



Review article

Cow management modulates gene expression in the mammary gland, a possible epigenetics role

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ABSTRACT

Epigenetics, the study of the change in gene expression that occurs without alteration in DNA sequences, leads to modifications that can be passed on by mitosis. It has been known for many years that cow management during lactation affects milk production. Now it is clear that some factors influence milk production even before the onset of lactation (during the dry period). In the last decade, a greater understanding of the molecular events that occur in the mammary epithelial cells provided an explanation for these changes. Gene expression in the mammary gland shows a temporal–spatial regulation. This is achieved by different regulatory layers of gene expression involving, for example, chromatin condensation and the combinations of several hormones and transcription factors. The goal of this review is to bring together an update of studies on gene expression in the mammary gland, highlighting the possible influence of cow management on epigenetic mechanisms. The impacts of milking frequency, mastitis, photoperiod and heat stress on gene expression and their effects on milk production were discussed. Understanding how the mammary gland responds to external factors will help to design better strategies and technologies to enhance milk production.

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1. Introduction

Conrad Waddington coined the term epigenetics as “the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being” (Waddington, 1942). More recently, Holliday (1990) described epigenetics as the temporal and spatial control of gene activity during development of complex organisms. Finally, Riggs and Porter (1996) modified the concept to the mitotically heritable changes in gene expression that occur without changes in DNA sequences. Some authors emphasize that the term epigenetics implies that the changes are transmitted to the offspring. In this review, we refer to epigenetics as the changes in gene expression that occur without modification in DNA sequences that can be passed along by mitosis.

Milk production is positively correlated with the number of epithelial cells in the mammary alveoli (for a review, see Boutinaud et al. (2004); Sorensen et al. (2006)). That number can be changed by different factors (such as nutrition (Silva et al., 2008), health (Wagner et al., 2009), and heat stress (Collier et al., 2006)). Changes in management that occur during lactation and even before the onset of lactation (dry period) can modify milk production. As discussed in this review, these changes sometimes persist over time after the factors are removed. External factors could trigger an epigenetic signal that could be maintained through mitosis over time. Understanding how the mammary gland responds to external factors will help to design better strategies and technologies to improve milk production.

2. Major genes in milk production

Caseins are a family of related proteins (α S1-CN, β -CN, α S2-CN and κ -CN) codified by four independent genes (CSN1S1, CSN2, CSN1S2 and CSN3) located in a cluster on chromosome 6 (Martin et al., 2002; Caroli et al., 2009) in sheep, goats and cows. The lactoglobulin gene (*LGB*), on the other hand, is encoded on chromosome 11 in the three species. The third main protein is lactalbumin, codified by the gene *LA* assigned to chromosome 3 in sheep (Ghali et al., 1991), while in goats, *LA* has been mapped on chromosome 6, and in cows on chromosome 5 (Hayes and Petit, 1993). Genes that codified for the major milk proteins (caseins, lactoglobulin and lactalbumin) genes are characterized by a high rate of polymorphism and are expressed in a co-dominant fashion.

Genes encoding major milk proteins display a tissue-specific development pattern of expression. This specificity is achieved by the combination of several hormones and transcription factors that set off intracellular signaling networks. These networks, in turn, act on the gene promoter sequences, leading to the expression of mRNA encoding milk protein. Milk protein gene promoters present a complex structure 1 kbp long named CoRes (composite response elements). CoRes are located in the promoter of caseins, *LA*

and *LGB* genes (Vanselow et al., 2006). These clusters contain putative binding sites for several transcription factors, Stat5 binding sites, and palindromic half-sequences of glucocorticoid response elements (Mukhopadhyay et al., 2001).

Milk protein genes are regulated by lactogenic hormones (i.e. prolactin, somatotropin, insulin), through a cascade of events mediated by Jak/Stat5 (Wakao et al., 1994). This intracellular signaling pathway transfers information from the cell membrane receptor to the nucleus. Once the lactogenic hormone binds to the membrane receptor, two Jak molecules become phosphorylated and subsequently phosphorylate Stat5. Then, the Stat5 factor transfers to the nucleus to bind a conserved DNA sequence motif, named GAS (vinterferon-activating sequence), at the promoter CoRes. This mechanism is modulated by the suppressor of cytokine signaling 3 (SOCS3). The regulation follows a negative feedback fashion: activated Stat5 stimulate the transcription of gene SOCS3, then SOCS3 proteins inhibit Jak, and as a result the pathway is turned off (Cooney, 2002) (see Fig. 1). If SOCS3 increases, as we will see later on, the expressions of milk proteins decrease.

Two isoforms of Stat5 have been described: Stat5A and Stat5B, both with a similarity of 96%; however, only Stat5A is mandatory for the continued production of milk (Liu et al., 1997). In mouse mammary glands, a total of approximately 8800 Stat5 were detected. In lactating animals, Kang et al. (2014) found that genes bound by Stat5 expressed specifically in mammary epithelium are highly activated during pregnancy. To study how gene milk protein responses to different concentrations of Stat5, Yamaji et al. (2013) generated mice carrying different combinations of Stat5A and Stat5B alleles. These authors observed that each combination resulted in different Stat5 levels. When Stat5 was reduced by ~70%, it was associated with a decrease of ~50% in CSN1S1, CSN2, CSN1S2 and CSN3 gene expression; when Stat5 was reduced by ~90%, the gene expression of caseins was reduced by ~98%. This showed that Stat5 concentration influences the expression of milk protein genes.

Both Stat5a and Stat5b, recognized the GAS site (Liu et al., 1995) at the CoRes promoter. There is a cross talk between Stat5 and glucocorticoid receptors (GR), thus explaining the synergic effect observed by prolactin and glucocorticoids in mammary gland cells (Lechner et al., 1997; Wyszomierski et al., 1999). On the other hand, progesterone inhibits lactation by interfering with prolactin receptor/Stat5 signaling and by blocking Stat5 to bind to response elements as progesterone receptors interact to GR half sites (Buser et al., 2007, 2011).

3. Gene expression at lactation

Methylation of CpG, the addition of the methyl group to cytosine, is associated with changes in gene expression patterns. In some CpG islands, monoallelic methylations are associated with imprinted mammalian genes and genes on the inactive X chromosome. Two different mechanisms can

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