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Review article

Recent advances on the circadian gene *PER2* and metabolic rhythm of lactation of mammary gland

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ABSTRACT

Due to regulation by circadian rhythm, the lactation of the mammary gland has rhythmicity. As one of prominent members of period protein family which regulates biological rhythms, PER2 plays an important role in developing the milk duct and maintaining the polarity and the morphology of the mammary epithelium; at the same time, it is also closely related with the metabolism of milk protein and milk fat. This paper summarized recent researches on *PER2* gene and related researches on mammary gland development and metabolism to provide some information for the studies of the theory and technology on physiological functions of the mammary gland and milk quality control.

1. Introduction

As one of prominent nutrition resources for human, dairy product, which is easy to digest, provides essential fatty acids, fat soluble vitamins, phospholipid classes, and a variety of essential amino acids (Jachik, 2004). Undoubtedly, the quality of dairy products mostly depends on the quality of raw milk. Thus, basic theory studies on raw milk quality control are conducive to promoting the depth of theoretical research of lactational metabolism and also to providing some new technical ideas for superior dairy production (Wang, 2012). Mammary gland is an active metabolic tissue which secretes raw milk and relates to the metabolism of milk protein, milk fat and lactose. Many factors regulate the lactational metabolism of the mammary gland. For example, estrogen, progesterone and prolactin directly or indirectly act on mammary gland development and metabolism (Neville et al., 2002); the expression patterns of liver genes including *PC*, *CoA*, *CPT1A*, and *ASCL1* are related to milk performance during early lactation (Weber et al., 2013); arginine can promote the casein genes expression of mammary epithelium through transcriptional activator mechanism (Wang et al., 2014); the membrane composition of bovine mammary epithelial cells regulates the size of milk lipid droplets and this process is not affected by cellular triglyceride content (Cohen et al., 2015). Along with further studies on lactation physiology, researchers found that lactation of the mammary gland and milk composition have rhythmicity, and they are regulated by the circadian system. It has been confirmed that partial circadian genes expressed in bovine mammary gland (Casey and Plaut, 2012; Plaut and Casey, 2012); and the expression patterns of these genes were strongly linked with the functional genes involving in the development and the metabolism of mammary gland (Metz et al., 2006; Wang et al., 2015). Circadian factor PER2, as an important member of period protein family which regulates biological rhythms, is strongly linked to the development of the mammary gland as well as the synthetic metabolism of milk protein and milk fat. This paper summarized the recent researches including *PER2* gene and the biological rhythm of development and lactation of the mammary gland, aimed to provide some information for the basic theoretical studies on the raw milk quality control.

2. Circadian rhythm mechanism

The circadian rhythms that are generated by molecular circadian clocks which are located in the hypothalamus (the master clock)

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and peripherally in organs with a periodicity of approximately 24 h are important in regulating a wide-range of cellular, metabolic, physiologic, and behavioral activities. Different species have slight differences in the compositions of biological rhythm system, but have a common formation mechanism of molecular oscillation which is generated by the transcription of a series of circadian genes and their post-transcription regulation (King and Takahashi, 2000; Albrecht and Eichele, 2003). The core elements of molecular oscillation include genes *CLOCK, BMAL1, PER, CRY* and their corresponding protein products, and the oscillation consists of several negative limbs of the circadian clock feedback loop (Kume et al., 1999; Shearman et al., 2000). As shown in Fig. 1, the biological rhythm starts at CT0 (0 h) with the dimer of the two protein components CLOCK and ARNTL1 (CLOCK/BMAL1 heterodimer) accumulating, which acts on the E-box enhancer in order to induce the transcription of genes *PER* and *CRY*. And then, PER and CRY protein express in endochylema and gradually enter into the nucleus after mutually combination. Consequently, concentrations of these protein increase until reaching the maximum levels at CT12 (12 h). In the nucleus, protein CRY inhibits the transcriptional activities of the CLOCK/BMAL1 heterodimer through directly acting on it. Meanwhile, the concentrations of protein PER and CRY begin to decrease owing to their gene transcription inhibition and protein degradation gradually. After peaking at CT15 - 18 (15 to 18 h), the intranuclear *BMAL1* mRNA falls down to the minimum level at the next day morning CT6 - 9 (6 to 9 h) actuating the rhythm of protein BMAL1 about 4 to 6 h later. Protein PER2 and CRY decline to the minimum levels at CT24 (24 h) while the CLOCK/BMAL1 heterodimer starts to accumulate and guides the gene *PRE/CRY* transcription again bringing out a new cycle (Zheng et al., 1998, 2001).

3. Circadian gene *PER2*

3.1. The regulation for circadian rhythm

As protein PER2 is one of prominent members of the period protein family, its gene *PER2* is one of the main control genes as one of the core elements of molecular oscillation and plays an important role in the regulation of the circadian rhythm (Steinlechner et al., 2002; Cruciani et al., 2008; Moriyama et al., 2008; Sakamoto et al., 2009). The gene *PER2* has polymorphism. Cruciani et al. (2008) sequenced the *PER2* gene of different people who came from different latitudes and regions. Their results showed that latitude had no influence on the *PER2* gene sequence, however different regions had, which implied that gene *PER2* might be a good population-specific positive selection for evolution studies. Shimomura et al. (2001) demonstrated that gene *PER2* had a high expression on rat suprachiasmatic nucleus all day long, and had a distinct rhythmicity 6 days postpartum in mice, which suggested that it might have the stimulation effect on secreting corticosteroid which controls time (Pilorz, 2006). The gene *PER2* mutation of mice results in no circadian rhythmicity under the continuous dark condition but robust circadian rhythmicity with a rhythm less than 24 h in constant light (Steinlechner et al., 2002). Nevertheless, *PER1* gene mutant mice demonstrate a rhythm more than 24 h (Steinlechner et al., 2002). Besides those results, an interesting finding described by Xiang et al. (2012) showed that, melatonin could stimulate the expression of the clock controlled genes *BMAL1* and *PER2* in human breast epithelial and breast cancer cells to recover the cellular rhythmicity.

3.2. The regulation for cellular proliferation and differentiation

The gene *PER2* plays an important role in the control of cellular proliferation and differentiation. After knock-down of the *PER2* clock gene in *Bombyx mori*, the rhythm of the silkworm incubation is affected, and the metamorphosis development process is cut down without affecting the amount of silk production (Sandrelli et al., 2007). According to those results, the authors suggested that gene *PER2* might affect the growth rate of silkworm. Yang et al. (2009a) found that down regulation of circadian clock gene *PER2* accelerated the proliferation of breast tumor cells and the growth of breast cancer by altering the daily growth rhythm through the siRNA and shRNA techniques *in vivo* and *in vitro*. Nakamura et al. (2008) concluded that the transcriptions of genes *PER* and *CRY* were regulated by the CLOCK/BMAL1 gene:crosstalk between the peroxisome proliferator-activated receptor/retinoid X receptor, that is, PPAR/RXR-regulated and CLOCK/BMAL1-regulated systems. At the cell level, researches showed that the gene *PER2* controls lipid metabolism and adipocyte cell differentiation by direct regulation

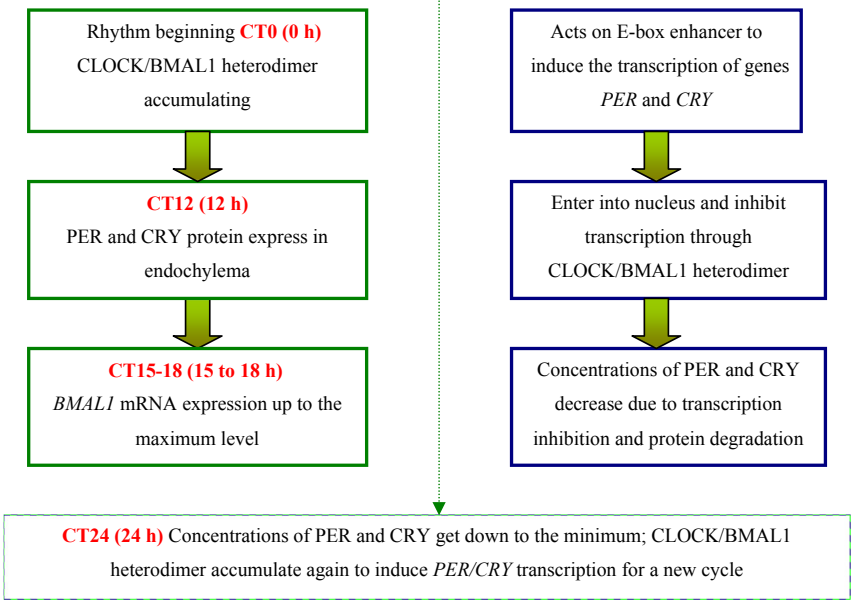

Fig. 1. Circadian rhythm pattern and its mechanism. CLOCK/BMAL1 heterodimer is the dimer of the two protein components CLOCK and ARNTL1.

of *PPARG*, the lack of gene *PER2* leads to the cellular differentiation from fibroblast to adipocyte (Gurnell, 2003; Grimaldi et al., 2010; Bionaz et al., 2013). Another research showed that, patients with breast cancer perform hypoxia which negatively correlate with PER2 protein by degrading PER2 protein mechanism (Hwang-Verslues et al., 2013); exactly the opposite, the normal expression of PER2 protein is of great importance in the inhibition for tumor cell differentiation.

3.3. The regulation for energy and lipid metabolism

Protein PER2 is significant to the regulation in energy and lipid metabolism. Verwey et al. (2008) found that daytime or nighttime restricted feeding in rats with negative energy balance disturbed the expression of *PER2* gene in the limbic forebrain and hypothalamus, and *PER2* expression peaked at about 12 h after feeding. As the researches on *PER2* clock gene knock-down mice showed, the rhythm of glucocorticoid and diurnal rhythm of eating pattern became disorders in mPer2-/- mice (Yang et al., 2009b). Meanwhile, Oike et al. (2011) examined the effects of a single time-delayed feeding on circadian rhythms in the liver of *Per2::Luc* (*Period2::-Luciferase*) reporter knock-in mice. Their results showed that, expressions of multiple clock genes including *Per2* were significantly increased within 1 h of feeding. And moreover, Grimaldi et al. (2010) considered that *PER2* could directly and specifically inhibit PPARγ which was the key nuclear receptor of adipogenesis, insulin allergy and inflammatory response, and lacking *PER2* gene would change the lipid metabolism which was characterized by the rapid decrease of total triacylglycerol and nonesterified fatty acid. Husse et al. (2012) verified that compared with wild-type mice, *PER1/PER2* double mutant mice showed blunted effects of timed sleep restriction (TSR) on food intake, leptin levels and lipid transport, suggesting a role of the *PER* gene in regulating the obesity and metabolic syndrome due to biological clock rhythm disorders. However, circadian clocks lose temporal precision with age and correlate with elevated incidence in dyslipidemia and metabolic syndrome in older adults. Subsequently, Keith et al. (2014) introduced that lipoic acid could remediate some of the dyslipidemic processes associated with advanced age, and this mechanism might be at least partially through entrainment of circadian clocks characterized by a significant phase-shift in the expression patterns of the circadian clock proteins including *PER2* in aged rats.

4. Circadian phenomena of cow physiological characters

Early in 1970, Gordon and Mcallister studied the rhythmicity of rumination and confirmed that the rumination rhythm varied between illumination treatments but not feeding times in adult sheep. Recent researches showed that, rhythmicity exist in lots of physiological phenomena of dairy cow. Aranas et al. (1987) reported that there was an apparent relationship between the aldosterone concentration in pregnant dairy cow blood and sampling time in Louisiana. Subsequently, the peripheral cortisol concentrations (Lefcourt et al., 1993) and the peripheral growth hormone concentrations (Lefcourt et al., 1995) were confirmed showing ultradian oscillation rhythms with a period around 120 min and a period around 80 min in lactating dairy cows. The concentration of peripheral prolactin showed ultradian rhythms in lactating dairy cows as well (Lefcourt et al., 1994). An apparent rhythmicity in the feed intake also exists in the dairy cow. Studies showed that, the feed intake within 2 h after starting to feed exceeded 16% of the daily intake and the second feeding peak period appeared at dusk while the third one in the morning (Harvatine and Allen, 2006; Devries et al., 2007; Hosseinkhani et al., 2008). What's more, Giannetto and Piccione (2009) tested 25 physiological variables of dairy cow and 12 of them showed daily rhythm such as urine, blood glucose and body temperature. In addition, biorhythmic variables in cow are modulated by the factors such as environment and feeding. Shehab-El-Deen et al. (2010) pointed out that, the rhythmicity change of blood glucose, serum urine nitrogen and serum total cholesterol were associated with summer heat stress in high-producing dairy cattle. Besides those physiological characters, the circadian rhythm of body temperature was also shifted by milking frequency (Kendall et al., 2008) and season (Kendall and Webster, 2009). Previous studies described above imply that it is possible to regulate metabolism and production through rhythmicity control. Coincidently, after comparing the circadian patterns of blood biochemical indexes of low-yielding hybrid cow (7.10 kg/d) and high-yielding cow (14.30 kg/d) (Butana × Friesian), Alameen et al. (2014) considered that the biorhythmicities and their variations were in relation to the level of milk production, and could be used as the representative indexes for cow metabolism and performance which needs to be confirmed in further studies.

5. Circadian gene and the development and metabolism of the mammary gland

There were apparent repetitive seasonal variations in the content of milk protein and milk fat which respectively peaked in December and January and fluctuated within the range of 0.25% all year round (Dahl et al., 2000). Besides the seasonal variations, milk yield and milk fat and protein percentages as well as somatic cell counts (SCC) also have diurnal variations according to the report from Quist et al. (2008). Milking time has significant influence on the yield and composition of milk. Gilbert et al. (1972) found that the milk yield was greater by 0.65 kg in the morning than in the evening but milk fat content was higher by 0.32%, and milk protein content was higher by 0.09% in the evening than in the morning. Collectedly, cow lactation activities have biorhythmicity which can be regulated by the impacts from environment, diet and milking processes (Harvatine, 2012), which indicates that we might regulate milk performance through the lactational rhythm pathway by controlling sorts of environmental factors in the practice.

Circadian genes are important for the body metabolism or physiological functions such as digestion, lactation and stress reaction (Feng and Lazar, 2012; Eckel-Mahan and Sassone-Corsi, 2013; Peek et al., 2013). Systemic inactivation of rhythmic expression gene *PPARG*, as an example, remarkably suppressed circadian variations in oxygen consumption, food and water intake, and ingestion in MoxCre/flox mice (Yang et al., 2012). Specifically, biological clock rhythm also regulates the lactation of the mammary gland. Research on asinine (donkey) milk demonstrated that the content of milk lipid, lactose and milk protein performed robust rhythmicity, but the underlying mechanism between the circadian rhythm and lactation metabolism was still not understood (Piccione et al., 2008). Subsequently, studies on the dam explained that, circadian system coordinated metabolic and hormonal changes needed to initiate and sustain lactation (Casey and Plaut, 2012). Research results showed that, approximately 7% of the genes expressed in mammary tissue during lactation had circadian patterns including core clock and metabolic genes, and the diurnal variation of composition of bovine milk were associated with changes in expression of mammary core clock genes (Plaut and Casey, 2012). Furthermore, Wang et al. (2015) investigated the expression patterns of the CLOCK network and the selected metabolic genes in cow mammary gland, liver, and adipose tissue during the transition from pregnancy into lactation, and the results showed that part of circadian genes such as *CLOCK, ARNTL, CRY2, CRY3, PER1, PER2, NR1D1* expression differed among tissues and

their expression patterns were closely associated with the metabolic function of the corresponding tissue.

5.1. The PER2 gene and the development of mammary gland

Protein PER2 plays a vital role in the development and differentiation of the milk duct and maintenance of polarity (Porter, 2011). Metz et al. (2006) reported that, the expression of mouse circadian gene *PER2* was higher in proliferating virgin and early pregnant mammary gland than in the lactation period. At the same time, the elevated *PER2* expression on the 16th day of pregnancy as well as the first and seventh day of lactation was positively correlated with *c-Myc* and *Cyclin D1* mRNA levels which were related to the cellular proliferation. Similarly, Casey et al. (2014) measured the abundance and temporal pattern of core clock genes' expression in different tissues including mammary gland from late pregnancy to early lactation in mice. As the results showed, the stoichiometric relationship of core clock proteins between CLOCK and *PER2* components remained 1:1 in the liver but increased to 4:1 in the mammary gland. Therefore, Casey et al. (2014) concluded that, the tissue-specific expression represented a significant function of core clock proteins in mammary development and physiological adaptation to lactation. The gene *PER2* also acts as a vital role in maintenance for breast acinar morphogens. Knock-down of either PER2 or BMAL1, by hampering the PER2-BMAL1 loop of the circadian clock, negatively affected estrogen receptor α circadian oscillations and 3D breast acinar morphogenesis (Rossetti et al., 2012).

5.2. The PER2 gene and the lactational metabolism

The study on circadian gene expression patterns at different stages and in different tissues from perinatal cow demonstrates the tight relationship between *PER2* gene and the metabolism of milk fat and milk protein (Wang et al., 2015). Among tissues, both of the genes *PER2* and *PPARG* have higher expression in adipose tissue while *PER2* gene can regulate lipid metabolism through inhibiting *PPARG* gene directly and specifically (Grimaldi et al., 2010) which is apparently significant for the energy requirement and lipid catabolism in postpartum lactating cow (McNamara et al., 1995); between stages, the remarkable increases were found in the expression of genes *PER2* and *PPARG* in the postpartum period compared to the late pregnant period (Wang et al., 2015) which jointly contribute to milk fat synthesis (Bionaz and Loor, 2008). However, in the study described by Metz et al. (2006), *PER1* expression in mouse mammary gland had no remarkable variation among time points including the 16th day of pregnancy, and the first and seventh day of lactation. This result was then proved in the transition dairy cows, showing no significant changes in gene *PER1* expression of mammary tissue around the time of delivery (Wang et al., 2015). On the other hand, Metz et al. (2006) also found mammary β-casein gene *Csn2* expression had a significant increase from the first day of lactation to the seventh day and peaked at the seventh day which was similar to the expression pattern of *PER2* gene in mammary tissue. Interestingly, a similar expression pattern of gene *PER2* (higher in postpartum than in pregnancy) was also detected in mammary tissue from the transition dairy cows (Wang et al., 2015). Those evidences described above indicated that the circadian gene *PER2* might have an important regulating function on the casein protein synthesis in mammary gland tissue.

6. Conclusion

In conclusion, there have been clear research reports about the rhythmicity of the lactation activities of the mammary gland which indicates the important regulating function of circadian rhythm on the development of mammary gland and its lactational metabolism. Among these circadian genes, *PER2* not only plays a prominent role in the development of the milk duct, the maintenance of polarity and morphology of mammary epithelial cells, but also relates to the synthetic metabolism of milk protein and milk fat in the mammary gland. It is however that, the expression patterns of circadian gene *PER2* in other tissues, the mechanisms underlying circadian regulation on lactational metabolism and milk fat and protein synthesis in mammary gland; whether the other relevant genes in circadian clock system have joint impacts and their interaction mechanism, etc., are still unknown. It is, therefore, necessary to conduct further investigations to clarify, in order to provide some new views and basic information for the theoretical studies on the raw milk quality control.

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