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New insights into the skeletal muscle circadian clock in ruminants

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Abstract

Circadian rhythms are endogenous oscillations with a period of approximately 24 h. They enable organisms to anticipate and adapt to daily environmental changes, such as light and temperature. As the largest metabolic and motor organ in the body, skeletal muscle plays a decisive role in determining meat production efficiency in ruminants. Skeletal muscle development is largely governed by the proliferation and myogenic differentiation capacity of skeletal muscle satellite cells (SMSCs). More than 2,300 genes in skeletal muscle exhibit circadian oscillatory expression and are extensively involved in myogenesis, transcriptional regulation, and metabolic processes. The rhythmic expression of these genes is modulated by external factors including the photoperiod, feeding behavior, gut microbiota, and physical activity. Disruption of the endogenous circadian timing system can inhibit SMSC proliferation and myogenic differentiation, thereby impairing normal muscle development. Therefore, this review focuses on key management aspects of ruminant production—such as environmental control, nutritional regulation, and exercise management—and systematically elaborates on how these husbandry strategies may influence SMSC fate by modulating the circadian clock, along with the underlying molecular mechanisms.

Keywords Circadian clock, Myogenic differentiation, Ruminants, Satellite cells, Skeletal muscle

Introduction

Ruminant meat is one of the fastest-growing segments of the global meat market, owing to its high nutritional quality and health benefits. According to the Food and Agriculture Organization, the global populations of cattle, sheep, and goats reached 1.58, 1.32, and 1.13 billion, respectively, in 2023. By 2050, the cattle population is projected to reach 2.6 billion, whereas the combined sheep and goat population is expected to reach 2.7 billion [1]. This expansion underscores the importance of ruminants in the global meat supply. However, ruminant production is more environmentally impactful than non-ruminant production, and its expansion challenges efforts to achieve carbon emission targets [2]. Increasing temperatures, recurrent droughts, and erratic rainfall are increasingly disrupting traditional grazing systems and undermining farm profitability [1]. To address these issues, producers must adopt precision livestock technologies and integrate molecular targeted interventions to increase meat yield [3]. Such integrated approaches are essential for increasing the efficiency and sustainability of ruminant production and for maintaining a stable market supply.

As the largest muscle tissue in ruminants, skeletal muscle development is coordinately regulated by polygenic and nutritional factors that directly influence meat yield and quality [4]. Skeletal muscle originates from myogenic progenitor cells within the embryonic

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dermomyotome of somites [5]. The proliferation and myogenic differentiation of these cells, which are hierarchically controlled by paired box (PAX) transcription factors, such as *Pax3* and *Pax7*, determine muscle developmental fate [6]. During embryogenesis, PAX3-positive progenitors, stimulated by Wnt and Sonic hedgehog signaling from the notochord, initiate the expression of myogenic regulatory factors (MRFs), including myogenic factor 5 (*Myf5*) and myogenic determining factor (*MyoD*), leading to the formation of primary myofibers [6, 7]. In the late fetal stages, a subset of PAX7-positive cells migrates to the periphery of myofibers, establishing the skeletal muscle satellite cell (SMSC) reservoir [8]. After birth, most SMSCs remain quiescent in the G0 phase [9]. Upon activation by muscle injury or growth signals, SMSCs re-enter the cell cycle via multilevel regulatory mechanisms involving Notch signaling, histone modifications, and miRNAs [10–12]. This activation is marked by *Pax7* downregulation, and *MyoD* and *Myf5* upregulation, which drive myoblast differentiation [13]. Subsequent myogenic differentiation involves sequential activation of *MyoD* and myogenin (*MyoG*), which is coordinated by Wnt/β-catenin signaling, m^6A RNA methylation, and non-coding RNA networks, which collectively promote myotube formation and myofiber maturation [14–16]. Although the key molecular mechanisms involved in SMSC proliferation and differentiation are known, current knowledge relies heavily on static single-time-point models, limiting insight into spatiotemporal dynamics and the development of precise adaptive strategies for improving meat production efficiency in ruminants.

More than 2,300 protein-coding genes in skeletal muscles exhibit circadian rhythmicity, many of which are involved in myogenesis, muscle repair, and energy metabolism [17]. However, mismanagement of lighting, feeding, exercise, or other husbandry factors can desynchronize the central clock in the suprachiasmatic nucleus (SCN) from peripheral muscle clocks, impairing skeletal muscle growth and development [18]. Key myogenic regulators involved in proliferation (*Pax7*, *MyoD*, and *Myf5*) and differentiation (*MyoD* and *MyoG*) are circadian clock-controlled genes (CCGs), indicating that the circadian clock temporally regulates SMSC fate over 24 h cycles [19]. This review examines how the circadian clock governs SMSC behavior and explores the roles of environmental factors, feeding rhythms, gut microbiota, and physical activity in modulating the muscle circadian system. This study aimed to provide a theoretical foundation and practical insights to support precise health management and enhance the meat productivity of ruminants.

Circadian clock machinery

Master circadian clock

The SCN, the master circadian clock in mammals, synchronizes daily physiological rhythms and facilitates the organism's anticipation and adaptation to environmental cycles, such as light and temperature. This coordination is achieved by regulating gene expression, hormone secretion, and metabolic pathways [20]. At the molecular level, the clock operates via interlocked transcriptional–translational feedback loops (Fig. 1a) [21]. In mammals, the core clock machinery comprises highly conserved genes, including brain and muscle ARNT-like protein 1 (*Bmal1*), circadian locomotor output cycles kaput (*Clock*), period (*Per*), and cryptochrome (*Cry*) [22]. BMAL1 and CLOCK form a heterodimer that binds to E-box enhancer elements and activates the transcription of *Per* and *Cry*. Following translation, PER and CRY translocate to the nucleus and inhibit BMAL1/CLOCK-mediated transcription, forming a core negative feedback loop (Fig. 1b) [23]. In a parallel loop, BMAL1/CLOCK activates transcription of the nuclear receptor reverse erb (REV-ERB) and D-box binding protein (DBP). REV-ERB and retinoic acid-related orphan receptor (ROR) compete for binding to ROR response elements (ROREs), modulating *Clock* and *Bmal1* expression, and establishing a secondary feedback cycle (Fig. 1c) [24]. The third regulatory layer involves competition between E4 promoter-binding protein 4 and DBP for D-box elements, further fine-tuning the circadian output (Fig. 1d) [25]. These interconnected feedback loops, operating through E-box, RORE, and D-box cis-regulatory elements, ensure the robustness and precision of the ~ 24 h circadian cycle [23].

Peripheral clocks

The core circadian clock components are expressed and functionally active in peripheral tissues, such as the intestine, liver, and skeletal muscle, where their molecular mechanisms remain highly conserved [26–28]. The light–dark cycle acts as the principal zeitgeber (ZT), synchronizing the central clock in the SCN via photic input through the retina. This central timing signal is then transmitted to peripheral tissues via neural, hormonal, and behavioral pathways, establishing a system-wide circadian network [29, 30]. Importantly, peripheral clocks are entrained by non-photic cues, including feeding-fasting cycles, temperature variations, and physical activity [29]. Desynchronization between the central and peripheral clocks can disrupt metabolic homeostasis, immune function, and tissue development and is linked to pathologies in skeletal muscle, including muscle atrophy, sarcopenia, and muscular dystrophy, underscoring the importance of rhythmicity in muscle maintenance and function [31, 32].

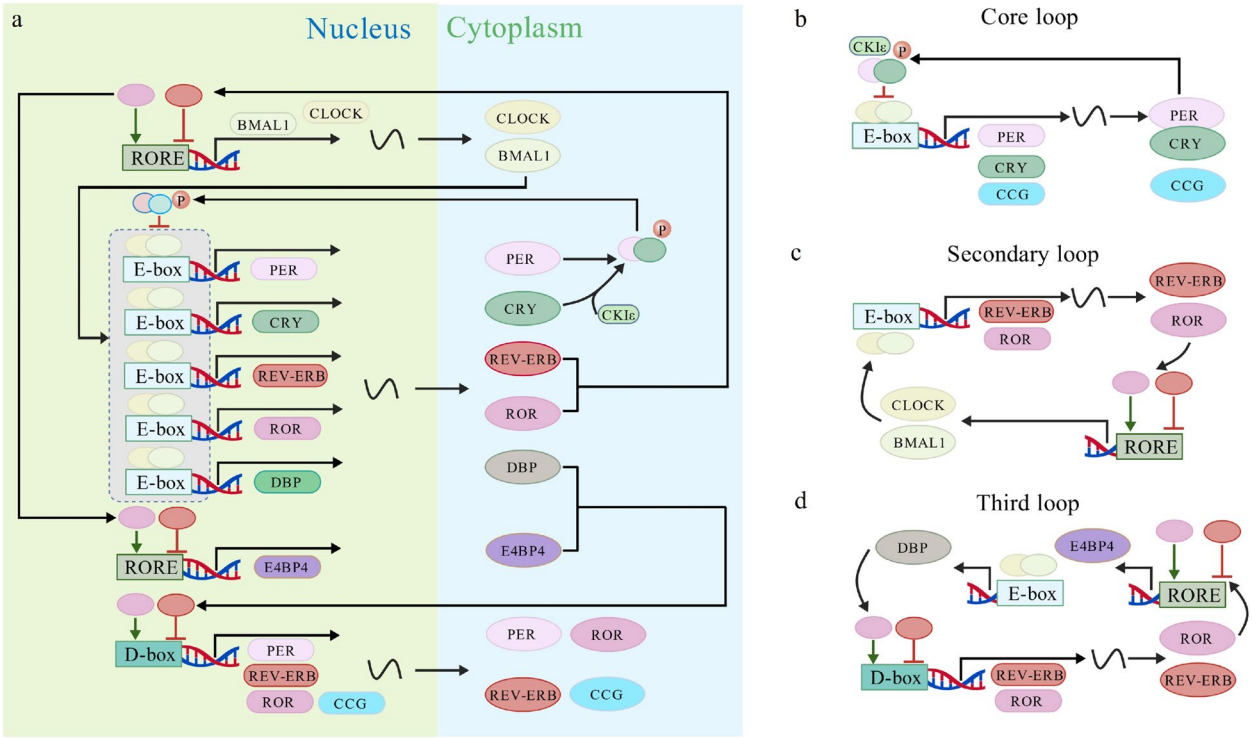

Fig. 1 Molecular mechanisms of the circadian clock. **a** Circadian clock feedback loop regulatory network. **b** Core loop. **c** Secondary loop. **d** Third loop. BMAL1, brain and muscle ARNT-like protein 1; CCG, clock-controlled gene; CKIε, casein kinase I epsilon; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; D-box, D-site binding element; DBP, D-site binding protein; E-box, enhance-box; E4BP4, E4-binding protein 4; PER, period; REV-ERB, reverse erb; ROR, retinoic acid receptor-related orphan receptor; RORE, ROR response element

The molecular clock in SMSC

Regulation of SMSC proliferation

Mammalian skeletal muscle develops from the paraxial mesoderm, with myogenic progenitors originating in the dorsolateral dermomyotome of somites (Fig. 2a) [5]. After birth, most SMSCs remain quiescent [9]. Activation triggered by local microenvironmental cues involves PAX7-dependent initiation of *Myf5* expression, followed by a decrease in *Pax7* [33]. Subsequently, the activated SMSCs induce *MyoD* expression, re-enter the cell cycle, and commit to the myoblast lineage (Fig. 2b) [13]. SMSC proliferation is precisely controlled by the circadian cycle (Fig. 2c) [19]. The *MyoD* promoter contains E-box elements and directly binds to the CLOCK:BMAL1 heterodimer, leading to rhythmic expression [34, 35]. Similarly, genetic disruption of *Bmal1*$^{-/-}$ or *Clock*$^{\triangle 19}$ in mice abolishes *MyoD* mRNA rhythms and impairs their muscle contractility [36]. Furthermore, SMSC proliferation is promoted by *Bmal1* overexpression but is likely suppressed by the PER/CRY complex through the inhibition of CLOCK:BMAL1 transcriptional activity [37]. This model is supported by *Per* knockout studies, in which SMSCs displayed a delayed cell cycle exit [38]. CRY protein degradation relieves transcriptional repression by CLOCK:BMAL1, thereby indirectly enhancing MYOD activity and promoting differentiation [39]. Conversely, *Cry2* knockout increases *Pax7* expression and stimulates proliferation [40]. Among the auxiliary clock pathways, *Ror*$^{-/-}$ leads to impaired motor function and reduced clock gene expression, whereas *Rev-erbα* knockout enhances myogenic gene expression and SMSC proliferation [41, 42]. These effects may be mediated by the ROR-mediated activation and REV-ERB-mediated repression of *BMAL1* transcription, indirectly influencing *MYOD*. However, circadian modulation of SMSC proliferation in ruminants remains largely unexplored. Given the intrinsic and evolutionarily conserved nature of circadian rhythms in regulating cellular functions and that myostatin, a key negative regulator of SMSC proliferation, maintains a phylogenetically conserved circadian regulatory mechanism across species, we hypothesized that the circadian clock governing SMSC proliferation may be evolutionarily conserved across species [43].

Regulation of myogenic differentiation

The shift from SMSC proliferation to differentiation is characterized by the downregulation of *Pax7* and

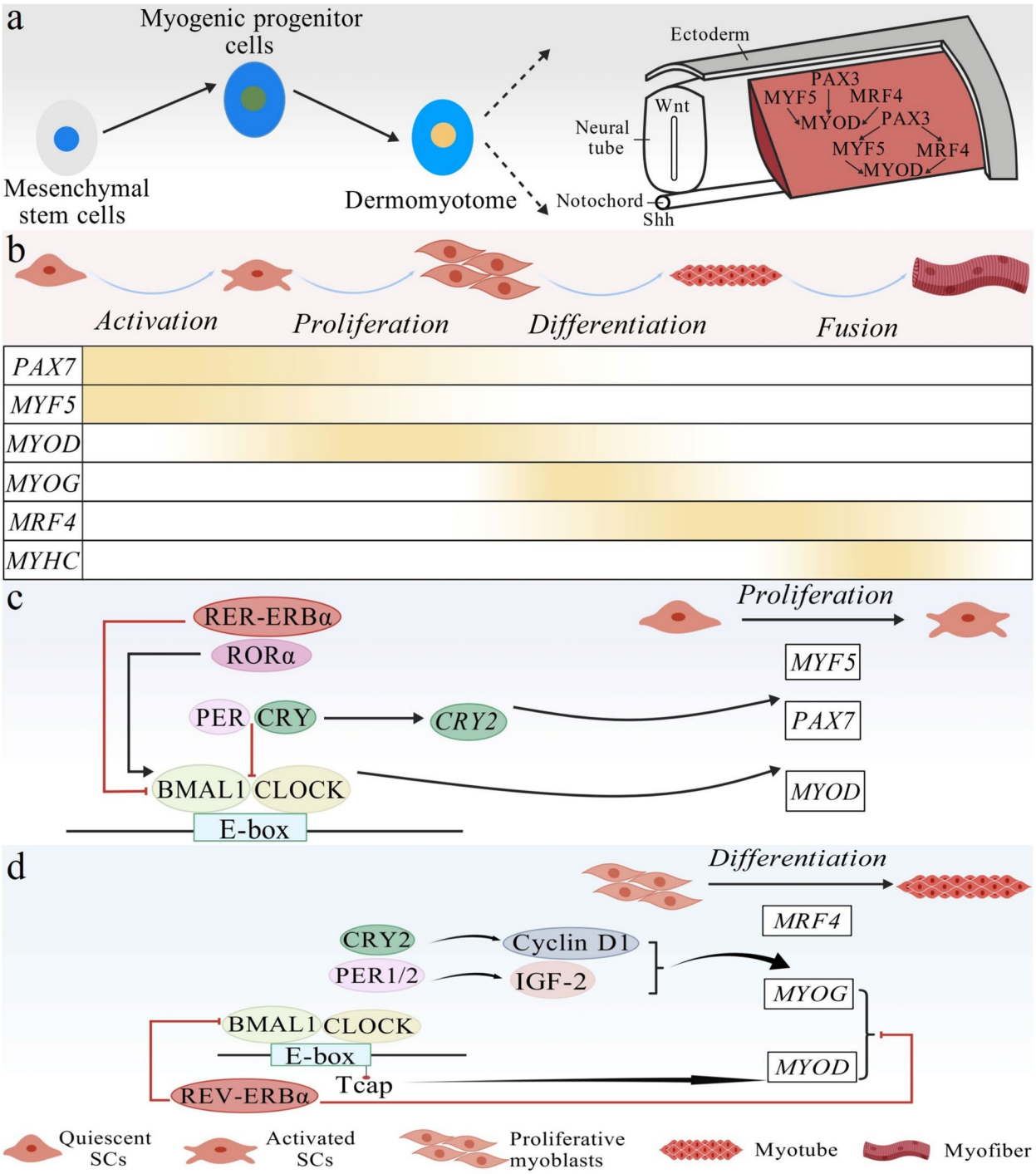

Fig. 2 Skeletal muscle development and circadian clock regulation. **a** Mechanisms orchestrating SMSC formation in the embryo. **b** Proliferation and myogenic differentiation of SMSCs during the growth period. **c** Circadian clock regulation of SMSC proliferation. **d** Circadian clock regulation of SMSC differentiation. BMAL1, brain and muscle ARNT-like protein 1; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; E-box, enhance-box; IGF-2, insulin-like growth factor 2; MRF4, myogenic regulatory factor 4; MYF5, myogenic factor 5; MYHC, myosin heavy chain; MYOD, myogenic determining factor; MYOG, myogenin; PAX3, paired box 3; PAX7, paired box 7; PER, period; REV-ERBα, reverse erb alpha; RORα, retinoic acid receptor-related orphan receptor α; SMSC, skeletal muscle satellite cell; Shh, sonic hedgehog; Wnt, wingless-type MMTV integration site family

sustained upregulation of *MyoD* [14]. MYOD activates MYOG and myogenic regulatory factor 4 (MRF4) to initiate myotube formation [14]. Ultimately, MYOD and MYOG cooperate to induce terminal differentiation markers, including *Mrf4* and myosin heavy chain (*MyHC*), thereby driving the assembly of multinucleated myofibers [44, 45]. BMAL1 is a key regulator of this process, enhancing myogenic differentiation by directly upregulating *Myf5* and *MyoD*; modulating Wnt pathway components such as Dishevelled 2, β-catenin, and transcription factor 3; and amplifying Wnt–MRF synergy [46, 47]. Non-ruminant animal models and empirical evidence in goats show that BMAL1-driven transcription of miR-27b suppresses *PAX3*, thereby inhibiting SMSC proliferation [48, 49]. CLOCK:BMAL1-activated MYOD binds to E-box elements in the Tcap promoter, reinforcing differentiation [50]. Although CLOCK:BMAL1 regulates miR-455, which targets *Clock* mRNA, the functional relevance of this feedback mechanism in myogenesis remains unclear [51]. PER1/2 supports myoblast differentiation by binding to the enhancer-promoter regions of insulin-like growth factor 2 (IGF-2), thereby increasing *Igf2* expression and *MyoG* [38]. CRY2 facilitates differentiation and cell fusion by regulating cyclin D1 and Tmem176b, thereby preventing premature cell cycle exit and maintaining *MyoG* levels [52]. In contrast, REV-ERBα acts as a negative regulator; its deletion upregulates *Myf5*, *MyoD*, *MyoG*, and *Wnt3a*, accelerating myotube formation (Fig. 2d) [42]. Several non-coding RNAs influence the fate of SMSCs through specific molecular mechanisms. For example, lncMD1 competitively binds to miR-133a-3p and miR-361-3p, thereby relieving the repression of the target genes *DCTN1*/*DCTN2*, inhibiting proliferation, and promoting differentiation [53]. However, whether the circadian clock modulates SMSCs through non-coding RNA networks remains predominantly unknown. In summary, the core circadian clock negative feedback loop promotes skeletal muscle growth and development by directly or indirectly regulating myogenic differentiation and cell fusion, providing a molecular basis for enhanced meat production.

Current evidence in ruminants vs. knowledge gaps

Research on the circadian regulation of SMSC proliferation and differentiation has focused on mouse and human models, with limited studies on ruminant models (Table 1). Consistent with non-ruminant model results, *REV-ERBα* overexpression in yaks suppresses SMSC proliferation and differentiation by downregulating the expression of *MYF5*, *MYOD*, and *MYOG* [54]. Studies on sheep and goats have shown that circadian oscillations of clock genes in skeletal muscles correlate with fetal and postnatal growth phases, suggesting a functional link between the muscle clock and developmental physiology [55, 56]. In cattle, *CRY* expression has been associated with meat production traits [57, 58]. However, evidence that the circadian clock directly targets and regulates the proliferation and differentiation of ruminant SMSCs remains scarce. To address these gaps, studies should focus on cross-species comparisons to delineate conserved and species-specific molecular mechanisms of circadian regulation in muscle development.

Table 1 Regulatory roles of the circadian clock in skeletal muscle: insights from non-ruminant and ruminant animal models

Clock gene	Non-ruminant models			Ruminant models			References
	Species	Tissue/Cell	Phenotype	Species	Tissue/Cell	Phenotype	
BMAL1/CLOCK	Mouse; Human	SMSCs	Drives E-box-mediated transcription of *MyoD* to promote muscle growth	Goat; Sheep	Skeletal muscle	Governs skeletal muscle development in fetuses and juveniles; however, the precise mechanism remains unknown	[37, 55, 56, 59]
PER/CRY	Mouse	SMSCs; Myoblasts	Inhibits CLOCK:BMAL1-mediated transcriptional activation of *MyoD*, thereby suppressing proliferation; *Per* and *Cry2* activate *MyoG* to promote myoblast differentiation	Cattle	Skeletal muscle	*CRY* is associated with carcass traits; however, the molecular mechanism remains unknown	[38, 52, 57, 58]
REV-ERBα/RORα	Mouse; Human	Myoblasts; Skeletal muscle	*Rev-erba* inhibits MRF expression to suppress myogenesis; *RORα* promotes BMAL1-mediated transcriptional activation of *MyoD* to facilitate myogenesis	Yak; Goat	SMSCs; Ear tissue	*REV-ERBα* inhibits MRF expression to suppress myogenesis; *RORα* is associated with growth traits; however, the molecular mechanism remains unknown	[41, 42, 54, 60, 61]

Environmental factors affecting the circadian rhythm of SMSCs

Photoperiod

As the primary ZT, the photoperiod transmits light signals to the SCN via the retina-hypothalamus pathway. The SCN synchronizes peripheral tissue clocks through neural and hormonal signals, establishing systemic circadian coordination (Fig. 3) [62]. *Per1* and *Per2* are central to this process and are key mediators of photic entrainment [63]. Light exposure induces glutamate and pituitary adenylate cyclase-activating polypeptide release in the SCN, increasing intracellular cAMP levels and activating the cAMP-response element binding protein (CREB), which initiates *Per1/2* transcription [64]. This pathway suggests that photoperiod influences ruminant SMSC proliferation and differentiation via circadian regulation. In support of this, extended photoperiods increase average daily gain, carcass weight, and IGF-1 levels in young goats, potentially through PER1/2-mediated activation of IGF-1 signaling and subsequent upregulation of *MYOG* [65]. Conversely, abrupt photoperiod changes disrupt the central–peripheral clock synchrony, reduce muscle *PER1/2* expression, and impair development in sheep [66]. Photoperiod indirectly modulates the clock by regulating melatonin secretion from the pineal gland [67]. Melatonin binds to MT1/MT2 receptors, activates the cAMP-PKA-CREB pathway, and influences *Per1/2* expression [68–70]. In pregnant sows, melatonin supplementation elevates fetal skeletal muscle *PER1/2* expression in the evening, which is concurrent with increased *PAX7* and *MYF5* levels, and enhances myogenic differentiation and birth weight [71]. Although the role of melatonin in ruminant SMSC regulation remains understudied, it may promote proliferation via Wnt pathway-mediated *Pax7* upregulation and

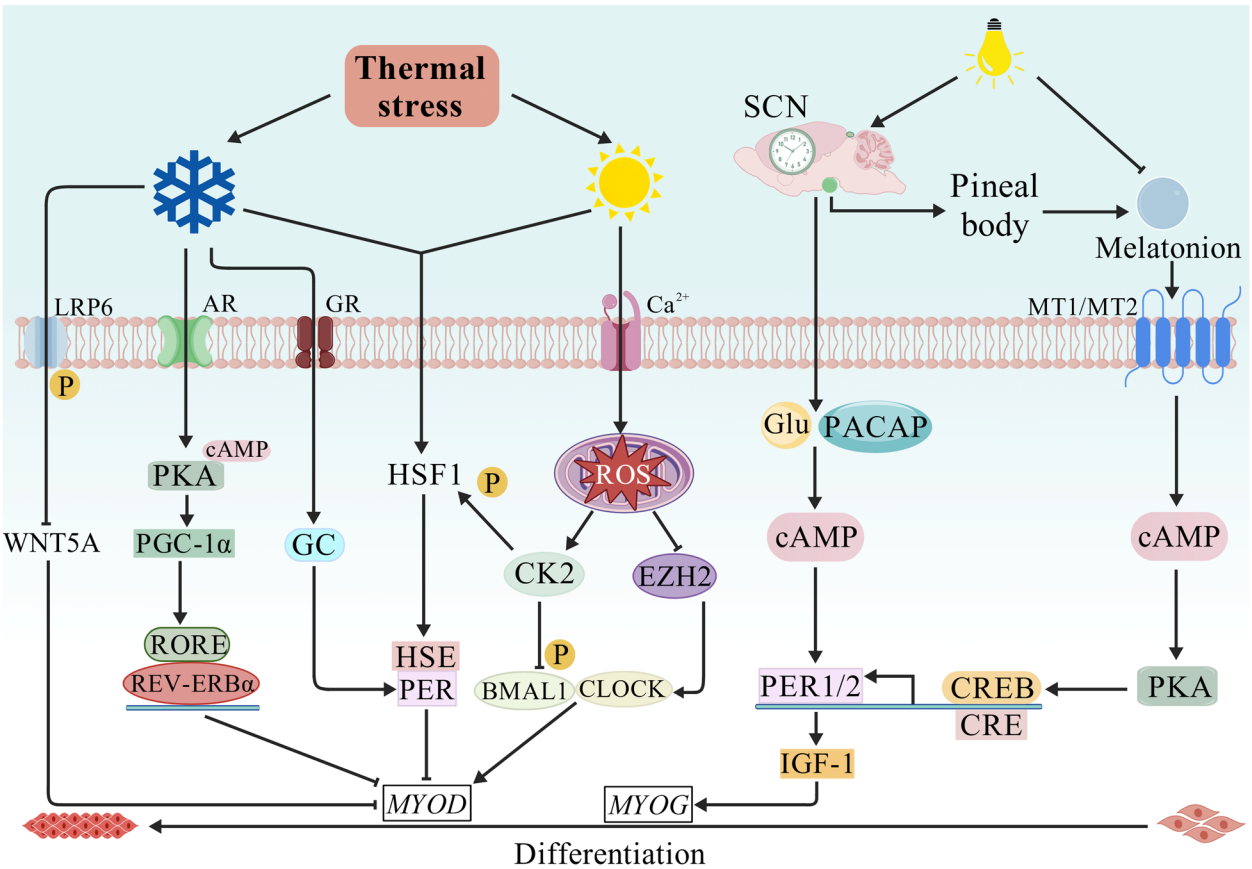

Fig. 3 The circadian clock mediates the regulation of skeletal muscle by light and thermal stress. AR, adrenergic receptor; BMAL1, brain and muscle ARNT-like protein 1; cAMP, cyclic adenosine monophosphate; CK2, casein kinase 2; CLOCK, circadian locomotor output cycles kaput; CRE, cAMP response element; CREB, cAMP-response element binding protein; EZH2, enhancer of zeste homolog 2; GC, glucocorticoid; GR, glucocorticoid receptor; HSE, heat shock response element; HSF1, heat shock factor 1; LRP6, low density lipoprotein receptor-related protein 6; MYOD, myogenic determining factor; PACAP, pituitary adenylate cyclase activating polypeptide; PER, period; PKA, protein kinase A; REV-ERBα, reverse erb alpha; RORE, ROR response element; ROS, reactive oxygen species; WNT5A, wingless-type MMTV integration site family member 5A

myostatin suppression, which is consistent with the observations in lambs [72, 73]. In conclusion, light exposure regulates *PER* expression via the cAMP–CREB pathway, which regulates the proliferation and myogenic differentiation of ruminant SMSCs through CCGs, thus supporting the design of precise lighting regimens to optimize meat production efficiency.

Thermal environment

Heat stress considerably hinders global meat production, affecting approximately 80% of cattle annually, with > 80% of goats and nearly 60% of sheep reared in hot, arid zones [74, 75]. As a significant ZT, high temperatures can disrupt circadian rhythms, compromising meat production [76]. Mechanistically, heat stress activates heat shock factor 1 (HSF1), which binds to heat shock response elements near the E-box sequences in the *Per2* promoter, potentially desynchronizing the central and peripheral clocks [77, 78]. This dysregulation may inhibit SMSC proliferation and differentiation via CCGs, consistent with the heat-induced downregulation of *PAX7*, *MYOD*, *MYF5*, *MYOG*, and *MYHC* in ovine myoblasts [79]. Heat stress causes direct clock interference and induces reactive oxygen species accumulation, which promotes BMAL1 phosphorylation via casein kinase 2 and disrupts the EZH2–CLOCK/BMAL1 interaction, collectively suppressing MYOD activity and myoblast differentiation [80–82]. Antioxidants, such as resveratrol and vitamin A, mitigate these effects and improve SMSC viability and production performance [83–86]. Cold stress may also impair SMSC function through circadian pathways, potentially via HSF1-PER2-mediated *MyoD* suppression or peroxisome proliferator activated receptor γ coactivator-1α (PGC-1α)-mediated *Rev-erbα* upregulation, which dampens *MyoD* rhythmicity [87–92]. Notably, heat/cold stress disrupts the circadian oscillation of body temperature in mammals, with lamb studies documenting fluctuations reaching 4 °C [93, 94]. In vitro studies employing square-wave temperature cycles to simulate circadian oscillations in body temperature have demonstrated that such thermal fluctuations can reset the circadian clock in myocytes [95]. However, whether extreme climatic conditions affect meat production in ruminants by modulating the circadian clock remains largely unknown. In summary, extreme climatic conditions may disrupt core body temperature and circadian clock oscillations, impair SMSC proliferation and differentiation, and reduce meat production

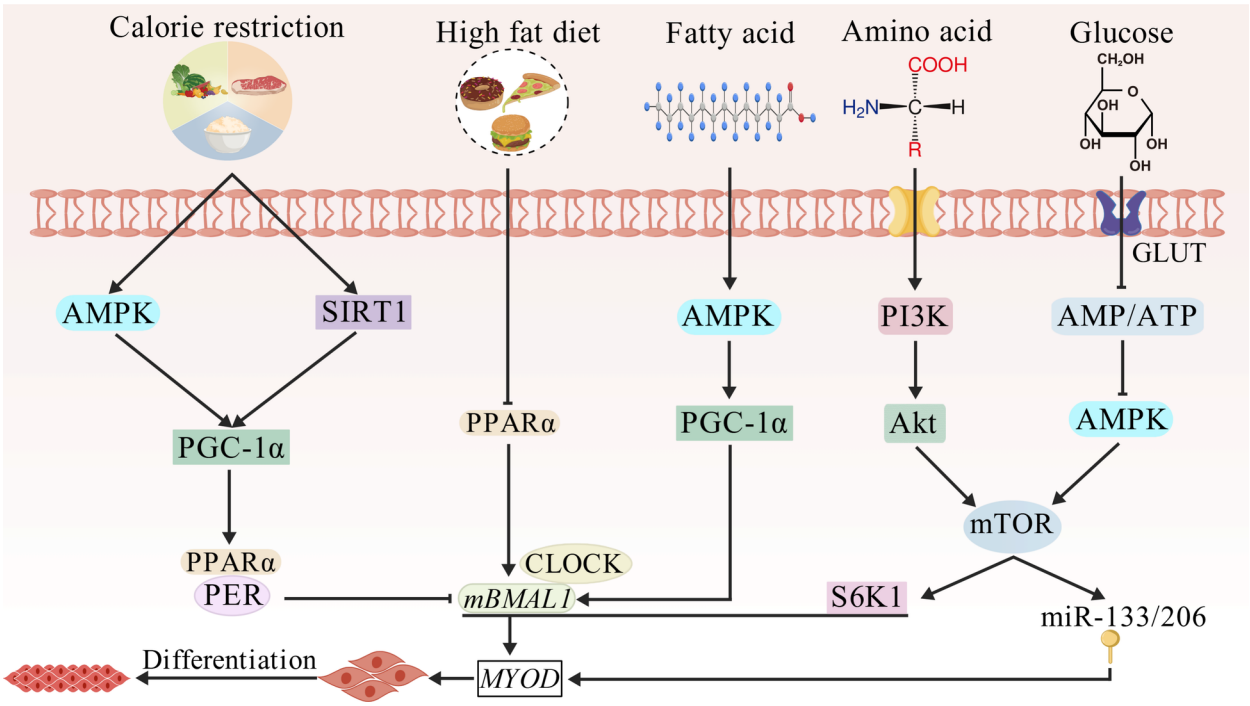

Fig. 4 The circadian clock orchestrates nutrient responses in skeletal muscle. Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; BMAL1, brain and muscle ARNT-like protein 1; CLOCK, circadian locomotor output cycles kaput; mTOR, mammalian target of rapamycin; MYOD, myogenic determining factor; PER, period; PGC-1α, peroxisome proliferator activated receptor γ coactivator-1α; PI3K, phosphatidylinositol 3-kinase; PPARα, peroxisome proliferator activated receptor α; SIRT1, silent information regulator 1; S6K1, ribosomal protein S6 kinase beta-1

in ruminants. These findings underscore the importance of precisely controlling the thermoneutral environment in ruminant husbandry.

Nutrition and exercise interfere with the circadian rhythm of SMSCs

Chrononutrition and feeding time

Nutrient sensing via the mammalian target of rapamycin (mTOR) pathway regulates myoblast differentiation, whereas miRNAs fine-tune SMSC fate determination (Fig. 4) [96, 97]. Amino acids activate phosphatidylinositol 3-kinase (PI3K)–mTOR–S6K1 signaling, enhance *BMAL1* transcription and MYOD activity, and promote miR-133/206 expression and myoblast differentiation [98]. Physiological glucose uptake suppresses AMPK, derepressing mTOR–BMAL1–MYOD–driven differentiation, whereas excessive glucose activates AMPK, inhibiting mTOR–BMAL1, and impairing differentiation [99, 100]. Fatty acids increase MYOD activity via the AMPK/PGC-1α/BMAL1 axis, whereas high-fat diets suppress CLOCK:BMAL1 DNA-binding and MYOD activity [101, 102]. Caloric restriction activates SIRT1/AMPK/PGC-1α signaling, promoting the PPARα–PER interaction and inhibiting CLOCK:BMAL1, ultimately affecting myogenesis [103, 104]. In *Bmal1*$^{flox/flox}$ mice, breakfast branched-chain amino acid supplementation increased MYF5 activity and muscle hypertrophy, mirroring leucine-induced growth in calves and goats [105–107]. Notably, temporal alignment of feeding with endogenous rhythms enhances myogenesis. Night-restricted feeding in rabbits upregulates *BMAL1*, *CLOCK*, and *MYOG*, and timed protein provision improves piglet growth [95, 108]. Conversely, mistimed feeding disrupts rhythms and promotes adipogenesis [109]. Although data on ruminants remain limited, these findings suggest that macronutrients modulate the circadian clock via intracellular energy sensors to regulate SMSC proliferation and differentiation, whereas disruption of feeding rhythms impairs muscle

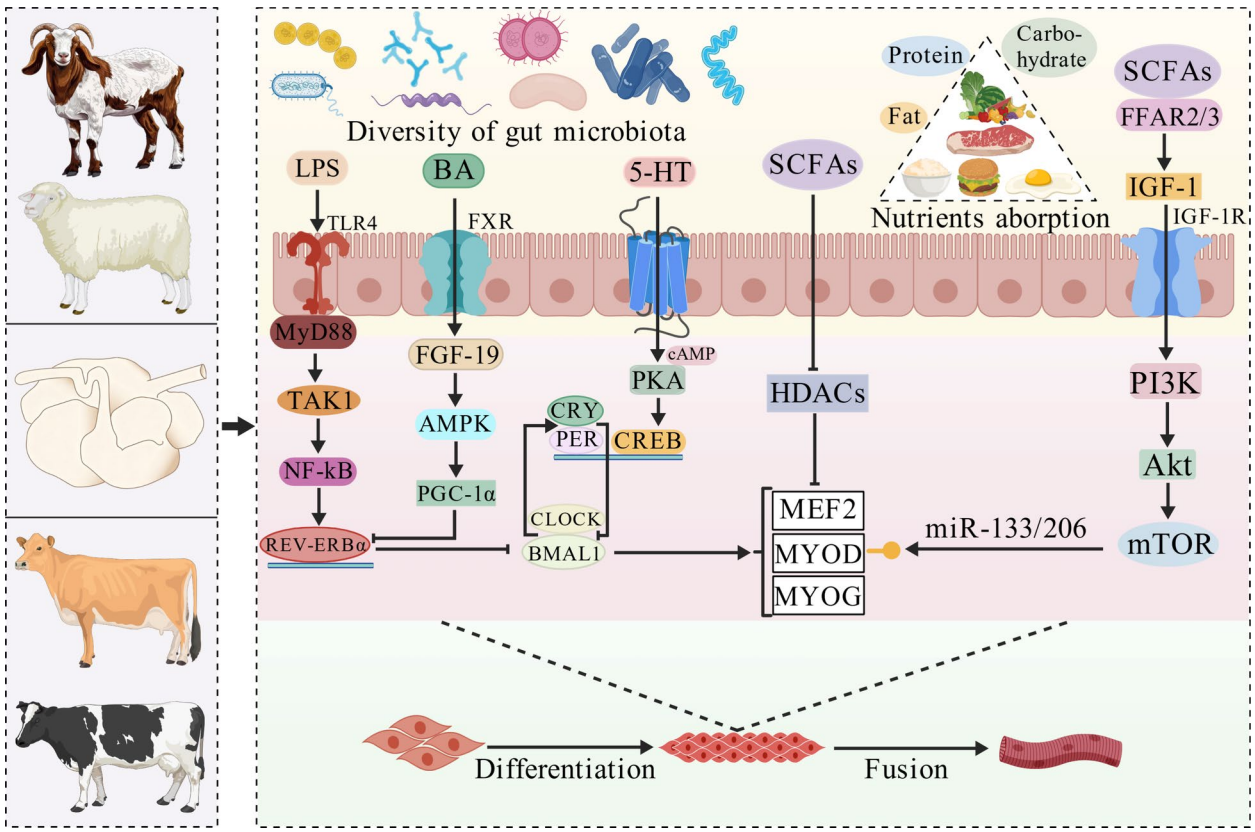

Fig. 5 Rumen microbiota regulates skeletal muscle through the circadian clock. Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; BA, bile acids; BMAL1, brain and muscle ARNT-like protein 1; cAMP, cyclic adenosine monophosphate; CLOCK, circadian locomotor output cycles kaput; CREB, cAMP-response element binding protein; CRY, cryptochrome; FFAR2/3, free fatty acid receptor 2/3; FGF-19, fibroblast growth factor 19; FXR, farnesoid X receptor; HDACs, histone deacetylases; IGF-1, insulin-like growth factor 1; LPS, lipopolysaccharide; MEF2, myocyte enhancer factor 2; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation primary response 88; MYOD, myogenic determining factor; MYOG, myogenin; NF-kB, nuclear factor kappa-B; PER, period; PGC-1α, peroxisome proliferator activated receptor γ coactivator-1α; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; REV-ERBα, reverse erb alpha; SCFAs, short-chain fatty acids; TAK1, transforming growth factor-β-activated kinase 1; TLR4, Toll-like receptor 4; 5-HT, 5-hydroxytryptamine

growth and compromises meat production. Collectively, these results highlight the potential of chrononutrition in increasing production efficiency in ruminant livestock systems.

The gut microbe–skeletal muscle axis

The gut microbiota, which exhibits diurnal rhythmicity in ruminants, interacts with the host circadian system (Fig. 5), suggesting its role as a mediator of gut–muscle crosstalk [110, 111]. Microbial metabolites such as short-chain fatty acids (SCFAs) bind to free fatty acid receptor 2/3, promoting IGF-1 release and activating PI3K/Akt/mTOR, potentially enhancing BMAL1–MYOD–miR-133/206 activity and myogenic differentiation [112, 113]. SCFAs inhibit histone deacetylase activity; reduce the acetylation of MYOD, MEF2, and MYOG; and suppress differentiation to maintain SMSC homeostasis [113]. Bile acids activate farnesoid X receptor and FGF19–AMPK/PGC-1α signaling, upregulating myosin, heavy chain 1B, and *PAX7* and increasing myofiber size [114–116]. Furthermore, ruminal microbes that display circadian oscillations are associated with melatonin biosynthesis [117]. Further validation in murine models demonstrated that these microbes modulate intestinal epithelial melatonin synthesis by regulating arylalkylamine N-acetyltransferase activity, suggesting that rumen-derived melatonin may regulate SMSC proliferation and differentiation via *PER1/2* [118]. Conversely, LPS promotes *Rev-erbα* via TLR4–NF-κB, inhibits *MyoD* and differentiation, and triggers muscle atrophy [119–121]. Bacterial serotonin may activate *Per1/2* via GPCR–cAMP–PKA–CREB, thereby inhibiting myogenesis, which is consistent with the pro-regenerative effects of serotonin inhibition [122–124]. Germ-free mice exhibit disrupted clock gene rhythms and muscle atrophy, whereas *Bmal1*$^{-/-}$ mice exhibit microbial rhythm loss, confirming bidirectional host–microbiome interactions [125, 126]. In lambs, *Clostridium butyricum* supplementation improves myofiber size and growth, suggesting that probiotics constitute a promising muscle-enhancing strategy, although circadian involvement requires further study [127]. In summary, rhythmic oscillations in the gut microbiota regulate the SMSC clock via metabolite production, thereby influencing myogenic differentiation and meat production in ruminants through CCGs.

Chronoexercise

Exercise and the circadian clock form a bidirectional regulatory network; core clock genes regulate exercise capacity by modulating metabolism and mitochondrial

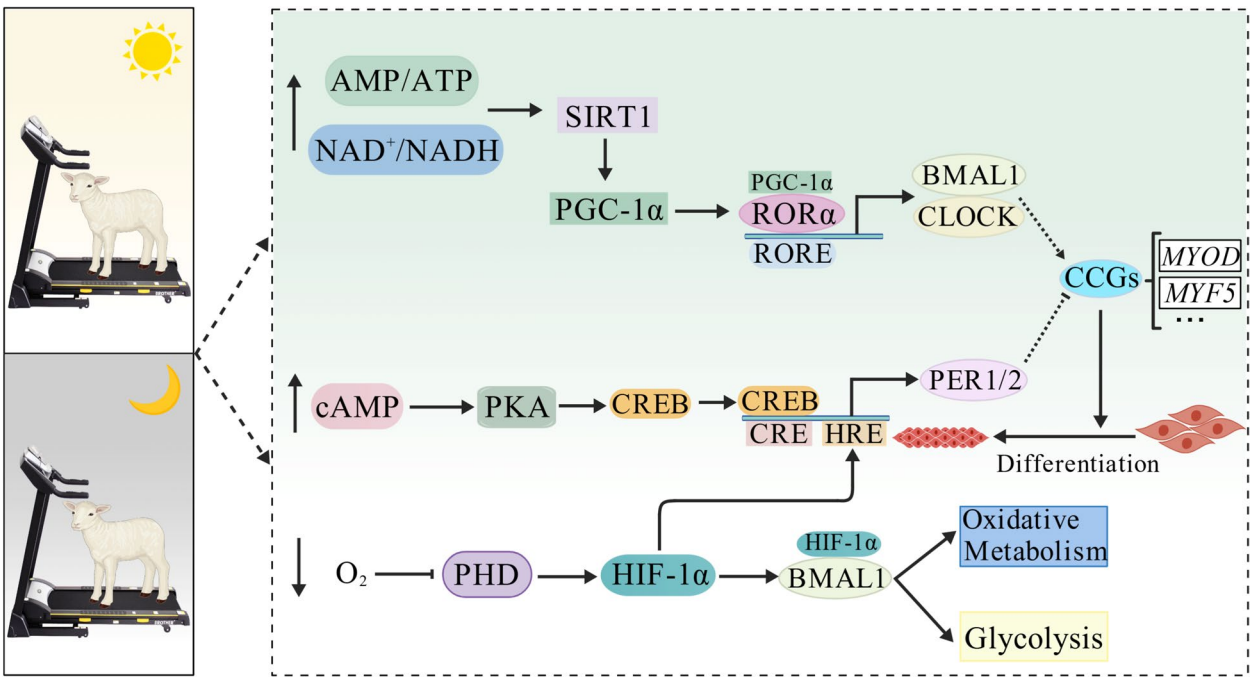

Fig. 6 Exercise regulates skeletal muscle through circadian clock-dependent mechanisms. BMAL1, brain and muscle ARNT-like protein 1; cAMP, cyclic adenosine monophosphate; CCGS, clock-controlled genes; CLOCK, circadian locomotor output cycles kaput; CRE, cAMP response element; CREB, cAMP-response element binding protein; HIF-1α, hypoxia-inducible factor 1-alpha; HRE, hypoxia response element; MYF5, myogenic factor 5; MYOD, myogenic determining factor; PER, period; PGC-1α, peroxisome proliferator activated receptor γ coactivator-1α; PHD, prolyl hydroxylase domain; PKA, protein kinase A; RORE, ROR response element; RORα, retinoic acid receptor-related orphan receptor α; SIRT1, silent information regulator 1

function, whereas exercise feedback adjusts the clock amplitude/phase and influences the muscle phenotype via CCGs (Fig. 6) [128–130]. Exercise-induced ATP/NADH depletion activates AMPK/SIRT1 and modulates PER2/CRY1 stability and clock periodicity [131]. Exercise upregulates *PGC-1α*, enhances mitochondrial biogenesis, and activates RORα/γ to reinforce BMAL1/CLOCK transcription and myofiber-type transition [132]. HIF-1α modulation integrates hypoxic and circadian signals, optimizing metabolic balance [133]. Through these pathways, exercise shifts the core clock gene expression, regulates protein turnover, activates SMSCs, and induces hypertrophy, collectively supporting muscle development. Grazing improves lamb finishing performance compared with that in indoor systems, and gestational exercise in cattle increases the number of offspring myofibers [134, 135]. The efficacy of such strategies is chronodependent, with afternoon exercises generally optimizing outcomes [136]. Thus, chronoexercise enhances the circadian expression of the SMSC clock by modulating energy metabolism and reinforcing the circadian amplitude/phase, which subsequently optimizes muscle fiber type composition through CCGs and promotes skeletal muscle growth. This mechanism provides a viable exercise management strategy to improve meat production in ruminants.

Conclusion

The circadian clock precisely regulates SMSC proliferation and differentiation in ruminants and is influenced by photoperiod, temperature, feeding patterns, gut microbiota, and exercise. Although multifactorial interactions remain understudied, these factors form interconnected networks. The gut microbiota mediates host rhythms and muscle development and responds to environmental and dietary cues, necessitating a deeper mechanistic insight. Elucidating clock–SMSC interactions will refine management and nutritional strategies, support muscle growth, and facilitate precision health farming. Future studies should dissect external factor–clock–muscle interactions to sustainably enhance meat production.

Abbreviations

Bmal1	Brain and muscle ARNT-like protein 1
CCGs	Clock-controlled genes
Clock	Circadian locomotor output cycles kaput
CREB	CAMP-response element binding protein
Cry	Cryptochrome
E-box	Enhance-box
HSF1	Heat shock factor 1
IGF	Insulin-like growth factor
MRF4	Myogenic regulatory factor 4
MRFs	Myogenic regulatory factors
mTOR	Mammalian target rapamycin
Myf5	Myogenic factor 5
MyHC	Myosin heavy chain
MyoD	Myogenic determining factor
MyoG	Myogenin
PAX	Paired box
Per	Period
PGC-1α	Peroxisome proliferator activated receptor γ coactivator-1α
PI3K	Phosphatidylinositol 3-kinase
REV-ERB	Reverse erb
RORE	ROR response element
RORα	Retinoic acid receptor-related orphan receptor α
SCFAs	Short-chain fatty acids
SCN	Suprachiasmatic nucleus
SIRT1	Silent information regulator 1
SMSCs	Skeletal muscle satellite cells
Wnt	Wingless-type MMTV integration site family
ZT	Zeitgeber

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Authors' contributions

QJW and YXC wrote the review. ZJZ, SG, and DLR conceived this review. YHL, YLC, and QJW revised and finalized the manuscript. All authors read and approved the final manuscript.

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Competing interests

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