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REVIEW PAPER

Mastitis impact on technological properties of milk and quality of milk products—a review

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Abstract The consequences of mastitis on the technological properties of milk and on the quality of milk products are widely reported in the literature. Besides, recent advances have shed light on the mechanisms involved in the udder response and subsequent milk changes in mastitis cases. This review gives an update on the literature regarding the impact of mastitis on milk composition and processing properties and collates recent data regarding the mechanisms involved in mastitis effects. It is an attempt to link field observations and experimental studies in order to better understand how mastites affect so dramatically the technological properties of milk. Both bovine and small ruminant milks are considered and a special emphasis is given on the role of staphylococci, streptococci, and *Escherichia coli*, the most common causative agents of mastitis.

乳腺炎对乳制品质量和乳加工特性的影响

摘要 关于乳房炎对乳的加工特性和乳制品质量影响的文献报道非常多。近年来关于此方面的研究重点在乳房炎对乳房的反应以及对影响乳成分变化的机制。本文对近年来乳房炎对乳组成和加工特性的影响及其影响机制方面的相关文献进行了对比和分析。目的是说明乳房炎的发生会对乳的加工特性产生巨大的作用。不但是对牛乳，而且一些小反刍动物乳的加

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工特性都受乳房炎的影响。值得强调的一个现象是葡萄球菌、链球菌属和大肠杆菌是乳房炎发病最主要的原因。

Keywords Mastitis · Milk · Ruminant · Dairy product · Bacterial pathogen

关键词 乳 · 反刍动物 · 乳制品 · 致病细菌

1 Introduction

Milk composition can be affected by a wide array of factors: breed, age, stage of lactation, and diet of the animal. In addition, infectious mastitis (hereafter referred to as mastitis), an inflammatory reaction of the mammary gland to an infection, is also known to have a multitude of effects on the quantity, quality, and processing properties of the produced milk. Mastitis is the most frequent disease in dairy herds and is the main source of economic loss in milk production worldwide. The average annual cost of mastitis caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus uberis*, and *Escherichia coli* is estimated to be 4,896 € in a herd of 100 dairy cows (Halasa et al. 2009). Beyond animal health and food safety issues, mastitis is also a problem for the dairy industry because of the induced milk changes. This review gives an update of the literature regarding the impact of mastitis on milk composition and processing properties and collates recent data regarding the mechanisms involved in these effects. Staphylococci, streptococci, and *E. coli* are the most common causative bacterial agents of mastitis in both bovine and small ruminant hosts and therefore have been more documented. Special emphasis is given to the impact on milk quality and technological properties.

2 Milk and milk product changes caused by mastitis

2.1 Milk changes

2.1.1 High somatic cell count as a marker of mastitis

Many reports have described the changes in milk yield and or composition associated with mastitis. Regarding quality control, the increase of somatic cell count (SCC) in milk is the main marker for the detection and diagnosis of mastitis (Viguier et al. 2009). The direct link between changes in SCC and the onset of mastitis has indeed been known for a long time. Therefore, in a wide array of scientific reports, authors have considered an increase in SCC as a marker of mastitis and the identification of the bacterial species causing the mastitis was most often neglected. However, recent data regarding the pathogenesis of mastitis has shown that the effects of mastitis on milk yield and composition may vary greatly with regard to the causative agent. These differences may in turn explain some previous conflicting reports in the field.

The host immune response to the different pathogens appears to vary among species (Bannerman et al. 2004b; Leitner et al. 2006) and each pathogen induces specific changes in the milk (Leitner et al. 2006). Normal SCC is 68,000 cells·mL^{-1} in cows

milk (Djabri et al. 2002), around 75,000 cells·mL^{-1} in ewes milk (Ariznabarreta et al. 2002; Gonzalo et al. 2002) and varies between 210,000 and 1,120,000 cells·mL^{-1} in goats milk (Leitner et al. 2004c; Manser 1986). A meta-analysis of the data concerning the rise in SCC during mastitis infection in cows has actually shown differences depending on the pathogen involved. SCC range from 105,000 cells·mL^{-1} in *Corynebacterium bovis* mastitis up to 1,151,000 cells·mL^{-1} in *E. coli* mastitis (Djabri et al. 2002). The two other major pathogens, *S. aureus* and *S. uberis* induce a SCC increase of 357,000 cells and 1,024,000 cells·mL^{-1}, respectively (Djabri et al. 2002).

The rise in SCC also varies depending on the causative pathogen during mastitis in small ruminants. In ewes, the SCC ranges from 187,000 cells·mL^{-1} in *Corybacterium* spp. mastitis up to 7,461,000 cells·mL^{-1} in *Pasteurella* spp. or *S. agalactiae* mastitis (Gonzalo et al. 2002). Coagulase negative staphylococci (CNS), micrococci, and corynebacteria induce mastitis with SCC under 200,000 cells·mL^{-1} (Raynal-Ljutovac et al. 2007). In *S. aureus* mastitis, SCC varies between 3,035,000 and 4,800,000 cells·mL^{-1} according to studies (Ariznabarreta et al. 2002; Gonzalo et al. 2002) (No data are available for *E.coli* and *S. uberis*). In goats milk, SCC ranges from 444,000 to 1,480,000 cells·mL^{-1} in CNS mastitis and rises to above 3,000,000 cells·mL^{-1} in *S. aureus* mastitis (Leitner et al. 2004c; Manser 1986). Variations in the SCC can be observed during mastitis with a specific profile for each pathogen. For example in coliform mastitis, the SCC is low before and after the clinical mastitis. On the contrary, in the case of clinical *S. aureus* mastitis, the SCC increases before and remains high after cure. In the same way, streptococci induce a continuous rise in SCC until clinical mastitis is settled and the SCC remains at a high level after mastitis (de Haas et al. 2002).

Different pathogens can also induce different symptoms and can be associated with different types of mastitis. Mastites indeed range from subclinical mastitis to clinical mastitis. These latter clinical mastites can be classified into mild, moderate, and severe mastitis (Table 1). In small ruminants, severe clinical mastitis can turn into gangrenous mastitis with the destruction of tissues and loss of the infected udder. A given pathogen

Table 1 Definition of the mastitis types with regard to the severity of the symptoms

Mastitis type	Definition[a]
Subclinical mastitis	Inflammation of the mammary gland that is not visible and requires a diagnostic test for detection. The most used diagnostic test is the milk somatic cell count. Subclinical mastitis is the most prevalent form of the disease
Mild clinical mastitis	Observable abnormalities in milk, generally clots or flakes with little or no signs of swelling of the mammary glands or systemic illness. Preferred terminology when describing severity of clinical cases
Moderate clinical mastitis	Visibly abnormal milk accompanied by swelling in the infected mammary quarter with an absence of systemic signs of illness. The terminology is preferred when describing the severity of clinical symptoms
Severe clinical mastitis	Udder inflammation characterized by sudden onset with grave systemic and local symptoms. This terminology is preferred to peracute clinical mastitis

[a] According to the mastitis terminology as defined in the Bulletin of the International Dairy Federation 338/1999

(for example *S. aureus*) can be associated with different types of mastitis, notably in small ruminants (Vautor et al. 2009). Consequences of each type of mastitis on milk quality will differ. For example, clots appear in milk from animals with clinical mastitis whereas none are present in milk from animals with subclinical mastitis. In the same way, mastitis can affect all quarters or only one (with the others remaining healthy).

It also appears that the SCC is not a good criterion to diagnose mastitis in goats. The SCC level in goats milk is indeed prone to significant changes through the lactation period (Galina et al. 1996; Haddadi et al. 2006). In nonmastitic goats milk, the SCC can vary between 200,000 to 500,000 cells at the beginning of lactation, to 200,000 to 350,000 in the peak of lactation and to 1,000,000 to 3,100,000 or more at the end (Bergonier et al. 1994). It has recently been reported that no changes in goats milk composition is observed when the SCC varies from 214,000 to 1 450,000 cells·mL^{-1} (Chen et al. 2010). The changes in milk presented in this paragraph are associated with a high SCC level but it has to be noted that these changes cannot be assigned to a clear and demonstrated onset of mastitis. In this paragraph, available data in the literature regarding the changes observed in cows, ewes, and goats milks when the SCC (regarded as a mastitis marker) increases will be summarised. Data regarding small ruminant milk changes are fewer than these for cows milk which are reported in more detail.

2.1.2 Negative correlation between SCC and milk yield

Regardless of the ruminant species, an increase in the SCC in bulk milk is generally associated with a decrease in milk yield (Barlowska et al. 2009; Baudry et al. 1997; Caruolo 1974; El-Saied et al. 1999; Gonzalo et al. 1994; Leitner et al. 2003; 2004a, b; Munro et al. 1984; Othmane et al. 2002; Pellegrini et al. 1997; Pizzillo et al. 1996; Ying et al. 2002; Zeng and Escobar 1996). The decrease in cows milk yield is observed at least 1 week before clinical mastitis is diagnosed (Bareille et al. 2003; Grohn et al. 2004; Hagnestam et al. 2007; Lucey et al. 1986; Ostergaard and Grohn 1999; Rajala-Schultz et al. 1999; Wilson et al. 2004). This time lag is probably due to the fact that mastitis is subclinical before the onset of clinical symptoms (Hagnestam et al. 2007). The period of lactation modulates the impact of mastitis. The effects of mastitis on production yields are indeed more severe when the mastitis developed in early lactation before the peak yield (Bartlett et al. 1991; Hortet and Seegers 1998; Rajala-Schultz et al. 1999; Santos et al. 2004; Wilson et al. 2004). Lower production yields are also a consequence of mastitis. After clinical mastitis, cows produce less milk throughout the rest of lactation in comparison to cows without mastitis (Bareille et al. 2003; Hagnestam et al. 2007; Wilson et al. 2004) and never return to their premastitic milk yield levels (Grohn et al. 2004; Wilson et al. 2004).

In cows, milk yield losses vary with the species of causative agent: among primipara, *S. aureus*, *Arcanobacterium pyogenes*, *E. coli*, *Klebsiella* spp. caused the greatest losses; among multipara, *Streptococcus* spp., *S. aureus*, *A. pyogenes*, *E. coli*, and *Klebsiella* spp. caused the most significant losses. Milk loss persisted until at least 70 days after diagnosis for *Streptococcus* spp., *Klebsiella* spp., and *A. pyogenes*. (Grohn et al. 2004). Loss in milk yield in *E. coli* clinical mastitis is 15 kg per day, whereas it is 1.6 kg per day in *S. aureus* clinical mastitis and 2.9 kg per day in *S. uberis* clinical mastitis (Coulon et al. 2002). Gram-negative cases had more severe milk loss (304 kg in multipara and 228 kg in primipara in the 50 days following

clinical mastitis) compared with gram-positive ones (128 kg in multipara and 133 kg in primipara in the 50 days following clinical mastitis) (Schukken et al. 2009).

In ewes, milk yield loss varies according to the causative pathogen and to unilateral or bilateral character of mastitis and ranges from 3% to 10%. Healthy ewes produce 880 mL of milk per day whereas ewes infected by major pathogens with bilateral mastitis produce 791 mL per day (Gonzalo et al. 2002). Even during subclinical mastitis, milk yield of the infected halves (0.36 kg/milking) significantly decreases ($P < 0.001$) in comparison to the milk yield of the uninfected halves (0.76 kg/milking) (Leitner et al. 2004a). This has also been described in goats, where milk yield decreases during subclinical mastitis (0.69 kg/milking in goats with mastitis compared with 0.98 kg/milking in healthy goats) (Leitner et al. 2004b).

2.1.3 Changes in milk associated with a rise in the SCC and variations according to pathogens

Global changes All available data concerning changes in milk due to mastitis are summarized in Table 2, many of which have already been reviewed (Auldist and Hubble 1998; Raynal-Ljutovac et al. 2007). In summary, it has clearly been determined that regardless of the ruminant species, there is a rise in the level of whey proteins (notably in serum albumin and IgG) and in sodium and a decrease in the level of lactose (except for goats milk for which the results are conflicting). Globally, there is a rise in the level of proteins and proteinous compounds linked to the inflammatory and immune response and a decrease in the endogenous milk proteins such as caseins. Some of the changes in milk composition appear to be advantageous for the defense of the mammary gland against bacterial pathogens (Schmitz et al. 2004). For example, a rise in the level of IgG2, which are opsonic antibodies has been observed, as has the level of lactoferrin, which has bacteriostatic activities while a decrease has been observed in the level of caseins, which normally inhibit the myeloperoxidase-mediated oxygen-dependent bactericidal activity of neutrophils (Cooray 1996; Watanabe et al. 2000). An effect of the SCC on milk pH has also been reported in cows, goats, and ewes milk which increases with increasing SCC (Raynal-Ljutovac et al. 2007; Vianna et al. 2008).

Data concerning the impact of mastitis on the total content of protein, fat and calcium are conflicting and no trends for these parameters can be determined at the moment. A clear and noncontroversial effect is a change in the protein profile: a rise in the level of whey proteins (with a change in whey protein composition) and changes in the casein profile. The impact of mastitis on caseins depends on the species of ruminant. Mastitic cows milk shows a decrease in casein (a decrease in β- and α-caseins, an increase in γ-casein) whereas the impact on ewes milk appears variable while no impact has been observed on goats milk. Beside casein concentration, it seems that mastitis affects the casein composition: concentration of soluble caseins has been shown to be higher and concentration of micellar caseins to be lower in mastitic milk than in healthy milk (detected by Wisconsin mastitis test) (Sharma and Randolph 1974). These phenomena can result from the regulation of the "lactation" genes in response to infection and from the induced hydrolysis of milk proteins observed when the SCC slightly increases, with or without clinical signs (Le Roux et al. 1995; Urech et al. 1999).

Table 2 Effect of mastitis on ruminant milk components (based on (Auldist and Hubble 1998; Raynal-Ljutovac et al. 2007))

Component	Effect on cow milk	References	Effect on ewe milk	References	Effect on goat milk	References
Fat	?	Andreatta et al. (2007), Auldist et al.(1995), Bansal et al. (2005), Barlowska et al. (2009), Miller et al. (1983), O'Brien et al. (2001), Randolph and Erwin (1974), Rogers et al. (1989a), Somers et al. (2003), Waes and Belleghem (1969), Wickstrom et al. (2009)	?	Albenzio et al. (2004), Alichanidis and Polychroniadou (1995), Bianchi et al. (2004), Diaz et al. (1996), Jaeggi et al. (2003), Nudda et al. (2003), Pellegrini et al. (1997), Pirisi et al. (2000, 1996), Revilla et al. (2007), Vivar-Quintana et al. (2006)	?	Baudry et al. (1997), Leitner et al. (2004b), Pasquini et al. (2002), Pisoni et al. (2004a, b), Ying et al. (2002)
Free fatty acid	↑	Auldist et al. (1996), Bachman et al. (1988), Lee et al. (1991), Murphy et al. (1989), Randolph and Erwin (1974)			–	Laurinaviciute et al. (2004)
Lactose	↓	Auldist et al. (1995), Coulon et al. (2002), Klei et al. (1998), Miller et al. (1983), Muir (1996), O'Brien et al. (2001), Ogola et al. (2007), Randolph and Erwin (1974), Rogers et al. (1989a), Somers et al. (2003), Waes and Belleghem (1969), Andreatta et al. (2007), Wickstrom et al. (2009)	↓	Albenzio et al. (2004, Alichanidis and Polychroniadou (1995), Bianchi et al. (2004), Bufano et al. (1996), Diaz et al. (1996), Duranti and Casoli (1991), Nudda et al. (2003, Pirisi et al. (2000, 1996), Revilla et al. (2007), Vivar-Quintana et al. (2006)	?	Jaubert et al. (1996), Pasquini et al. (1996), Zeng and Escobar (1996), Leitner et al. (2004b)
Total protein	?	Andreatta et al. (2007), Ashworth et al. (1967), Barlowska et al. (2009), Haenlein et al. (1973), Klei et al. (1998), Lee et al. (1991), Mazal et al. (2007), Miller et al. (1983), O'Brien et al. (2001), Randolph and Erwin (1974), Rogers et al. (1989b), Somers et al. (2003), Urech et al. (1999), Waes and Belleghem (1969), Wickstrom et al. (2009)	?	Albenzio et al. (2005), Albenzio et al. (2004), Alichanidis and Polychroniadou (1995), Bianchi et al. (2004), Bufano et al. (1996), Diaz et al. (1996), Duranti and Casoli (1991), El-Saied et al. (1999), Jaeggi et al. (2003), Nudda et al. (2003), Pellegrini et al. (1997), Pirisi et al. (2000, 1996), Vivar-Quintana et al. (2006)	?	Pisoni et al. (2004a, b), Pizzillo et al. (1996), Ying et al. (2002)
Total casein	↓	Ballou et al. (1995), Coulon et al. (2002), Haenlein et al. (1973), Klei et al. (1998), Lee et al. (1991), Mazal et al. (2007), Muir (1996), O'Brien et al. (2001), Ogola et al. (2007), Politis and Ng-Kwai-Hang (1988b), Urech et al. (1999), Waes and Belleghem (1969), Wickstrom et al. (2009)	?	Albenzio et al. (2005, 2004), Bianchi et al. (2004), Diaz et al. (1996), Duranti and Casoli (1991), Jaeggi et al. (2003), Nudda et al. (2003), Pellegrini et al. (1997), Pirisi et al. (2000, 1996), Revilla et al. (2007, 2009)	–	Leitner et al. (2004b), Pizzillo et al. (1996)
β-Casein	↓	Ali et al. (1980), Auldist et al. (1995), Haenlein et al. (1973), Hogarth et al. (2004), O'Brien et al. (2001), Rogers et al. (1989b), Verdi et al. (1987)	↓	Bianchi et al. (2004), Duranti and Casoli (1991), Revilla et al. (2009)		

α-Casein	↓	Anderson and Andrews 1977; Haenlein et al. 1973; Hogarth et al. 2004; Verdi et al. 1987)	?	Bianchi et al. (2004), Duranti and Casoli (1991), Revilla et al. (2009)		
κ-Casein	?	Anderson and Andrews (1977), Haenlein et al. (1973), Rogers et al. (1989b), Verdi et al. (1987)	?	Bianchi et al. (2004), Revilla et al. (2009)		
γ-Casein	↑	Ali et al. (1980), Auldist et al. (1995), O'Brien et al. (2001), Rogers et al. (1989b), Urech et al. (1999), Verdi et al. (1987)	↑	Bianchi et al. (2004)		
Proteose peptone 5	↑	Urech et al. (1999)				
Whey protein	↑	Auldist et al. (1995), Coulon et al. (2002), Haenlein et al. (1973), Mazal et al. (2007), Muir (1996), O'Brien et al. (2001), Ogola et al. (2007), Politis et al. (1989b), Politis and Ng-Kwai-Hang (1988b), Rogers et al. (1989b), Urech et al. (1999), Weaver and Kroger (1977)	↑	Albenzio et al. (2004), Diaz et al. (1996), Duranti and Casoli (1991), Nudda et al. (2003), Pellegrini et al. (1997), Pirisi et al. (2000, 1996), Revilla et al. (2009)	↑	Jaubert et al. (1996), Le Mens et al. (1996), Leitner et al. (2004b), Morgan and Gaspard (1999), Pasquini et al. (1996)
α-Lactalbumin	↓	Anderson and Andrews (1977), Caffin et al. 1983), Hogarth et al. (2004), Rogers et al. (1989b), Schanbacher and Smith (1975)	↓	Revilla et al. (2009)		
β-Lactoglobulin	↓	Anderson and Andrews (1977), Caffin et al. (1983), Hogarth et al. (2004), Rogers et al. (1989b), Schanbacher and Smith (1975)	?	Duranti and Casoli (1991), Revilla et al. (2009)		
Serum albumin	↑	Baranova and Belov (1993), Harmon et al. (1976), Kitchen et al. (1980), Poutrel et al. (1983), Rogers et al. (1989b)	↑	Duranti and Casoli (1991)	↑	Leitner et al. (2004b)
Immunoglobulin G	↑	Anderson and Andrews (1977), Baranova and Belov (1993), Caffin et al. (1983), Harmon et al. (1976), Rogers et al. (1989b), Schanbacher and Smith (1975)	↑	Duranti and Casoli (1991)	↑	Jaubert et al. (1996), Morgan and Gaspard (1999)
Lactoferrin	↑	Hagiwara et al. (2003), Harmon et al. (1976), Kawai et al. (1999), Rainard et al. (1982)			↑	Chen et al. (2004)
Transferrin	↑	Rainard et al. (1982)				
Plasmin	↑	Ballou et al. (1995), O'Brien et al. (2001), Politis et al. (1989b), Politis and Ng-Kwai-Hang (1988a)			↑	Leitner et al. (2004b)
Noncasein N	↑	Rogers et al. (1989b)				

Table 2 (continued)

Component	Effect on cow milk	References	Effect on ewe milk	References	Effect on goat milk	References
Na	↑	Auldist et al. (1995), Janota and Glabowna (1982), Kitchen et al. (1980), Muir (1996), Ogola et al. (2007), Rogers et al. (1989a), Tallamy and Randolph (1970), Wegner and Stull (1978)	↑	Pirisi et al. (2000)	↑	Morgan and Gaspard (1999)
K	↓	Auldist et al. (1995), Ogola et al. (2007), Rogers et al. (1989a), Tallamy and Randolph (1970)	↓	Pirisi et al. (2000)	↑	Ying et al. (2002)
Total Ca	?	Auldist et al. (1995), Bogin and Ziv (1973), Coulon et al. (2002), Muir (1996), Ogola et al. (2007), Rogers et al. (1989a), Singh and Ganguli (1975), Tallamy and Randolph (1970)	?	Bianchi et al. (2004), Pellegrini et al. (1997), Pirisi et al. (2000, 1996)	–	Leitner et al. (2004b)
Cl	↑	Ashworth et al. (1967), Muir (1996), Ogola et al. (2007), Rogers et al. (1989a), Schalm et al. (1971), Waes and Belleghem (1969)			↑	Morgan and Gaspard (1999)
Total Mg	?	Bogin and Ziv (1973), Singh and Ganguli (1975), Tallamy and Randolph (1970), Wegner and Stull (1978)				
Pi	?	Ali et al. (1980), Bogin and Ziv (1973), Coulon et al. (2002), Singh and Ganguli (1975), Tallamy and Randolph (1970)	–	Pellegrini et al. (1997), Pirisi et al. (2000)		

Arrows indicate an increase (↑) or a decrease (↓); a question mark indicates that the relationship is suspected but not clearly demonstrated; a dash (–) indicates that no variation was observed

A decrease in fat concentration during mastitis can be expected due to a reduced synthetic and secretory capacity of the mammary gland (Auldist and Hubble 1998; Raynal-Ljutovac et al. 2007). However, results are unclear. A rise in free fatty acids has been reported in mastitic cows milk. This may be explained by the alteration of the milk fat globule membrane by leucocyte lipases or by plasmin through the hydrolysis of lipoproteins, both of which may enhance lipolysis. Nevertheless, results regarding lipoprotein lipase activity in mastitic milk are also contradictory: some authors found that its activity increased (Azzara and Dimick 1985b; Erwin and Randolph 1975; Randolph and Erwin 1974; Tallamy and Randolph 1970) during mastitis while others found that it decreased (Anderson 1982; Fitz-Gerald et al. 1981) or found no significant differences (Salih and Anderson 1979). Altogether these results appear somehow conflicting and it is difficult if not impossible to draw a clear conclusion upon the impact of high SCC on milk composition for most parameters. This can partly be explained by the sample methods used to study milk changes. Indeed, some studies are based on tank milk analysis, whereas others are based on milk pooled from the four quarters of one cow and others on single quarter milk. It can be hypothetized that analyses carried out on these different milk samples might indeed lead to variable results. However, it has been reported that changes in the bulk milk are similar to changes in the quarter milk (Le Roux et al. 2003). Many other criteria concerning ruminant management (genetic characteristics, physiological stage, and dietary factors) (Coulon et al. 2002; Raynal-Ljutovac et al. 2007) can be implicated. Finally, conflicting results can also be explained by the different pathogens involved in mastitis. As mentioned above, in most studies, the SCC is the sole marker considered to define mastitic milk and the causative agent is not sought and identified. Yet, mastitis symptoms and impacts on milk yield or composition might dramatically differ depending on the bacterial species involved in the onset of the disease.

Pathogen-specific changes in milk composition Among the pathogenic bacteria involved in mastitis, some induced changes in milk composition whereas others do not or barely affect milk composition. For example, *C. bovis* does not alter milk composition whereas milk modifications are more marked in the case of *E. coli* mastitis than in the case of mastitis induced by another pathogen (Coulon et al. 2002).

Each pathogen induces specific modification in milk during mastitis. For example, specific volatile metabolites detected in mastitis milk samples are formed by and are specific to each pathogen (Hettinga et al. 2009). Other components are more or less affected depending on the pathogen. *S. uberis* mastitis is typically associated with an increase in protein content, in casein, in calcium (Coulon et al. 2002) and in lactoferrin (Chaneton et al. 2008). On the contrary, *Streptococcus dysgalactiae* mastitis is associated with a significant increase in proteose peptone and plasmin, and no changes in fat, casein or protein content (Leitner et al. 2006; Merin et al. 2008). *S. agalactiae* mastitis is characterized by a decrease in specific milk proteins (caseins, α-lactalbumin, and β-lactoglobulin).

The impact of *E. coli* mastitis on milk has been particularly studied, either under field conditions or in experimental infections (Fig. 1). During *E. coli* mastitis, lactoferrrin (whose concentration increases with the acuteness of coliform infections), protein content, proteose peptone and plasmin significantly increase

whereas caseins, casein/protein ratio, calcium and phosphorus significantly decrease (Coulon et al. 2002; Kawai et al. 1999; Leitner et al. 2006; Michelutti et al. 1999). In *E. coli* mastitis, changes in whey proteins are rapidly observed and include a lower abundance of α-S1 casein, β-casein, κ-casein, α-lactalbumin, and β-lactoglobulin, and a huge increase in bovine serum albumin. The presence of abundant proteins such as serotransferrin, fetuin (α-2-HS-glycoprotein), fibrinogen, and α-1-acid glycoprotein, and minor proteins such as α-1-antiproteinase, complement C3 and C4, TTR, proteinS100-A12, and several antimicrobial peptides (AMP) in the cathelicidin family have also been reported (Boehmer et al. 2008). Proportions of β- and α-caseins are significantly lower at 24 h (−49%) and between 48 and 72 h (−62%) respectively after *E. coli* injection (Michelutti et al. 1999).

Finally, *S. aureus* clinical mastitis is associated with a rise in lactoferrin, protein content, proteose peptone, plasmin and a decrease in casein/protein ratio, calcium, and phosphorus (Coulon et al. 2002; Hagiwara et al. 2003; Kawai et al. 1999; Leitner et al. 2006). Few changes are noticed during *S. aureus* subclinical mastitis which is only associated with a decrease in lactose content (−2.1 g kg^{-1}) and casein/protein ratio (−2%) (Coulon et al. 2002) (Fig. 2). No difference between lactoferrin and SCC levels during chronic cows mastitis due to *S. aureus* or CNS have been reported (Komine et al. 2004).

As described in the first part, it is really difficult if not impossible to determine a global trend for changes in milk parameters linked to mastitis. For example, it has not been possible to determine whether there is an increase or a

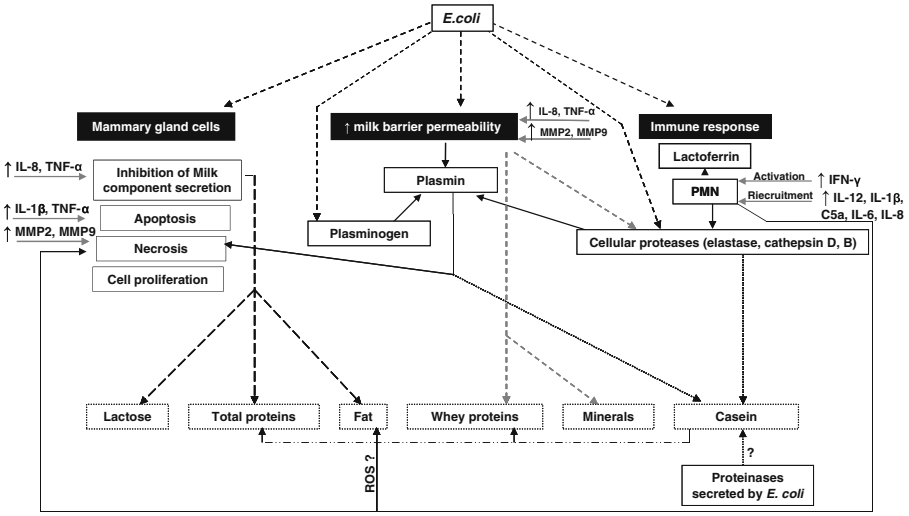

Fig. 1 Relationships between *Escherichia coli* intramammary infection, responses induced in the mammary gland and changes observed on milk components. *Black arrows* (*dashed bold lines* ▪ ▪ ▶) indicate a direct impact observed in infections with live *E. coli*; *grey arrows* (*dashed bold lines* ▪ ▪ ▶) indicate a direct impact of experimental injection of *E. coli* lipopolysaccharide (LPS). All the other *lines* and *arrows* indicate a link reported in the literature (the various styles do not have any significance and are used for the readability of the figure). *PMN* polymorphonuclear neutrophils, *MMP* matrix metalloproteinases, *ROS* reactive oxygen species. *Arrows* indicate an increase (up) or a decrease (down). *Question marks* indicate that the relationship is suspected but not clearly demonstrated

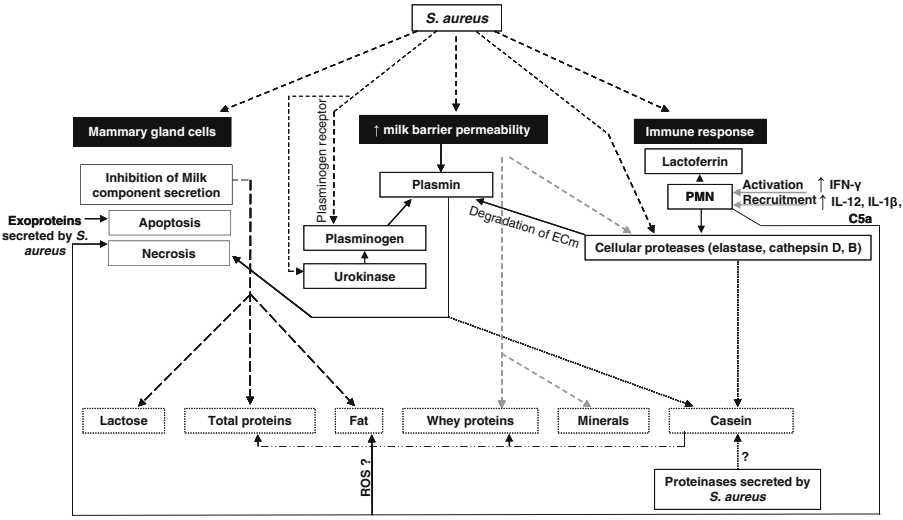

Fig. 2 Relationships between *Staphylococcus aureus* intramammary infection, responses induced in the mammary gland and changes observed on milk components. *Black arrows* (*dashed bold lines*▪ ▪ ▶) indicate a direct impact observed in infections with live *S. aureus*. All the other *lines* and *arrows* indicate a link reported in the literature (the various styles do not have any signification and are used for the readability of the figure). *PMN* polymorphonuclear neutrophils, *MMP* matrix metalloproteinases, *ROS* reactive oxygen species. *Arrows* indicate an increase (up) or a decrease (down). *Question marks* indicate that the relationship is suspected but not clearly demonstrated

decrease in calcium concentration in mastitic milk in comparison to normal milk. This may be explained by the fact that *S. uberis* mastitis is characterized by a rise in calcium whereas *E. coli* and *S. aureus* mastitis are characterized by a decrease in calcium. This demonstrates that determination of the pathogen involved in mastitis is crucial to understand the milk changes observed. The current scientific knowledge regarding, notably, the caracterisation of the impact of the pathogen presence on the mammary gland can partly explain why the impact on milk varies among pathogens.

2.2 Impact of high SCC on dairy products

A wide proportion of milk is transformed and besides the risks of bacterial contamination accompanying products based on raw milk, changes in the composition of mastitic milk can impair the transformation processes. Even when the composition of raw milk is hardly affected by mastitis, the quality of dairy products can deteriorate (Merin et al. 2008). The impacts of mastitis on dairy products, including pasteurized or UHT milks, cheeses and yogurts, are presented in the following paragraphs.

2.2.1 Development of off-flavors in high SCC pasteurized and UHT milk

Pasteurized or UHT milk made with high SCC milk are characterized by the developement of off-flavors which correspond to flavor or odor defects

(rancidity, bitterness, oxidation, astringency, etc.). Three parameters can induce the development of off-flavors in pasteurized milk: development of bacteria in milk, proteolysis, and or lypolysis of milk components. The two latter phenomena do not necessarily rely on the development of bacteria and result from changes in endogenous enzymatic activities induced by the infection in mastitic milk. When the bacterial counts in raw milk are low (i.e., <25,000 CFU·mL^{-1}), the only parameters that are likely to alter the milk flavor are the proteolysis and lipolysis of the milk components. At higher bacterial counts, the bacterial enzymatic activities might act synergistically with these phenomena to induce off-flavors (Barbano et al. 2006). Mastitic pasteurized or UHT milk is characterized by high levels of native proteases and lipases, mainly due to increased SCC and has been shown to be more susceptible to the development of off-flavors than pasteurized or UHT milk with a low SCC (Fernandes et al. 2008; Santos et al. 2003). For example, in high SCC pasteurized milk, the increase in free fatty acids (resulting from lipolysis) and casein hydrolysis were three and two times greater, respectively, than in low SCC pasteurized milk (Ma et al. 2000). Elevated levels of free fatty acids have been associated with rancidity (Ma et al. 2000; Shipe and Senyk 1981). Extensive proteolysis in milk can so result in the accumulation of small hydrophobic peptides, causing bitterness (Rouseff 1990) and astringency (Lemieux and Simard 1994). High SCC pasteurized milk has scored higher for bitterness and astringency or rancidity than low SCC milk (Ma et al. 2000; Rouseff 1990).

By increasing the SCC, mastitis can thus be responsible for the development of off-flavors in consumption milk, even after pasteurization or UHT treatment.

2.2.2 Impact on yogurts

The SCC has little impact on cows yogurt but can induce off-flavor development when exceeding 3,000,000 cells·mL^{-1} in ewes yogurt (Vivar-Quintana et al. 2006). Regarding cows yogurts, the level of SCC does not seem to affect pH and titrable acidity, fat and protein content or microbiological characteristics (Fernandes et al. 2006; Oliveira et al. 2002). On the contrary, the pH of high SCC ewes yogurt decreased much faster (when SCC is above 3,000,000 cells·mL^{-1}) during fermentation and was significantly lower after 15 days of storage (Vivar-Quintana et al. 2006). The use of high SCC milk in the manufacture of yogurt seems to reduce the storage period and shelf life of the product. The use of cows milk containing less than 400,000 cells·mL^{-1} allowed the yogurt to be stored for 30 days without organoleptic changes being detected. On the contrary, high SCC cows yogurt have been characterized by a loss of consistency after 20 days of storage at 5 °C and a decrease in taste after 30 days of storage at 5 °C (Oliveira et al. 2002). In the same way, the viscosity of yogurts made with high SCC milk increased during storage whereas no evolution was observed for yogurts made with low SCC milk (Fernandes et al. 2006). It is worth noting that only a few problems have been associated with cows high SCC yogurt (Fernandes et al. 2006; Oliveira et al. 2002; Rogers and Mitchell 1994; Schott 1967) whereas ewes high SCC yogurts have been associated with a bitter and piquant taste (Vivar-Quintana et al. 2006). Beside the impact on taste and shelflife,

no correlation between the appearance and aroma and SCC level has been observed (Oliveira et al. 2002).

2.2.3 Impact on cheeses

Cheese production represents a major use of milk especially regarding ewes and goats milk which are mostly dedicated to cheese production. Studies on the impact of SCC on the cheesemaking process or quality are however scarce and the impact of high SCC on cheese properties has not yet been clearly determined. The impact appears to vary among cheese types but in summary, the use of high SCC milk seems to impair coagulation properties, to increase moisture content in most cows cheeses and induce off-flavor development. The impact of high SCC on the cheesemaking process and cheese properties are discussed in the following sections and summarized in Table 3.

Coagulation properties Although some studies have reported no effect of high SCC (>500,000 cells·mL^{-1}) milk on rennet coagulation properties, in most studies, a high SCC is associated with a significant increase in rennet clotting time, with a lower curd firmness and a slower rate of curd firming, which can lead to poor yield and low quality of the resultant cheese. There is a high positive correlation between pH and coagulation properties (Raynal-Ljutovac et al. 2007). The rise in pH observed in high SCC milk can be partly responsible for the coagulating problems observed with mastitic milk.

Of note, casein concentration in milk affects the renneting behaviour of milk. Peptides which are liberated from caseins during the proteolysis of milk seem to have a negative effect on the clotting time and the curd firmness. For example, proteose peptones, casein derivates, have been shown to be involved in issues with the curd formation. Casein proteolysis and the subsequent liberation of peptides may explain part of the rennet coagulation issues. Moreover, starter activity and growth are reduced in mastitic milk. High SCC (>400,000 cells·mL^{-1}) milk prolonged the fermentation process by as much as 2 to 4 h. Acid producing microorganisms (i.e., starter LAB) are more affected by the antimicrobial components produced during mastitis than aroma-producing microorganisms (nonstarter LAB and ripening flora). The effect of high SCC might nevertheless depend on the LAB species considered as the acidifying activity of *Streptococcus thermophilus* is increased while that of *Lactobacillus acidophilus* is inhibited.

From a microbial perspective, the impact of some mastitic pathogens has been clearly shown to negatively affect coagulation. For example, *S. dysgalactiae* has such a huge impact on milk composition that no curd has been produced from infected milk in experimental cheesemaking. *S. dysgalactiae* infection results in reduced yields in both cheese and yogurt production. *S. dysgalactiae* directly generates (through its enzymatic activities) or activates the formation of short-chain peptides, which interfere with the coagulation process. Clotting time has also been shown to be significantly higher in *S. aureus* mastitic milk than in normal milk and curd firmness slightly decreased. Altogether these data show that most mastitis pathogens directly or indirectly affect milk coagulation by impacting either rennet or starter activity.

Table 3 Effect of high SCC milk on cheese characteristics

Ruminant	Type of cheese	Effect of mastitis	Reference
Cow	Swiss-type cheese	Protein content ↓ and pH – Fat content ↑ and protein whey ↑	Cooney et al. (2000)
	Cheddar	Protein content ↓, fat content ↓, casein content ↓, cheese yield ↓, texture ↓, and flavor ↓ Moisture ↑	Ali et al. (1980), Auldist et al. (1996), Barbano et al. (1991), Donelly and Barry (1983), Grandison and Ford (1986), Leavitt et al. (1982), Marino et al. (2005), Mitchell et al. (1986), Munro et al. (1984), Politis and Ng-Kwai-Hang (1988a), Rogers and Mitchell (1994), Verdi et al. (1987)
	Cottage cheese	Protein content ↓ and cheese yield ↓ Moisture ↑	Vianna et al. (2008)
	Pratto cheese	Protein content – and fat content – Moisture ↑, clotting time ↑ and pH ↑ Texture ↓ and flavor ↓	Mazal et al. (2007), Vianna et al. (2008)
	Mozzarella cheese	Yield – and physical parameters – Protein content ↓ and casein content ↓ Free fatty acids ↑	Andreatta et al. (2007)
Ewe	Zamorano-type cheese	Yield –, moisture –, and firmness – Hardness, cohesiveness ↓, and flavor ↓ Grainy ↑, crumbly, adhesiveness ↑, guminess, and chewiness	Revilla et al. (2007, 2009)
	Manchego type	Total protein ↓, casein ↓, and fat content ↓ Free fatty acid ↑, moisture ↑, clotting time ↑, rancidity ↑, crumbly, and mealy texture ↑	Jaeggi et al. (2003)
	Canestrato pugliese cheese	Moisture ↑ Fat content ↓ Proteose peptone –	Albenzio et al. (2004)
Goat	Soft ripened goat cheese	–	Morgan and Gaspard (1999), Zeng and Escobar (1996)

Arrows indicate an increase (↑) or a decrease (↓); a dash (–) indicates that no variation was observed

By affecting the renneting step, high SCC reduces the production yields of some cheeses, e.g., cottage cheese, cheddar, whereas it does not affect the yield of Prato cheese, mozzarella, or zamorano.

On the contrary, concerning goats cheese yield, studies have clearly shown that high SCC has no impact.

Moisture content Moisture content is generally increased in cows cheese made from high SCC milk. This was observed in dramatically different cheese types including cheddar, cottage, and Prato cheeses. The mechanism by which SCC influences cheese moisture has not yet been clearly determined. Goats cheese made with high

electrical conductivity milk, which corresponds to cheese made with mastitic milk, is also associated with higher moisture content in comparison to cheese made with milk from healthy goats (Romero et al. 2010).

Moisture content of fresh ewes milk increases with SCC but the difference does not seem to be significant after 3 months of ripening between cheeses made with low or high SCC.

Impact of mastitis on cheese composition Higher levels of proteolysis have been observed in cheeses made with high SCC regardless the cheese type. This has been observed in Swiss-type cheeses, cottage cheese, cheddar, Prato cheese, and mozzarella. Mastitic milk influences primary proteolysis of caseins which results in the increased proteolysis of β-caseins during the early stages of cheese ripening. Moreover, it induces an accelerated breakdown of α_{S1}-casein. As a consequence, protein losses in the whey is increased.

Fat losses in the whey also increase whereas fat content in cheese decreases except in Prato cheese.

Mastitis can induce the production off-flavors and texture defects The use of high SCC milk also negatively impacts on flavor, body and texture grades. For example, cheddar cheeses made with high SCC milk have been described as having a "lipolytic" or "oxidized" flavor and the milk used to prepare these cheeses had a higher concentration of free fatty acids, which can induce rancidity in dairy products (Auldist et al. 1996). Flavor or texture defects have also been reported for mozzarella, Prato or ewes cheeses made with high SCC milk. This was explained by higher levels of lipolysis or proteolysis in the cheese (Andreatta et al. 2007).

Sensory characterictics of goats soft cheeses do not seem to be affected by high SCC (Chen et al. 2010; Morgan and Gaspard 1999; Zeng and Escobar 1996). Technological factors, notably the short ripening time in comparison with semi-hard cows or ewes cheese, may explain the minor influence of SCC on texture and flavors of goats soft cheeses (Raynal-Ljutovac et al. 2007). Indeed, it has been shown that high SCC (1,000,000 cells·mL^{-1}<SCC<1,500,000 cells·mL^{-1}) in goats milk also affects the sensory quality of aged cheeses (Chen et al. 2010).

Published literature has clearly shown that mastitis is a major problem in the transformation of milk mainly because of a lower acceptance by the consumer due to flavor and texture defects. Moreover, dairy products made from mastitic milk seem to have a shorter storage time compared with dairy products made from normal milk and always develop off-flavors especially in ewes and cows milk cheeses.

In most of the studies presented here concerning both milk and dairy products, the pathogen responsible for mastitis was not identified. As described in the first part, reported data regarding many of the milk components are conflicting. This could be explained by the very different impact of the causative microbial agents on milk and on the mammary gland immune response and so on the milk composition. Except for cheddar, studies on the impact of mastitis on cheeses are scarce and the impact of the different causative agents should be tested. We will indeed see hereafter that the

impacts of mastitis on the mammary gland and subsequently on milk changes vary with the causative agents.

3 How do bacteria induce various milk changes?

Changes in milk composition due to mastitis can be explained by the physical damage of the mammary tissue, which reduces the synthesis and secretory function of the mammary gland (Kitchen 1981). Gene expression profile of mammary cells is modified in incidences of mastitis. Notably, genes encoding antimicrobial proteins are induced. Mastitis also induces a rise in endothelium permeability which increases the passage of components from the blood to the milk and the activity of endogenous and exogenous enzymes that destroy some milk components. Among the causative agents of cows mastitis, *S. aureus* is the most prevalent bacterium involved in contagious mastitis, with *E. coli* and *S. uberis* being the main environmental pathogens (Chaneton et al. 2008). These species are also the most studied among bacteria involved in mastitis. In small ruminants, *S. aureus* is the main agent implied in clinical mastitis and CNS in subclinical mastitis (Bergonier et al. 2003).

The aim of this part is to present up to date knowledge about the role played by the main bacterial species implicated in mastitis and how they affect the composition of milk and dairy products. In light of these data, it is possible to compare how these mastitis causative agents differentially affect milk quality.

3.1 Direct impact of bacteria on milk composition?

E coli appear to be capable of degrading caseins in vitro (Haddadi et al. 2005). Casein proteolysis is greater in an *E. coli* experimental infection compared with LPS induced mastitis (Moussaoui et al. 2002; Moussaoui et al. 2004). This observation seems to be related to a direct or indirect role of *E. coli* in casein proteolysis. The in vitro activity of four proteases of the *E. coli* strain P4 on caseins was very low. To explain caseinolysis, the authors hypothesized that these proteases are produced at a higher level in vivo or that they posess a higher caseinolytic activity. Alternatively, *E. coli* might have an indirect role on caseinolysis by increasing the secretion of endogenous proteases or factors acting on the maturation of somatic cells (Dufour et al. 2009). The mechanisms involved in caseinolysis observed during *E. coli* mastitis remain to be further determined (Fig. 1).

S. aureus also produces proteases (serine protease, cysteine proteases, metalloprotease) that are capable of degrading caseins (Karlsson and Arvidson 2002). For example, SplB and SplC can degrade casein (Reed et al. 2001). CNS also produce proteases (Devriese et al. 1985; Miedzobrodzki et al. 1989; Zhang and Maddox 2000). But as for *E. coli,* no proof has so far clearly demonstrated that *S. aureus* or CNS produce in vivo enzymes implied in caseinolysis.

3.2 Impact of the immune response on milk changes

Humoral and cellular defenses of the mammary gland in response to infection affect milk composition or milk product quality.

3.2.1 Humoral defenses

The complement system, lactoferrin, transferrin, lysosyme, lactoperoxidase-thiocyanate-peroxide-system, xanthine oxydase, antibodies are components of the humoral defenses (Rainard and Riollet 2006). They are present in normal milk but increase during mastitis (Carlsson et al. 1989; Hiss et al. 2008; Schmedt Auf Der Gunne et al. 2002; Seifu et al. 2005). Some of these immune response components can be the source of problems related to milk product manufacturing. For example, the presence of immunoglobulins in milk induces the formation of agglutins, which can inhibit acid production in raw and pasteurized whole or skim milk. This has been shown to cause problems in the manufacture of cottage cheese (Salih and Sandine 1984) but not in the manufacture of hard cheeses. During cottage cheese manufacture, lactic streptococcal agglutinins can cause the starter bacteria to separate from the milk components or result in the uneven distribution of lactic acid production in the milk (Emmons et al. 1963; Emmons et al. 1966; Lucas 1962; Salih and Sandine 1980). On the contrary, during the manufacture of hard cheese, the rennet coagulum immobilizes the bacteria in the curd and prevents their migration to the surface. However, the selection of strains which are resistant to agglutination for the manufacture of cottage cheese can overcome this problem.

The lactoperoxidase system can also inhibit the activity of starter cultures. But, as for agglutins, a screening of starter bacteria for resistance to the lactoperoxidase system can overcome the problem (Seifu et al. 2003). Nevertheless, this can change yogurt properties due to alterations in the formation of the gel network (Ozer et al. 2003) and the texture which is softer and smoother in yogurt made with milk with high lactoperoxidase level (Hirano et al. 1998). It can also induce the oxidation of proteins in milk (Ostdal et al. 2000).

Contrary to agglutins and lactoperoxidase, lysosyme does not seem to induce problems in the manufacture of milk products. Observations of lactic acid bacteria (LAB) challenged by lysozyme during the production of Grana Padano (Grazia et al. 1984; Neviani et al. 1996; Ottogalli et al. 1983) or Gouda (Bester and Lombard 1990) cheeses have shown that the functionality of the LAB population is not impeded. Most of *Lactobacillus* sp. and *S. thermophilus* possess a natural resistance to lysozyme or have developed a resistance by repeated exposure (Neviani et al. 1996; Ottogalli et al. 1983). Trials with goats milk have also demonstrated that the presence of lysosyme throughout the cheesemaking process is not detrimental to production (Scharfen et al. 2007).

Methods used to measure the concentration or activity of some milk components (e.g., lactoferrin and lactoperoxydase system) are more or less sensitive, especially when comparing ruminant species. For example, ELISA kits used for the measurement of bovine lactoferrin do not work on goats milk (Hodgkinson et al. 2008) and false-positive results have often been obtained not only for lactoferrin but also for the lactoperoxidase system (Raynal-Ljutovac et al. 2005). To overcome this problem, techniques used to measure lactoferrin have been adapted at least to goats milk (Chen et al. 2004; Hodgkinson et al. 2008).

Few data are available regarding the impact of each pathogen on the increase in the components of humoral defenses. Among the three main mastitis agents, *S. uberis*, *E. coli*, and *S. aureus*, all of which induce an increase in the lactoferrin

content in milk, *S. uberis* induces the greatest increase but is also the most resistant to lactoferrin activity (Carlsson et al. 1989). Finally, as reported here, solutions have been found to solve most of the manufacturing troubles encountered with components of humoral defenses.

3.2.2 Cellular defenses

As reported above, the increase in the SCC varies according to the pathogen and/or to the mastitis type and symptoms. Besides the variations in the SCC levels in response to pathogens, cytokine profiles can also be different. Several cytokines (IFN-γ, interleukin (IL)-6, IL-10, IL-12, and C5a) are commonly induced by *E. coli*, *S. aureus*, and *S. uberis*, as shown in Table 4. Nevertheless, some differences are observed, notably concerning the time of cytokine induction. For example, in experimentally induced mastitis by *Staphylococcus epidermidis* (CNS) in ewe, a permanent increase in the level of IL-8 (even 10 weeks after infection) and a transient increase in the level of IL-1β have been reported (Winter et al. 2003).

Each cytokine will have consequences on the milk barrier permeability, on the gene expression profile, or on the polymorphonuclear leukocytes (PMN) recruitment. Their implication in the mechanisms of milk modification is further described in the following sections.

The main consequences of the presence of pathogens are the recruitment of leucocytes, notably PMN, the synthesis of antimicrobial peptides or proteins by cells from the mammary gland and the release of cytokines. This will induce consequences on the properties of milk and milk products.

Release of leucocyte proteinases induces casein proteolysis As discussed in previous paragraphs, the presence of a pathogen results in an increase in the SCC, notably in PMN. The level or activity of leucocyte proteases (listed in Table 5) also increases during mastitis (Barbano et al. 1991). The origin of this increase in proteases during mastitis is linked to an increase in PMN and could be explained by two mechanisms: the proteases can be released by vesicules like lysosomes from PMN or caseins or fat globules can be endocytised by PMN with the degradation products being released into the milk after intracellular digestion (Le Roux et al. 2003).

The order in which caseins are degraded by leucocyte proteinases are firstly α_{S1}-casein, followed by β-casein and to a lesser extent κ-casein (Grieve and Kitchen 1985; Napoli et al. 2007) and α_{S2}-casein (Napoli et al. 2007). It has also been shown that α_{S1}-casein breakdown was associated with the presence of proteinases of somatic cells with high SCC (Verdi et al. 1987).

Elastase

Elastase is a serine protease that digests a wide variety of protein substrates (Brink et al. 1956). It lyses bovine β- (Considine et al. 1999) and α_{S1}-caseins (Considine et al. 2000). An increased activity of elastase is detected during mastitis in PMN (Haddadi et al. 2006; Prin-Mathieu et al. 2002). Peptides present in milk are linked to elastase activity (Wedholm et al. 2008) and certain fragments in high SCC milk have been ascribed to elastase activity (Moussaoui et al. 2003; Nabhan et al. 2004). Elastase contributes to increased proteolysis in

Table 4 Inflammatory mediators' variation during *Staphylococcus aureus, Escherichia coli*, and *Streptococcus uberis* mastitis

Pathogen	Inflammatory mediators	Reference
E. coli	IFN-γ	Bannerman (2009), Lee et al. (2006)
	IL-1β ↑	Bannerman et al. (2004b), Riollet et al. (2000), Shuster et al. (1995, 1997, 1996)
	IL-6 ↑	Hagiwara et al. (2001), Nakajima et al. (1997), Ohtsuka et al. (2001), Shuster et al. (1997)
	IL-8 ↑	Bannerman et al. (2004b), Lee et al. (2003), Riollet et al. (2000), Vangroenweghe et al. (2005, 2004)
	IL-10 ↑	Bannerman et al. (2004b)
	IL-12 ↑	Lee et al. (2006)
	TGF-α ↑	Chockalingam et al. (2005, Sheffield 1997)
	TGF-β ↑	Chockalingam et al. (2005)
	TNF-α ↑	Bannerman et al. (2004b), Lee et al. (2003), Riollet et al. (2000), Shuster et al. (1995, 1997, 1996)
	LBP ↑	Bannerman et al. (2004b)
	C5a ↑	Bannerman et al. (2004b), Riollet et al. (2000), Shuster et al. (1997), Vangroenweghe et al. (2004)
S. aureus	IFN-γ ↑	Bannerman (2009), Riollet et al. (2000)
	IL-1β ?	Bannerman (2009), Griesbeck-Zilch et al. (2008), Riollet et al. (2000)
	IL-6 ↑	Griesbeck-Zilch et al. (2008), Hagiwara et al. (2001), Nakajima et al. (1997), Ohtsuka et al. (2001), Shuster et al. (1997)
	IL-8 ?	(Bannerman 2009; Griesbeck-Zilch et al. 2008; Lee et al. 2006; Riollet et al. 2000; Tao and Mallard 2007)
	IL-10 ↑	Bannerman et al. (2004b)
	IL-12 ↑	Alluwaimi et al. (2003), Lee et al. (2006)
	TGF-α ↑	Bannerman et al. (2006), Sheffield (1997)
	TGF-β ↑	Bannerman et al. (2006)
	TNF-α protein –	Bannerman et al. (2004a), Riollet et al. (2000)
	TNF-α RNA ↑	Bannerman et al. (2004a), Griesbeck-Zilch et al. (2008), Lutzow et al. (2008)
	LBP ↑	Bannerman et al. (2004a)
	C5a ↑	Bannerman et al. (2004a), Riollet et al. (2000)
	IL-15 ↑	Tao and Mallard (2007)
	IL-17 ↑	Tao and Mallard (2007)
	IL-18 ↑	Tao and Mallard (2007)
S. uberis	IFN-γ ↑	Bannerman (2009), Swanson et al. (2009)
	IL-1β ↑	Bannerman et al. (2004a), Rambeaud et al. (2003), Swanson et al. (2009)
	IL-6 ↑	Swanson et al. (2009)
	IL-8 ?	Bannerman et al. (2004a), Rambeaud et al. (2003), Swanson et al. (2009)
	IL-10 ↑	Bannerman et al. (2004a), Swanson et al. (2009)
	IL-12 ↑	Bannerman et al. (2004a)
	TNF-α ↑	Bannerman et al. (2004a), Rambeaud et al. (2003), Swanson et al. (2009)
	C5a ↑	Bannerman et al. (2004a)

Arrows indicate an increase (↑) or a decrease (↓); a question mark indicates that the relationship is suspected but not clearly demonstrated; a dash (–) indicates that no variation was observed

Table 5 List of endogenous proteases involved in casein lysis

Protease	Origin	Type	Substrate	Reference
Plasmin	Milk–blood during mastitis?	Serine protease	β-, α_{S2}-, and α_{S1}-caseins	Bastian and Brown (1996), Fox and McSweeney (1996)
Cathepsin D	Leucocyte proteinase	Aspartyl protease	α_{S1}- and β-caseins (κ- and α_{S2}-caseins)	Grieve and Kitchen (1985), Napoli et al. (2007)
Cathepsin G	Leucocyte proteinase	Neutral serine protease	β- and α_{S1}-caseins (κ-and α_{S2}-caseins)	Considine et al. (2002a)
Cathepsin B	Leucocyte proteinase	Cysteine protease	β- and α_{S1}-caseins (κ- and α_{S2}-caseins)	Considine et al. (2004)
Elastase	Leucocyte proteinase	Serine protease	β- and α_{S1}-caseins (κ-and α_{S2}-caseins)	Considine et al. (1999, 2000)

milk with an SCC above 500,000 cells·mL^{-1} (Wedholm et al. 2008). It also influences the rheology of rennet gels and may influence the coagulation properties of milk (Considine et al. 2002b), which could partly explain changes observed in coagulation of high SCC milk.

Cathepsins D, G, and B

Cathepsin G is a neutral serine proteinase that displays specificity on β- and α_{S1}-caseins (Considine et al. 2002a). Therefore, it is possible that indigenous cathepsin G in milk may be present at significant levels to impact on the proteolysis of milk proteins.

Cathepsin B and D have been shown to be involved in the proteolysis of high SCC milk (Wedholm et al. 2008). Cathepsin B is a cysteine proteinase that can partially resist heat treatments such as conventional pasteurization. It was shown to be capable of cleaveing β- and α_{S1}-caseins (Considine et al. 2004) and hence is involved in milk proteolysis. A correlation between cysteine proteinase and SCC has previously been shown (Larsen et al. 2004; O'Driscoll et al. 1999; Somers et al. 2003; Suzuki and Katoh 1990). Cathepsin B also seems to be involved in proteolysis during cheddar cheese ripening (Marino et al. 2005) and peptides derived from its activity have been detected in high SCC milk (Wedholm et al. 2008). Finally, similar to elastase, cathepsin B has been shown to affect the rheology of rennet gels and to influence the coagulation properties of milk (Considine et al. 2002b).

Cathepsin D is a lysosomal enzyme (Kelly et al. 2006) and is regarded as a macrophage proteinase. It hydrolyses the four types of caseins and is capable of catalysing milk coagulation (Kaminogawa et al. 1980; Larsen et al. 1996; McSweeney et al. 1995), which may explain the presence of clots in mastitic milk (Kelly et al. 2006). Its level has been positively correlated with SCC (Larsen et al. 2006; O'Driscoll et al. 1999; Somers et al. 2003). Procathepsin D, the proenzyme of cathepsin D, and cathepsin appear to have remained partially active after commercial pasteurization processes (Larsen et al. 2000). Increasing evidence has indicated a role for this enzyme in proteolysis in cheese during ripening (Marino et al. 2005), especially in cheese where rennet activity is low, such as Swiss

cheese, Quarg, and Feta (Hurley et al. 2000; Larsen et al. 2000). The activity of cathepsin D is higher in milk with a high SCC than in milk with a low SCC and contributes to the proteolysis observed in *S. uberis* mastitic milk (Larsen et al. 2004). Moreover, peptides derived from cathepsin D activity have been identified in high SCC milk (Wedholm et al. 2008) and extensive hydrolysis of α_{S1}-casein in high SCC milk seems to be related to cathepsin D activity (Somers et al. 2003). Link between pathogen and PMN proteases?

No data is available regarding the role of each pathogenic bacterium on leucocyte protease release or activity. This has only been studied in *E. coli* mastitis, where the level or activity of endogenous proteases increases and may explain caseinolysis (Moussaoui et al. 2002). But as shown earlier, the increase in the SCC varies dramatically depending on the pathogen. Thus, it could be hypothetized that the release of proteases increases with SCC and may vary depending on the pathogen. Moreover the activity of elastase and cathepsin G, the predominant proteases produced by somatic cells during mastitis (Azzara and Dimick 1985b) is promoted by pro-inflammatory cytokines at a transcriptional level (Haddadi et al. 2006; Le Roux et al. 2003): IL-1 and IL-8 for collagenase IV (Opdenakker et al. 2001) and IL-6, IL-2, tumor necrosis factor alpha (TNF-α) for elastase, or cathepsin G (Bank and Ansorge 2001). The cytokine profile appears to be pathogen specific which suggests that it may differentially impact on protease gene transcription.

The mechanism involved in how PMN proteases can lyse caseins has yet to be determined. Moreover up to now, no study has compared the impact of pathogen species on this phenomenon. The specific increase in SCC and cytokine specific profiles suggest that it may be different depending on the pathogen but this still has to be demonstrated.

Release of other enzymes Several indigenous enzymes increase during inflammation, notably there is an exponential increase in enzymes originating from phagocytes (*N-acetyl*-D-glucosaminidase, beta-glucuronidase, and catalase) (Pyörälä 2003). They are released into milk from neutrophils during phagocytosis and cell lysis, and to some degree, damage epithelial cells (Kitchen et al. 1984).

It could be hypothesized that phagocytes also release lipases. A high level of lipolysis is actually associated with a high level of PMN but the mechanism by which PMN affect fat lipolysis remains to be determined (Gargouri et al. 2008). Milk SCC are suspected to be involved in the lipolysis of the fat globule triglycerides and thus in off-flavor development due to free fatty acids (Azzara and Dimick 1985a; Gargouri et al. 2008; Ma et al. 2000; Murphy et al. 1989; Santos et al. 2003). Moreover, lipases can resist pasteurization (Ma et al. 2000; Shipe and Senyk 1981) and high SCC pasteurized dairy products are thus more likely to develop off-flavors than low SCC ones.

3.3 Increased endothelial permeability

Mastitis is characterized by an increase in milk barrier permeability. In the presence of a pathogen, macrophages release IL-8 and TNF-α, which results in PMN recruitment from

blood to milk (Watanabe et al. 2008; Lehtolainen et al. 2004; Shuster et al. 1996; Watanabe et al. 2000). This requires an increase in endothelial permeability, which induces not only the transfer of PMN from blood to milk but also other blood components such as bovine serum albumin (BSA). Lipolysis in milk can be explained by the disturbance of the milk–blood barrier which allows the transfer of esterases from blood to mastitic milk (Hettinga et al. 2009). Another example of increased permeability is found in transferrin (an iron transporter), which is not produced in the mammary gland of ruminant (Sanchez et al. 1992) but comes from blood serum (Ollivier-Bousquet 1998) and rapidly increases in *E. coli* mastitis (Rainard and Caffin 1983) .

Indigenous proteases can degrade the extracellular matrix and are involved in the impairment of the milk barrier permeability. Elastase and cathepsin G degrade fibronectin, thrombospondin, and von Willerbrand factor (Bonnefoy and Legrand 2000). BSA concentration varies significantly according to the pathogen (Coulon et al. 2002). If the BSA content is considered as a marker of the impairment of the blood barrier, it could then be concluded that the permeability of the blood barrier increases by a different mechanism depending on the pathogen. BSA content in *E. coli* mastitic milk is significantly higher than in *S. aureus* mastitic milk, which is itself significantly higher than in *S. uberis* mastitic milk (Coulon et al. 2002).

3.4 Inhibition of milk component production

Mastitis is characterized by a decrease of and changes in milk components, which is illustrated by a decrease in lactose. Loss in milk yield can be attributed to the loss of mammary epithelial cells by necrosis or apoptosis during *E. coli*, *S. aureus*, or *S. uberis* mastitis (Bayles et al. 1998; Long et al. 2001; Singh et al. 2006) or either by downregulation of milk genes.

Most of the pathogens involved in mastitis induce cellular apoptosis during infections (Weinrauch and Zychlinsky 1999). Experimentally induced mastites with *E. coli* (Long et al. 2001), *S. uberis* (Swanson et al. 2009) and *S. agalactiae* (Sheffield 1997) promote apoptosis and cell proliferation. The increased apoptosis can be explained by the induction of pro-apoptotic cytokines such as TNF-α (Mebmer et al. 1999) or IL-1. Increased cell proliferation may be part of the self-cure after mastitis. Besides, *S. aureus* (Bayles et al. 1998) and *S. dysgalactiae* (Almeida and Oliver 1995) can be internalized by epithelial or endothelial cells and can thus induce apoptosis of bovine mammary epithelial cells.

E. coli and *S. aureus* have been shown to induce necrosis of the mammary epithelium, especially during severe mastitis (Zhao and Lacasse 2008). *E. coli* produces proteinases that contribute to the degradation of extracellular matrices (Haddadi et al. 2005; Haddadi et al. 2006). Total level of gelatinases (notably matrix metalloproteinases, MMP-2, and MMP-9), which destroy basal membrane and interstitial tissue proteins was actually 300-fold higher in milk from cows with *E. coli* mastitis than in milk from healthy cows and they injured the basal membrane and interstitial tissues (Raulo et al. 2002). *S. aureus* infected quarters present less alveolar luminal area and more stromal area than uninfected quarters and thus exhibited less secretory and synthetic ability (Sordillo et al. 1989).

Downregulation of genes implied in milk component synthesis could be explained by a direct role of pathogens or by an increase in cytokines. Some

cytokines can actually directly induce suppression of some protein secretion. For example, injection of IL-8 induced a decrease in α-, β-caseins suggesting that IL-8 is involved in suppressing the secretion of milk-specific proteins (Watanabe et al. 2008). TNF-α has an impact on mammary epithelial cells (Ip et al. 1992; Rejman et al. 1993). Injection of recombinant TNF-α induced a decrease in milk production, in protein content of milk and an increase in fat content (Kushibiki et al. 2003). TNF-α was also shown to inhibit casein secretion by bovine cells in vitro (Hurley et al. 1994) and to induce a decrease in α-casein, β-casein, α-lactalbumin, and β-lactoglobulin concentrations in milk (Watanabe et al. 2000). The presence of TNF-α in the mammary gland induced an increase in lactoferrin concentration (Watanabe et al. 2000) although it has been shown that TNF-α does not directly induce lactoferin production (Hurley et al. 1994): effects of some cytokines or hormones can indeed be mediated by TNF-α (Cerami 1992), which could explain the increase of lactoferrin in the mammary gland after TNF-α injection.

E. coli induced a complete reprogramming of the metabolism of the mammary gland during infection (Gunther et al. 2009): within 24 h, *E. coli* mastitis induced a downregulation of "lactation" genes and an upregulation of "defense" genes via remethylation of some promoter areas such as the α_{S1}-casein promoter, which results in a complete shut-down of casein synthesis (Vanselow et al. 2006). On the contrary, subclinical *S. aureus* mastitis is characterized by a sustained casein synthesis and no remethylation of the genes remethylized during coliform mastitis (Vanselow et al. 2006). In this way, transcription of genes encoding β-casein is not altered after *S. aureus* infusion and normal milk protein gene expression is maintained despite remodeling of the mammary gland tissue (Lutzow et al. 2008).

3.5 Plasmin increase during mastitis

Plasmin is a serine protease that plays a role in several physiological processes in mammals. For example, it is a key enzyme in fibrinolysis or degrades various extracellular matrix components. Its inactive precursor is plasminogen, whose conversion to plasmin is activated by proteolysis and regulated by activators and inhibitors (Lahteenmaki et al. 2001). Plasmin is the main proteinase in bovine milk. It hydrolyses β- and α_{S2}-caseins, and, more slowly, α_{S1}- and γ-caseins, proteose peptones, and possibly λ-casein. It has a pH optimum around 7.5 (Bastian and Brown 1996; Fox and McSweeney 1996). In mastitis, increased SCC has been correlated with an increased plasmin activity (Albenzio et al. 2005; Kalit et al. 2002; Politis et al. 1989a; Saeman et al. 1988; Somers et al. 2003) which can be explained by the conversion of plasminogen to plasmin (Verdi and Barbano 1991) and or by plasmin transport from blood (Politis et al. 1989b). Conversion of plasminogen to plasmin can be induced by activators, whose levels increase due to the increase in epithelial barrier permability (Dano et al. 1985) and to their synthesis by PMN (Moir et al. 2001; Politis et al. 1991). Other physiological components (epidermal growth factor, insulin-like growth factor I, and prostaglandin E2) and some PMN proteases (elastase and cathepsin G) increase the activity of plasminogen activators (Le Roux et al. 2003).

Regardless of the bacterial species, the plasmin activity in milk from the infected glands actually increased by ~2-fold compared with uninfected quarters (Leitner et al. 2006). Moreover, milk plasmin activity appears to remain higher than before

infection even after elimination of the infection suggesting that the detrimental effect of mastitis on milk quality persists after elimination of the infection and low SCC being achieved (Saeman et al. 1988).

It has been shown that bacteria regulate directly or indirectly plasmin activity. *Streptococci* produce streptokinase that forms a complex with plasminogen and plasmin and thus activates plasminogen (Lahteenmaki et al. 2001). *S. uberis* synthetises a streptokinase-type plasminogen activator, PauA which can activate bovine plasminogen (Rosey et al. 1999). Some species of streptococci posess a plasmin receptor (GAPDH and enolase) which can immobilize plasmin and so activates plasminogen (Berge and Sjobring 1993; Lincoln and Leigh 1998; Pancholi and Fischetti 1998). *S. aureus* can enhance the production of urokinase, a plasminogen activator in bovine epithelial cells. So, *S. aureus* contributes directly to induce an increase in plasmin concentration (Zavizion et al. 1997). Finally, *S. aureus* also plays a role in plasminogen activation through the synthesis of plasminogen receptors, which immobilize plasmin on the cell wall and so indirectly activates plasminogen (Kuusela and Saksela 1990; Kuusela et al. 1992). *E. coli* posesses a filamentous surface appendage fimbriae and flagella that form a class of plasminogen receptor. The flagellar filaments of *E. coli* bind plasminogen and induce its activation by tissue type plasminogen activator (Lahteenmaki et al. 2001).

Plasmin influences the quality of dairy products (Bastian and Brown 1996), notably by hydrolyzing caseins. This in turn influences milk coagulation properties, cheese yield (McSweeney et al. 1994) and cheese ripening (O'Farell et al. 2002). Moreover, plasmin is heat stable with large amounts surviving pasteurization. Even after UHT treatment,

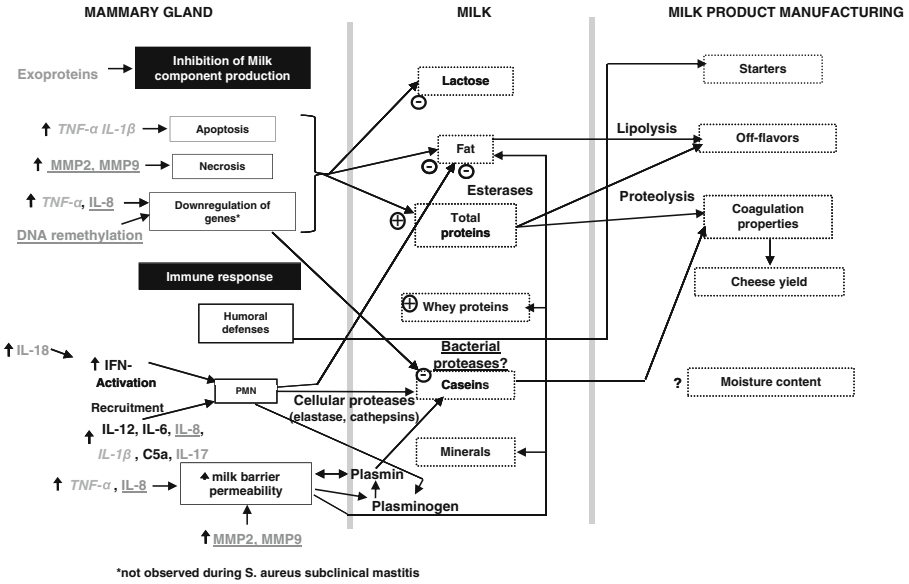

Fig. 3 Schematic view of the potential links between the impact of the three major mastitis pathogens on the mammary gland and the milk and milk products quality. Factors in *grey underlined*, indicate effects reported in the literature for *Escherichia coli;* in *grey*, effects reported for *Staphylococcus aureus*; in italic, effects reported for both *Streptococcus uberis* and *E. coli*; in *black underlined*, both *S. aureus* and *E. coli*; in *black*, *S. uberis*, *S. aureus*, and *E. coli*. *Minus* and *plus symbols* indicate an inhibition and an activation, respectively. *Question marks* indicate that the relationship is suspected but not clearly demonstrated

30% to 40% of plasmin activity can be detected in the milk (Alichanidis et al. 1986). Proteolysis of β-casein by plasmin has been shown to play a role in cheese flavor enhancement (Farkye and Landkammer 1992; Farkye and Fox 1992). Plasmin activity changes according to the pH and so varies from one dairy product to another. For example, it slightly increases during cheddar (Barrett et al. 1999) or Danbo (Benfeldt et al. 1997) cheese ripening and decreases during Saint-Paulin cheese ripening (Bastian et al. 1991). It appears that proteolysis due to plasmin produces off-flavors earlier than lipolysis due to lipase in pasteurized milk with high SCC (Ma et al. 2000).

4 Conclusions

Mastitic milk costs amount to billion dollar losses for dairy factories worldwide (Napoli et al. 2007). In most studies, the increase in SCC is considered a marker of mastitic milk. Numerous studies have reported on the impact of an increased SCC on milk and subsequent changes in most parameters related to the biochemical aspects and cheese processing. These modifications in the milk composition have a variable impact on the quality of dairy products. In general, an increase in SCC has a negative influence on cheese processing and in pasteurized milk grading during storage. The scientific literature is quite abundant regarding these observed impacts but nevertheless, the reported observations sometimes appear contradictory. Besides, more and more is known regarding the impact of various pathogenic bacteria on the mammary gland physiology upon intramammary infection. Some recent advances in the bacteria–host interactions have revealed that the udder response to the infection might differ from one pathogen to another. This review shows that some intriguing observations in the field of SCC and milk modifications could be explained by the specific bacteria–host interactions. It appears that a gap exists between these two scientific fields. An attempt to link these two fields is presented in Fig. 3. In the future, it would be more accurate and would result in clearer conclusions if the phenomenon was studied as a whole, including relationships between the nature of the mastitis causative agents, and the subsequent impacts on udder (including SCC as one parameter among others), milk quality and milk products, especially when subclinical mastitis is considered because such milks are collected, processed and used for human consumption. Identifying the causative pathogens rather than using the increase in SCC so as to detect mastitis may be more relevant, notably in order to determine if the milk can be used and to which extent.

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