection [9], as mammary inflammation increases sodium, chloride, and bicarbonate ions, positively correlating conductivity with SCC.

3.3 Impact on Dairy Processing

High-SCC raw milk can cause off-flavors in pasteurized milk, ultra-high temperature (UHT) milk, and yogurt due to extensive protein hydrolysis generating hydrophobic peptides that produce bitter, astringent tastes. High SCC also shortens product shelf life and impairs coagulation properties, increasing moisture content and reducing cheese yield, causing substantial economic losses [13]. Mastitic milk exhibits reduced solids-not-fat, diminished coagulation strength, and decreased thermal stability during concentration as dry matter content increases [51]. Specific impacts include: (1) reduced fat content affecting butter yield and flavor, with effects intensifying during storage; (2) low casein content impairing cheese quality; (3) presence of bacteriostatic factors like immunoglobulins inhibiting yogurt fermentation; (4) catalase in high-SCC milk catalyzing peroxide cleavage of unsaturated fatty acids, creating off-flavors; and (5) altered mineral content (increased sodium/chloride, decreased calcium/potassium) causing pH fluctuations, delayed rennet coagulation, and bitter/salty tastes [52].

Di Marzo et al. [38] investigated spray-dried milk powder from different SCC levels, finding that protein and ash content correlated with SCC increases. Skim milk powder (SMP) contained more hydroxymethylfurfural than whole milk powder (WMP). Rising SCC adversely affected solubility indices and increased scorched particles in both SMP and WMP. Particle size distribution also differed significantly, with WMP showing more uniform, larger structures while SMP

had greater specific surface area. Thus, increased milk SCC negatively impacts milk powder quality.

4. Measures to Control and Reduce Milk Somatic Cell Count

Milk SCC directly reflects overall herd management level. Ensuring herd health, reducing SCC, and improving milk yield and quality for optimal economic returns requires multifaceted approaches, including enhanced farm hygiene, standardized milking procedures, and effective control/treatment measures [40]. For cows with subclinical or clinical mastitis, green and safe antibiotic alternatives that leave no residues and don' t induce resistance can be employed, such as natural plant extracts, saponins, and citrus compounds in feed to enhance immunity [53]; supplementation with trace elements and vitamins can also reduce mastitis incidence [54].

Stelwagen et al. [55] found that glucocorticoids like prednisolone increased blood-milk barrier integrity in LPS-challenged cows, reducing somatic cell formation and inflammation. Ding et al. [56] demonstrated that novel microecological preparations containing *Lactobacillus* and *Bacillus subtilis*, combined with short-chain organic acids (fumaric, citric, and acetic acid), effectively treated subclinical mastitis while reducing SCC and improving milk quality. Additionally, from a nutrigenomics perspective, advancing existing technologies to study nutrition-disease impacts on somatic cell formation and milk component synthesis offers new insights. For instance, RNA extraction from milk for nutrigenomic research eliminates the need for invasive tissue sampling, improving animal welfare while reducing economic and time costs [57], providing novel approaches for studying mammary health, nutritional metabolism, and SCC regulation.

5. Summary and Outlook

Milk SCC is a vital indicator of mammary health in dairy cows. Elevated SCC negatively impacts milk yield and quality. Exogenous pathogen infection induces mastitis, increasing SCC and adversely affecting cow health, milk composition, yield, quality, and dairy product flavor. Extensive research has been conducted on SCC detection, biomarkers for clinical and subclinical mastitis, and prevention/treatment measures. However, the relationship between endogenous metabolic diseases and milk production/quality remains unclear, and the mechanisms of mammary infection by different exogenous pathogens require further elucidation. Advances in molecular biology, particularly omics technologies, may enable rapid pathogen identification and targeted prevention/treatment. In conclusion, further research is needed to explore the relationships between milk SCC, milk yield, and milk quality to provide theoretical guidance for healthy dairy farming, efficient production, and premium milk sourcing.

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Note: Figure translations are in progress. See original paper for figures.