REVIEW

Timing metabolism in cartilage and bone: links between circadian clocks and tissue homeostasis

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Abstract

The circadian system in mammals is responsible for the temporal coordination of multiple physiological and behavioural processes that are necessary for homeostasis. In the skeleton, it has long been known that metabolic functions of chondrocytes, osteoblasts and osteoclasts exhibit intrinsic circadian rhythms. In addition, results from animal models reveal a close connection between the disruption of circadian rhythms and skeletal disorders such as rheumatoid arthritis, osteoarthritis and osteoporosis. In this review, we summarise the latest insights into the genetic and biochemical mechanisms linking cartilage and bone physiology to the circadian clock system. We also discuss how this knowledge can be utilised to improve human health.

Key Words

- ▶ circadian clock
- ▶ articular cartilage
- ▶ bone
- ▶ metabolism

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Introduction

Circadian (from the Latin *circa diem*, meaning ‘about a day’) rhythms in behaviour and physiology are a hallmark of life on earth. The 24-h environmental cycles generated by the planet’s rotation around its axis have been wired into the molecular machinery of cells from all domains of life (Bell-Pedersen *et al.* 2005). This endogenous timekeeping mechanism, known as circadian clock, allows organisms to anticipate the periodic fluctuations brought on by the 24-h solar cycle, aligning biological functions with external changes (Pittendrigh 1993).

Skeletal homeostasis is an intrinsically dynamic process whose complexity not only derives from the number of molecules involved and their multifaceted interactions, but also from their precise spatial and temporal control. Remarkably, physiological functions such as longitudinal bone growth, bone remodelling, chondrocyte metabolism and cartilage matrix turnover exhibit 24-h rhythms, being controlled by the peripheral

circadian clocks present in most of the cell types in cartilage and bone (Dudek & Meng 2014, Yang & Meng 2016). Alterations in the circadian rhythm of skeletal biology are associated with the development of various disorders, including osteoarthritis (OA), rheumatoid arthritis (RA) and osteoporosis (OP) (Kawai & Rosen 2010, Gibbs & Ray 2013, Berenbaum & Meng 2016).

In this review, we summarise the current understanding of the links between the circadian clock and skeletal metabolism. Specifically, we discuss how the circadian clock is implicated in the regulation of several facets of cellular metabolism that are essential for bone and cartilage homeostasis. We also elaborate on the utilisation of animal models to dissect the roles of circadian pathways in skeletal metabolism and pathophysiology of diseases. Finally, we provide an overview of the latest advances in chronotherapy and other translational aspects of circadian biology and discuss how these can be

used to improve existing therapies and develop new ones for musculoskeletal conditions.

Circadian rhythms in mammals: a coordinated network of hierarchical oscillators

The mammalian circadian system comprises a multitude of oscillators organised in a hierarchy (Fig. 1) (Honma 2018). The central clock, located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, is directly entrained by photic information transmitted to the SCN via the retinohypothalamic tract (Gooley *et al.* 2001, Hattar *et al.* 2002, Panda *et al.* 2002a). Non-photic stimuli such as behavioural arousal, melatonin and serotonergic activation are also capable of resetting the central clock; these cues are usually conveyed to the SCN via the geniculohypothalamic tract and the dorsal and median raphe nucleus (Challet & Pévet 2003, Dibner *et al.* 2010). The SCN clock regulates daily oscillations in mammalian behaviour and physiology, including locomotor activity, sleep–wake cycles, blood pressure, body temperature, pineal melatonin secretion and adrenal corticosterone release (Moore & Eichler 1972, Moore & Klein 1974, Eastman *et al.* 1984, Kramer *et al.* 2001, Scheer *et al.* 2005, Buijs *et al.* 2014). Additionally, the central clock acts as a pacemaker that relays crucial timing information to autonomous peripheral oscillators through neural and humoral outputs, such as parasympathetic and sympathetic

innervation and glucocorticoid hormones (Balsalobre *et al.* 2000, Albrecht 2012, Buijs *et al.* 2014).

Circadian rhythms in the expression of genes and proteins have been reported in cells and tissues from across all organ systems. Genome-wide transcriptome studies have demonstrated that between 3 and 16% of the transcripts detected in peripheral tissues are rhythmically expressed (Panda *et al.* 2002b, Storch *et al.* 2002, Zvonic *et al.* 2006, Gossan *et al.* 2013, Dudek *et al.* 2016, 2017, Yang *et al.* 2017). In fact, a systems-level analysis of the murine transcriptome indicated that more than half of the genes encoding proteins are rhythmic in at least one tissue (Zhang *et al.* 2014). Notably, there is little overlap between the genes under circadian control in each tissue, demonstrating that the temporal orchestration of cellular metabolism is tissue specific (Mohawk *et al.* 2012, Buhr & Takahashi 2013, Zhang *et al.* 2014). This is reflected in the broad range of molecular pathways that are coordinated by the circadian clock, ranging from photoreception in the retina to xenobiotic detoxification in the liver and kidneys (Gachon *et al.* 2006, Storch *et al.* 2007). These tissue-specific gene expression patterns are presumably related to the gradual emergence of circadian rhythms during development through mechanisms that are deeply interlocked with cellular differentiation processes (Reppert & Schwartz 1986, Davis & Gorski 1988, Jud & Albrecht 2006, Yagita *et al.* 2010, Umemura *et al.* 2017).

Peripheral clocks rely on a unique combination of timing cues to fine-tune cellular functions. Although the central clock does not drive peripheral oscillators,

Figure 1

Hierarchical organisation of the mammalian circadian system. The central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus receives light/dark information from the retina through the retinohypothalamic track. Intercellular coupling between neurons ensures synchronised circadian rhythms of the SCN (top right). Periodic signals (e.g. humoral and neuronal) released from the central clock convey timing information to entrain circadian oscillators located in peripheral tissues. For most peripheral tissues, there is no coupling or weak coupling between cells. However, robust tissue-level oscillations can be achieved due to stochastic population entrainment. Peripheral circadian clocks modulate tissue-specific rhythmic expression of genes involved in metabolism, thermoregulation and many other physiological outcomes.

information originating in the SCN is essential for the synchronisation of phases between cells of the same tissue and establishing a stable phase interval between different tissues (Yoo *et al.* 2004, Guo *et al.* 2006). Nonetheless, the maintenance of systemic synchrony in mammals seems to be far more complex than initially suggested (Kowalska & Brown 2007, Husse *et al.* 2015). This is evidenced by parabiosis studies between intact and SCN-lesioned mice demonstrating that nonneural cues are sufficient to sustain circadian rhythms in the liver and kidneys, but not in the heart, spleen and muscle (Guo *et al.* 2005). In addition, the loss of synchrony in peripheral tissues caused by

deletion of BMAL1 in the SCN was distinctively rescued by light/dark cycles and restricted feeding depending on the peripheral oscillator (Izumo *et al.* 2014). Nonetheless, more studies are necessary to fully comprehend how peripheral clocks interact with each other and with the SCN and how this regulation is achieved.

The molecular circadian clock

On a molecular level (Fig. 2), the circadian clock consists of intricate self-regulatory transcription-translation

Figure 2

Molecular mechanisms of the mammalian circadian clock. The circadian transcriptional-translational feedback loop comprises CLOCK-BMAL1 heterodimers that bind to E-box elements in the promoter region of clock-controlled genes, namely *Per1/2*, *Cry1/2*, *Rev-erba/b*, *Rora/c*, *Dbp*, *Tef* and *Hlf*. In the cytoplasm, PER1/2 and CRY1/2 form a complex and are phosphorylated by CK1ε/δ. The resulting complex represses the transcriptional activity of CLOCK-BMAL1. Cytoplasmic degradation of PERs and CRYs is mediated by CK1ε/δ, AMPK and GSK3β, respectively. REV-ERBs and RORs drive another feedback loop that participates in the transcriptional control of *Bmal1*. A third feedback loop involves the transcriptional activators DBP, TEF and HLF and the repressor NFIL3 that bind rhythmically to D-box elements. AMPK, 5' adenosine monophosphate-activated protein kinase; BMAL1, brain-muscle-arnt-like protein 1; CLOCK, circadian locomotor output cycle kaput; CRY1/2, cryptochrome 1/2; CK1ε/δ, casein kinase 1 ε/δ; DBP, D-box-binding protein; GSK3β, glycogen synthase kinase 3β; HLF, hepatic leukaemia factor; NFIL3, nuclear factor interleukin 3 regulated; P, phosphate residue, PER1/2, period 1/2; RORα/γ, retinoic acid receptor-related orphan nuclear receptor α/γ; RRE, retinoic acid response elements; TEF, thyrotroph embryonic factor.

feedback loops whose interactions govern the rhythmic expression of clock-controlled genes (Reppert & Weaver 2002, Mohawk *et al.* 2012). The positive arm of the main feedback loop is formed by the transcriptional factor CLOCK (circadian locomotor output cycles kaput) and its heterodimeric partner BMAL1 (brain and muscle Arnt-like protein-1) (King *et al.* 1997, Gekakis *et al.* 1998, Lowrey & Takahashi 2011). The CLOCK-BMAL1 complex binds to E-box elements in the promoter region of target genes, including *Period* (*Per1*, *Per2* and *Per3*) and *Cryptochrome* (*Cry1* and *Cry2*), which are members of the negative arm of the feedback loop (Gekakis *et al.* 1998, Kume *et al.* 1999, Shearman *et al.* 2000). In the cytosol, PER and CRY interact with each other to form a complex and are phosphorylated by serine/threonine casein kinase 1 δ (CK1 δ) and CK1 ϵ (Lee *et al.* 2001, Gallego & Virshup 2007). This PER-CRY repressor complex is then translocated into the cell nucleus where it represses its own transcription by interacting with CLOCK-BMAL1 (Lee *et al.* 2001, Lowrey & Takahashi 2011). As repression progresses, specific E3 ubiquitin ligase complexes ubiquitinate PER and CRY proteins, marking them for degradation by the proteasome (Gallego & Virshup 2007, Preußner & Heyd 2016). Once the turnover of the repressor complex reaches a certain threshold, negative feedback is relieved and transcription of *Per* and *Cry* starts anew, initiating a new circadian cycle.

In addition to *Per* and *Cry*, the CLOCK-BMAL1 complex also activates the transcription of NR1D1 (nuclear receptor subfamily 1, group D, member 1) and NR1D2 (nuclear receptor subfamily 1, group D, member 2) that encode the nuclear receptors REV-ERB α and REV-ERB β , respectively. Rhythmic expression of REV-ERB α leads to the repression of *Bmal1* thereby inducing a rhythm in these genes that is in antiphase with *Per* expression (Preitner *et al.* 2002). Retinoic acid-related orphan receptor (ROR) proteins (ROR α and ROR γ) compete with REV-ERBs for their shared DNA-binding elements (Preitner *et al.* 2002, Sato *et al.* 2004, Zhang *et al.* 2015), which results in the transcriptional activation of *Bmal1* by ROR α and its repression by REV-ERB α (Solt *et al.* 2011). In this way, the REV-ERB-ROR feedback loop interconnects the positive and negative arms of the main feedback loop.

A third transcriptional loop driven by CLOCK-BMAL1 involves the proline and acidic amino acid-rich basic leucine zipper (PAR-bZIP) factors D-box-binding protein (DBP), thyrotroph embryonic factor (TEF) and hepatic leukaemia factor (HLF). These proteins interact with the repressor NFIL3 (nuclear factor interleukin-3 regulated), which is driven by the REV-ERB/ROR loop,

at sites containing D boxes (Mitsui *et al.* 2001, Gachon *et al.* 2004). Together, these integrated feedback loops generate intricate transcription-translation circuits with various phases of expression that vary according to the combination of *cis* elements in the promoters and enhancers of target genes (Ueda *et al.* 2005).

Articular cartilage

Articular cartilage (AC) is present in the articular surfaces of diarthrodial joints. AC is a specialised connective tissue that consists of a dense extracellular matrix (ECM) comprising protein fibres (collagen and elastic fibres) and ground substance (proteoglycans, glycosaminoglycans and glycoproteins), surrounding a sparse population of chondrocytes, the only cell type in this tissue (Mescher 2016). The regenerative potential of AC is inherently limited, meaning that once damaged this tissue is very difficult to repair (Iwamoto *et al.* 2013). Articular chondrocytes live in a challenging physicochemical environment: no innervation, no blood or lymphatic vessels, high osmotic pressure, acidic pH and low oxygen levels (Ng *et al.* 2017). As these cells rarely divide, cartilage homeostasis depends on the fine balance between chondrocyte anabolism and catabolism and their temporal regulation (Archer & Francis-West 2003). Disruption of chondrocyte metabolism has been linked to musculoskeletal disorders such OA and RA, which are characterised by a shift towards chondrocyte catabolism and progressive ECM degeneration (Golding & Marcu 2009).

Evidence of circadian rhythms in articular cartilage

Circadian variations in cartilage were first described by studying the mitotic activity of chondrocytes in the epiphyseal growth plate of mice and rats, with the highest mitotic index occurring in the early morning (Simmons 1962, 1964a, Kember & Walker 1971, Stevenson *et al.* 1990). Several studies have also reported that the incorporation of [³⁵S]sulphate, [³H] proline, [³H]galactose, [¹⁴C]proline/[¹⁴C]glycine or [³H] thymidine increased during the light phase in rat and mouse growth plates (Simmons 1964a,b, Walker & Kember 1972, Raugstad *et al.* 1979, Russell *et al.* 1983, Igarashi *et al.* 2013). In patients with knee OA and RA, the levels of cartilage oligomeric matrix protein (COMP) in serum presented a circadian variation (Andersson *et al.* 2006). Day/night variations could also be observed

for other biomolecules related to cartilage metabolism in OA patients, namely aggrecan, type II collagen, hyaluronic acid, keratan sulphate and transforming growth factor- β (TGF- β) (Kong *et al.* 2006). Nonetheless, the lack of a normal control group in these studies limits the interpretation of these findings.

In the last decade or so, bioluminescence imaging techniques have greatly improved our knowledge of the molecular clocks driving circadian rhythms in various tissues. These techniques make use of reporter mice harbouring the firefly luciferase gene fused in-frame with the 3' end of the *Per2* gene (PER2::Luc), which permits real-time monitoring of circadian rhythms (Yoo *et al.* 2004). In 2013, Okubo and colleagues proved that the articular and epiphyseal cartilage of femoral bone from PER2::Luc mice have strong circadian oscillations in *ex vivo* culture for several months (Okubo *et al.* 2013). Similar approaches have revealed circadian rhythms in explant cultures of cartilage isolated from the xiphoid process and the femoral head of PER2::Luc mice (Gossan *et al.* 2013, Dudek *et al.* 2016). Circadian rhythms can also be observed in human primary and immortalised cell lines of chondrocytes transduced with lentiviral clock gene reporters (Gossan *et al.* 2013, Dudek *et al.* 2016).

Global transcriptome analyses have confirmed the rhythmic expression of core clock genes in cartilage isolated from the xiphoid process and femoral head of mice and from the ribs and femoral head of rats (Gossan *et al.* 2013, Honda *et al.* 2013, Dudek *et al.* 2016). By collecting samples from mice and rats constantly kept in darkness it has been possible to identify global circadian patterns of gene expression (Gossan *et al.* 2013, Honda *et al.* 2013). In both organisms, approximately 4% of the expressed genes showed statistically significant circadian rhythms (Gossan *et al.* 2013, Honda *et al.* 2013). Interestingly, many of these rhythmic genes are involved in cellular processes that are crucial for the maintenance of cartilage homeostasis, such as ECM structural components (e.g. aggrecan and collagen) and remodelling enzymes (e.g. *Adamts1*, *Adamts4* and *Adamts9*), calcium-dependent metalloproteinases (e.g. *Mmp14*), inhibitors of metalloproteinases (e.g. *Timp3* and *Timp4*) and growth factors (e.g. *Tgfa*, *Tgfb3* and *Egf*) (Gossan *et al.* 2013, Honda *et al.* 2013, Yang & Meng 2016). Most importantly, these studies point towards a circadian regulation of cartilage metabolism with a time-of-day-dependent segregation of anabolic and catabolic pathways (Gossan *et al.* 2013, Honda *et al.* 2013).

Links between dysregulation of circadian rhythms and articular cartilage homeostasis

In recent years, evidence has emerged that disruption of circadian rhythms by environmental or genetic factors may contribute to the development of skeletal disorders. In aged mice, the amplitude of circadian oscillations is reduced approximately 40% in comparison to young mice; and it is known that age is one of the main risk factors for the development of OA (Hugle *et al.* 2012, Gossan *et al.* 2013). This reduction in the amplitude of circadian oscillations could impact on the regulation of downstream genes involved in cartilage metabolism. It has also been reported that long-term environmental disruption of light/dark cycles that mimics many years of rotating shift work or chronic jet lag promotes the development of an OA-like phenotype in murine knee cartilage (Kc *et al.* 2015).

In mice, targeted deletion of *Bmal1* in chondrocytes (*Col2a1-Bmal1*^{-/-}) abolished the time-dependent expression of many rhythmic genes and led to early-onset cartilage degeneration (Table 1) (Dudek *et al.* 2016). Most importantly, gene expression studies in *Col2a1-Bmal1*^{-/-} mice demonstrated that BMAL1 is essential to maintain the balance between anabolic and catabolic factors in chondrocytes (Dudek *et al.* 2016). In the absence of this core clock component there is a dysregulation of the TGF- β and NFATc2 signalling pathways (Dudek *et al.* 2016). TGF- β plays a crucial role not only in cartilage development during embryogenesis but also in the maintenance of its functional and structural integrity throughout adult life (Finnson *et al.* 2012, Wang *et al.* 2014). In aged murine chondrocytes this cytokine was associated with a diminished repair capacity (Scharstuhl *et al.* 2002, Blaney Davidson *et al.* 2005, Fortier & Miller 2006). Furthermore, dysregulation of the TGF- β signalling pathway has been correlated with an increased expression of *MMP13* in human osteoarthritic cartilage (Blaney Davidson *et al.* 2009). The NFAT (nuclear factor of activated T cells) family of transcription factors also participates in several biological processes essential for cartilage health (Ranger *et al.* 2000, Greenblatt *et al.* 2013). NFATc2 has been shown to regulate the differentiation of adult mesenchymal stem cells into cartilage in mice (Ranger *et al.* 2000). In *Nfatc2*^{-/-} mice, ectopic endochondral ossification is initiated at three months of age, and at a later stage extensive cartilage degradation may occur (Ranger *et al.* 2000, Wang *et al.* 2009). Loss of NFATc2 causes a metabolic imbalance in chondrocytes that is characterised by the overexpression of inflammatory (e.g. *Il1b* and *Il6*) and catabolic pathways

Table 1 Summary of the phenotypes observed in articular cartilage from mouse models deficient in core circadian clock components.

Mouse strain	Phenotype	Molecular changes	References
<i>Bmal1</i> ^{-/-}	Smaller body size	Decreased expression of <i>Alp</i> , <i>lhh</i> and <i>Col10a1</i> in rib growth plate	(Takarada <i>et al.</i> 2012)
<i>Col2a1-Bmal1</i> ^{-/-}	Age-related progressive knee cartilage degeneration Cell death and extracellular matrix loss	Decreased expression of <i>Acan</i> , <i>Col2a1</i> , <i>Ctgf</i> , <i>Id3</i> , <i>Nfatc2</i> /NFATc2, <i>Nr1d1</i> , <i>Per2</i> , p-SMAD1/5, p-SMAD2, <i>Serpine1</i> and <i>Sox9</i> /SOX9 in hip cartilage	(Dudek <i>et al.</i> 2016)
<i>Clock</i> ^{Δ19}	Progressive proteoglycan loss in knee cartilage	Increased expression of <i>Il1b</i> , <i>Il6</i> /IL6, <i>Mcp1</i> and nuclear P65 in knee cartilage Decreased expression of cytoplasmic P65 and IκB in knee cartilage	(Yuan <i>et al.</i> 2019)

(e.g. *Mmp13*, *Adamts5* and *Timp1*) and a decrease in anabolic signalling (e.g. *Sox9*, *Acan* and *Col2a1*) (Wang *et al.* 2009). Remarkably, expression of NFATc1 in lesioned cartilage from OA patients is downregulated in comparison with paired macroscopically normal samples (Greenblatt *et al.* 2013). Cartilage-specific ablation of NFATc1 in *Nfatc2*^{-/-} mice induced the spontaneous development of an OA-like phenotype that recapitulates all the main features of human OA, that is, prevalence of matrix catabolism, osteophyte formation and subchondral bone changes (Greenblatt *et al.* 2013).

Mice carrying a mutation in *Clock* (*Clock*^{Δ19}) presented accelerated cartilage degeneration in comparison to the wild type (Table 1) (Yuan *et al.* 2019). An increase in the expression of genes encoding proinflammatory cytokines such as IL-1β and IL-6 was also observed (Yuan *et al.* 2019). Interestingly, dysfunctional CLOCK decreased acetylation of NF-κB at Lys310 and increased its phosphorylation at Ser276 thereby promoting its translocation into the nucleus (Yuan *et al.* 2019). Future studies should investigate whether reduced NF-κB acetylation in a wild-type mouse recapitulates the same phenotype.

Analysis of gene expression patterns in human cartilage revealed that circadian rhythm pathways were among the most disrupted in OA patients (Akagi *et al.* 2017, Soul *et al.* 2018). Several studies have also demonstrated that expression of *BMAL1*/BMAL1 is significantly reduced in human osteoarthritic cartilage (Dudek *et al.* 2016, Snelling *et al.* 2016, Yang *et al.* 2016a, Akagi *et al.* 2017). Knockdown of *BMAL1* in human chondrocytes altered TGF-β signalling and was associated with increased expression of catabolic factors (e.g. *MMP1*, *MMP3*, *MMP13* and *ADAMTS5*) (Snelling *et al.* 2016, Yang *et al.* 2016a, Akagi *et al.* 2017, Khurana *et al.* 2019).

Disruption of rhythmic genes other than the core clock components has also been associated with abnormal cartilage metabolism. Autophagy, a cellular mechanism

that allows the rapid elimination of abnormal proteins and/or organelles, is involved in the maintenance of AC cartilage by modulating chondrocyte function and survival (Bohensky *et al.* 2007, 2009). In OA, a decrease in chondrocyte autophagy was accompanied by an increase in cell death and matrix degradation (Caramés *et al.* 2012). Thus, apoptosis inhibition has been proposed as a therapeutic intervention for OA (Kim & Blanco 2007). Interestingly, expression of *Xiap* (X-linked inhibitor of apoptosis) was shown to be rhythmic in wild-type mouse xiphoid cartilage (Gossan *et al.* 2013). XIAP inhibits at least two members of the caspase family of cell death proteases, caspase-3 and caspase-7, and has shown anti-apoptotic activity in chondrocytes (Scott *et al.* 2005, Böhm *et al.* 2010). Therefore, loss of *Xiap* rhythmicity during ageing might lead to an increase in apoptotic processes, contributing to OA pathogenesis.

Genes encoding matrix-degrading enzymes such as *Adamts4* and *Mmp14* were also found to be rhythmic in murine cartilage (Gossan *et al.* 2013, Honda *et al.* 2013). ADAMTS4 is one of the major proteases responsible for the degradation of cartilage proteoglycans, namely aggrecan (Verma & Dalal 2011). In human cartilage, this aggrecanase can be induced by proinflammatory cytokines and is upregulated in OA (Roach *et al.* 2005, Naito *et al.* 2007, Song *et al.* 2007). Another important protease is MMP14, a membrane-anchored enzyme that modulates the cellular availability of TGF-β (Velasco-Loyden *et al.* 2004) and participates in the activation of other metalloproteinases, namely MMP13 and MMP9, potentially amplifying its role in arthritis (Knäuper *et al.* 2002, Chellaiah & Ma 2013). Ablation of *Mmp14* led to the development of severe arthritis in ageing mice that resembles both murine collagen-induced arthritis and human RA (Holmbeck *et al.* 1999).

Serum levels of parathyroid hormone (PTH) exhibit a circadian variation, with a peak occurring in the early

morning (Jubiz *et al.* 1972, Fuleihan *et al.* 1997). In mouse, bioluminescence imaging has shown that PTH is capable of resetting PER2::Luc circadian oscillations in a time- and dose-dependent manner in the femoral head growth plate (Okubo *et al.* 2015). Both PTH and PTHrP (parathyroid hormone-related peptide) can exert physiological effects through PTH1R (PTH 1 receptor), a receptor that is expressed in the femoral head growth plate of mice (Okubo *et al.* 2015). The rate of chondrocyte differentiation is modulated by a negative feedback loop involving Indian hedgehog (IHH) and PTHrP. IHH, which is secreted by newly formed hypertrophic chondrocytes, stimulated the expression of PTHrP, which in turn retarded the formation of these cells (Vortkamp *et al.* 1996). Remarkably, expression of *Ihh* in the growth plate of mice exhibited circadian variation; and *Bmal1*^{-/-} mice had decreased expression of *Ihh* in the growth plate (Table 1) (Takarada *et al.* 2012). In light of this evidence, it has been suggested that PTHrP also conveys time information to articular chondrocytes (Okubo *et al.* 2015), although definitive evidence is still lacking.

Bone

Bone is a specialised connective tissue that provides mechanical integrity for locomotion, protection to vital organs (e.g. brain, heart and lungs) and encloses the medullary cavities containing bone marrow wherein haematopoiesis occurs (Morgan *et al.* 2013, Ho *et al.* 2015). It also functions as a calcium and phosphate reservoir, being involved in the metabolic pathways associated with mineral homeostasis (Copp & Shim 1963). Bone is predominantly composed of inorganic materials of which calcium hydroxyapatite is the most abundant; the organic component, which is embedded in the calcified bone matrix, is enriched in type I collagen, but also includes proteoglycans, glycoproteins and calcium-binding proteins (Morgan *et al.* 2013).

To preserve its function and structure, bone undergoes two processes, modelling and remodelling, which depend on the coordinated action of the three major cell types present in the adult skeleton: osteoblasts, osteocytes and osteoclasts (Allen & Burr 2014). In bone modelling, the uncoupled action of osteoblasts and osteoclasts on separate surfaces ensures appropriate bone morphology and mass; it occurs primarily during childhood and at low rates throughout adult life in response to changes in mechanical loading (Allen & Burr 2014, Bartl & Bartl 2017). In contrast, bone remodelling is characterised

by the coupled action of osteoclasts and osteoblasts on the same surface; it takes place in the mature skeleton as an adaption to mechanical loading and calcium and phosphate metabolism (Allen & Burr 2014, Bartl & Bartl 2017). Bone homeostasis can only be maintained when there is a strict temporal control of osteoclast-mediated bone resorption and osteoblast-mediated bone formation.

Evidence of circadian rhythms in bone

Initial studies into the circadian regulation of bone metabolism revealed that bone formation is diurnally regulated in rat metaphyseal bone; the most intense period of bone matrix mineralisation occurred during the night-time and was in antiphase with matrix synthesis (Simmons & Nichols 1966, Russell *et al.* 1984, Igarashi *et al.* 2013). Diurnal variations in the levels of serum markers of bone metabolism have also been reported, including N- and C-telopeptide, osteocalcin, pyridinoline, FGF23, tartrate-resistant acid phosphatase, alkaline phosphatase, calcium, phosphorus, calcitonin and PTH (Gundberg *et al.* 1985, Greenspan *et al.* 1997, Srivastava *et al.* 2001, Shao *et al.* 2003, Kawai *et al.* 2014, Swanson *et al.* 2017).

More recently, peripheral clocks in bone have been investigated at the molecular level. Transcriptome analysis of cavari bone from mice kept in a 12-h light/12-h darkness cycle revealed that 26% of the genes represented on the microarray exhibited a circadian expression profile (Zvonic *et al.* 2007). Many of these rhythmic genes were related to bone metabolism, including genes involved in BMP-, Wnt- and FGF-mediated signalling, as well as genes encoding matrix structural components (e.g. fibrillins and collagens) and remodelling enzymes (e.g. *Adamts1*, *Adamts3* and *Adamts5*) (Zvonic *et al.* 2007, Yang & Meng 2016). To the best of our knowledge, genome-wide circadian transcriptome/proteome studies have not been performed in long bones or cells derived from it. Nonetheless, robust circadian oscillations of PER2::Luc have been identified in *ex vivo* cultures of both long (proximal femoral ends and radiuses) and flat bones (calvariae and scapulae) (Okubo *et al.* 2013). Despite these progresses, evidence for sustained molecular circadian rhythms in isolate bone cells (osteoblasts, osteoclasts and osteocytes) remains lacking.

Links between dysregulation of circadian rhythms and bone homeostasis

The molecular clock is an important regulator of bone metabolism and circadian rhythm disruption has

been increasingly recognised as a contributing factor to pathophysiological changes in bone. For instance, population-based studies indicated that rotating shift work, which is characterised by a chronic and repeated misalignment between internal clock time and external time cues, was associated with low bone mineral density in trabecular and cortical bones (Quevedo & Zuniga 2010), and a greater risk of hip and wrist fractures (Feskanich *et al.* 2009).

Leptin is a hormone predominantly secreted by adipocytes that participates in the regulation of bone remodelling, acting both on osteoblasts and osteoclasts to maintain bone mass constant (Ducy *et al.* 2000, Takeda *et al.* 2002, Eleftheriou *et al.* 2005). Interestingly, mice lacking *Per1* and either *Per2* (*Per1*^{-/-}*Per2*^{-/-}) or the *Per2* Per-Arnt-Sim (PAS) domain (*Per1*^{-/-}*Per2*^{m/m}) presented a

significant increase in bone mass that affected vertebrae and long bones, suggesting that bone remodelling could be under circadian control (Table 2) (Fu *et al.* 2005). *Cry1*^{-/-}*Cry2*^{-/-} mice also exhibited a similar phenotype (Fu *et al.* 2005). Biochemical and histomorphometric analyses established that this high bone mass phenotype was linked to an increase in the number of osteoblasts, increased mineral apposition and bone formation rate (Fu *et al.* 2005). Evidence was also presented that leptin-mediated modulation of osteoblast function comprises two antagonistic pathways: on one hand, signalling through β 2-adrenergic receptors upregulated *Per1* and *Per2*, which in turn suppressed the expression of G1 cyclins and osteoblast proliferation; on the other hand, leptin acted through the AP-1 family of transcription factors to stimulate osteoblast proliferation and bone formation

Table 2 Summary of the phenotypes observed in bone from mouse models deficient in core circadian clock components.

Mouse strain	Phenotype	Molecular changes	References
<i>Bmal1</i> ^{-/-}	Ectopic ossification of tendons and ligaments associated with bone insertion sites	Not shown	(Bunger <i>et al.</i> 2005)
	Increased rates of bone formation and mineral apposition Increased number of osteoblasts	Not shown	(Fu <i>et al.</i> 2005)
	Low bone mass	Not shown	(Kondratov <i>et al.</i> 2006, Samsa <i>et al.</i> 2016, Takarada <i>et al.</i> 2017)
		Increased expression of <i>Mmp9</i> , <i>CatK</i> , <i>Trap</i> , <i>Rank</i> , <i>Calcr</i> and <i>Rankl</i> in femur	(Takarada <i>et al.</i> 2017)
	Decreased number of active osteoblasts and osteocytes Reduced ability of bone marrow mesenchymal stem cells to differentiate into osteoblasts	Not shown	(Samsa <i>et al.</i> 2016)
<i>Bmal1</i> ^{osc/-}	High bone mass Reduced bone resorption	Decreased expression of <i>Acp5</i> and <i>Nfatc1</i>	(Xu <i>et al.</i> 2016)
<i>Bmal1</i> ^{osx/-}	Low bone mass Increased bone resorption	Not shown	(Takarada <i>et al.</i> 2017)
<i>Per1</i> ^{-/-} <i>Per2</i> ^{-/-} <i>Per1</i> ^{-/-} <i>Per2</i> ^{m/m}	High bone mass Increased number of osteoblasts, mineral apposition and bone formation rate	Not shown Decreased expression of <i>Bmal1</i> , <i>Clock</i> , <i>Cry1</i> , <i>Per1</i> , <i>Per2</i> and <i>Osx</i> Increased expression of <i>Ccnd1</i> , <i>Ccnd3</i> , <i>Ccne</i> , <i>c-Fos</i> , <i>JunB</i> and <i>Fra2</i>	(Fu <i>et al.</i> 2005)
<i>Cry1</i> ^{-/-} <i>Cry2</i> ^{-/-}		Not shown	
<i>Per2</i> ^{m/m}	High bone mass Increased osteoblast number and bone formation rate	Not shown	(Maronde <i>et al.</i> 2010)
<i>Cry2</i> ^{-/-}	High bone mass Normal osteoblast number, but decreased osteoclast activity	Not shown	

(de Crombrughe 2005, Fu *et al.* 2005). A subsequent study performed in *Per2^{m/m}Cry2^{-/-}* mice indicated that these clock genes affect distinct bone formation pathways, with *Cry2* and *Per2* modulating osteoclast and osteoblast function, respectively (Table 2) (Maronde *et al.* 2010).

In adult mice, ablation of *Bmal1* resulted in a low bone mass phenotype that is characterised by significant reductions in bone mineral density and volume (Table 2) (Kondratov *et al.* 2006, Samsa *et al.* 2016, Takarada *et al.* 2017). These mice had a significantly lower number of active osteoblasts and osteocytes than wild-type littermates, which could be explained by a reduced ability of bone marrow mesenchymal stem cells to differentiate into osteoblasts (Samsa *et al.* 2016). Moreover, it has been reported that BMAL1 is involved in osteoclastogenesis by regulating the calcitriol-induced expression of *Rankl* in osteoblasts (Takarada *et al.* 2017). These findings contrast another study in *Bmal1^{-/-}* adolescent mice that showed an increase in the number of osteoblasts, accompanied by increased rates of bone formation and mineral apposition (Fu *et al.* 2005). A recent study showed that tamoxifen-induced post-natal ablation of *Bmal1* in adult mice did not recapitulate the skeletal phenotype presented by *Bmal1^{-/-}* (Yang *et al.* 2016b). Altogether, these data suggest BMAL1 could have distinct roles in the regulation of bone homeostasis throughout development and post-natal stages.

The role of BMAL1 in bone remodelling processes is not limited to osteoblasts. In mice, targeted deletion of *Bmal1* in osteoclasts led to the development of a high bone mass phenotype (Table 2) (Xu *et al.* 2016). The observed reduction in bone resorption was related to the direct upregulation of *Nfatc1*, a master regulator of osteoclast differentiation, by the CLOCK-BMAL1 complex (Kim & Kim 2014, Xu *et al.* 2016). Furthermore, it was demonstrated that expression of BMAL1 is reduced in bone marrow cells isolated from a type 2 diabetes rat model (Li *et al.* 2018). Complementary *in vitro* studies suggested that this core clock protein fine tunes the equilibrium between osteogenesis and osteoclastogenesis through modulation of the NF- κ B signalling pathway (Li *et al.* 2018).

Hypophosphatemia during skeletal development impairs the mitochondria-mediated apoptosis of hypertrophic chondrocytes, leading to abnormal growth plate maturation and bone mineralisation (Sabbagh *et al.* 2005, Miedlich *et al.* 2010). Expression of clock genes in fracture calluses from hypophosphataemic mice was higher than that in control littermates, suggesting that phosphate metabolism is involved in the regulation of the circadian clock in bone (Noguchi *et al.* 2018).

Remarkably, network analysis identified *Ezh2* (enhancer of zeste homolog 2), a key epigenetic regulator of skeletal longitudinal growth, as one of the main molecules associated with hypophosphatemia (Dudakovic *et al.* 2015, Lui *et al.* 2016, Noguchi *et al.* 2018). Previous work revealed that EZH2 binds to the promoter region of *Per1* and *Per2*; and targeted silencing of this histone methyltransferase disrupted circadian rhythms (Etchegaray *et al.* 2006). In adolescent mice, ablation of *Ezh2* in bone marrow nestin-expressing cells resulted in premature cellular senescence and a depleted pool of mesenchymal progenitor cells; this was associated with impaired osteogenesis and a higher risk of developing osteoporosis later in life (Li *et al.* 2017).

Besides controlling mineral homeostasis, the skeleton is also an active modulator of energy metabolism (Kawai & Rosen 2010). CLOCK-BMAL1 heterodimers directly control the expression of *Noc* (nocturnin), a RNA deadenylase that participates in the post-transcriptional regulation of metabolic genes (Li *et al.* 2008, Stubblefield *et al.* 2012). *In vitro* studies demonstrated that *Noc* modulates the fate of bone marrow stromal cells by promoting adipogenesis and suppressing osteoblastogenesis (Kawai *et al.* 2010a). *Noc^{-/-}* mice presented a high bone mass phenotype and a reduced number of adipocytes in the bone marrow, indicating a shift in stromal cell differentiation that favours osteoblastogenesis (Kawai *et al.* 2010a, Guntur *et al.* 2011). NOC has been shown to bind to PPAR γ (peroxisome proliferator-activated receptor γ), promoting its nuclear translocation and activity (Kawai *et al.* 2010a). PPAR γ activation favoured the differentiation of bone stromal cells into adipocytes and suppressed osteogenic signalling pathways such as BMP, TGF- β and WNT, as well as osteoblast-specific transcription factors (e.g. *Runx2*, *Sox9*, and *Sp7*) (Shockley *et al.* 2009). *In vivo* silencing of *Pparg* caused a reduction in the number of bone marrow adipocytes that was accompanied by increased trabecular bone formation (James *et al.* 2014). Furthermore, overexpression of the clock gene *Rev-erba* (a direct target of PPAR γ) in bone mesenchymal stem cells inhibited cell proliferation and osteogenesis (Fontaine *et al.* 2003, He *et al.* 2015).

IGF-1 (insulin-like growth factor type 1) is an anabolic factor that plays an important role in the differentiation of mesenchymal stem cells into osteoblasts (Xian *et al.* 2012, Crane *et al.* 2013). In mouse femur, circadian expression of *Igf1* was in antiphase with the clock-regulated transcription of *Noc*; and NOC was shown to interacting with the longer form of the 3' untranslated region of *Igf1* to reduce the expression of this growth factor (Kawai *et al.* 2010b). Circadian rhythms in IGF-1 signalling were

perturbed in *Cry*-deficient mice; and it was proposed that CRY-mediated regulation of STAT5B (signal transducer and activator of transcription 5) phosphorylation could mediate the downregulation of *Igf1* (Chaudhari *et al.* 2017). Moreover, IGF-1 can induce the phosphorylation of PTH1R *in vitro*, enhancing osteoblast to osteocyte transition and providing another link between the circadian clock, IGF-1 and PTH (Jubiz *et al.* 1972, Fuleihan *et al.* 1997, Qiu *et al.* 2018). More recently, it has been demonstrated that IGF-1-mediated signalling is sufficient to modulate the phase and amplitude of circadian rhythms *in vivo* and *in vitro* through increased PER synthesis (Crosby *et al.* 2019); future studies should seek to investigate whether these mechanisms are also relevant for skeletal homeostasis.

Systemic signalling through glucocorticoids is also a fundamental time cue for the circadian regulation of bone homeostasis. The addition of dexamethasone, a glucocorticoid hormone analogue, to osteoblasts and osteoclasts stimulated the rhythmic mRNA expression of circadian genes, as revealed by time course qPCR (Komoto *et al.* 2012, Fujihara *et al.* 2014). The circadian profile of osteoclast-specific genes such as *Ctsk* and *Nfatc1* disappeared in bone tissue from adrenalectomised mice; and these oscillations were restored by intraperitoneal injection of dexamethasone (Fujihara *et al.* 2014). In addition, overexpression of the transcriptional regulator *Gilz* (glucocorticoid-induced leucine zipper) enhanced osteogenic differentiation of bone marrow stromal cells *in vitro* by blocking the transcription of *Pparg* (Shi *et al.* 2003, Zhang *et al.* 2008, Pan *et al.* 2014).

Clinical relevance of circadian biology for skeletal disorders

The numerous connections between the circadian clock and skeletal homeostasis bring about the possibility of targeting circadian rhythms to improve existing therapies and develop new routes. One approach is to adopt the concept of 'chronotherapy', in which the drug regimen is tailored to a patient's circadian rhythm in order to maximise treatment effectiveness and reduce adverse effects (Selfridge *et al.* 2016). Over 40 years ago, it was reported that OA and RA symptoms can be improved by timing the intake of indomethacin and flurbiprofen; and treatment efficiency was correlated with the individual circadian variation of pain (Huskiisson *et al.* 1970, Kowanko *et al.* 1981, Levi *et al.* 1985). More recently, it was demonstrated that timing teriparatide dosing affected the circadian rhythms of bone resorption markers in postmenopausal

osteoporotic women (Luchavova *et al.* 2011). One of the most compelling examples of how circadian biology could be important when defining chronotherapeutic strategies comes from the use of glucocorticoids to treat RA. A landmark study revealed that coordinating glucocorticoid administration with the nocturnal rise in circulating levels of IL-6 substantially reduced joint pain and stiffness in comparison to standard morning administration (Arvidson *et al.* 1997). Subsequent clinical trials with modified-release prednisone which enables convenient bedtime administration demonstrated that this timed drug delivery noticeably increased treatment response rates and improved physical function (Buttgereit *et al.* 2008, 2010, 2013). These results emphasise the importance of implementing chronotherapy when designing clinical trials and evaluating treatment outcomes.

Another strategy to treat circadian disruptions is to use small molecules that directly target the clock or closely related pathways (Wallach & Kramer 2015). As the circadian clock is involved in the regulation of a multitude of signalling pathways, this approach might prove advantageous in comparison to polytherapy wherein two or more drugs are used to target distinct pathways. In fact, several compounds targeting clock proteins such as CRY1/2 and ROR have already been described, with beneficial effects in animal models for metabolic diseases (Hirota *et al.* 2012, He *et al.* 2016, Dierickx *et al.* 2019). For example, nobiletin is a naturally occurring polymethoxylated flavone present in citrus peels that enhances the amplitude of circadian rhythms in mouse (He *et al.* 2016). Remarkably, treatment of diet-induced obese mouse with nobiletin counteracted metabolic syndrome and increased energy expenditure and locomotor activity (He *et al.* 2016). RORs were identified as direct protein targets for nobiletin, acting as an agonist and enhancing *Bmal1* transcription (He *et al.* 2016). Additionally, synthetic REV-ERB agonists have been shown to alter circadian expression patterns of metabolic genes in the liver, skeletal muscle and adipose tissue; and these changes resulted in increased energy expenditure (Solt *et al.* 2012). In the case of skeletal disorders, the therapeutic potential of small-molecule modulators remains largely unexplored; yet, these compounds offer promising approaches to modulate circadian timing and restore cellular homeostasis.

Lastly, behavioural interventions such as the maintenance of robust daily schedules in feeding and sleep/wake cycles have been increasingly recognised as potential approaches to strengthen circadian rhythms (Schroeder & Colwell 2013, Longo & Panda 2016). However, peripheral

clocks seem to have evolved distinctive entrainment mechanisms by which the endogenous circadian clock is reset or synchronised with exogenous time cues, indicating the need to identify tissue-specific time cues (Guo *et al.* 2005, Izumo *et al.* 2014). Molecular components of the circadian clock have previously been identified as mechanosensitive in mammals and fruit flies (Kanbe *et al.* 2006, Simoni *et al.* 2014). In skeletal disorders, a balanced physical exercise schedule has been shown to be effective in improving musculoskeletal functions and reducing symptom severity (Roddy *et al.* 2005, Cooney *et al.* 2011, Moreira *et al.* 2014). From a circadian viewpoint, it is worth considering not only the duration and frequency of exercise, but also its timing; scheduled exercise that is optimised according to an individual's chronotype, a human attribute that defines whether an individual prefers to be active and alert during the morning versus evening, is likely to be more effective than the random and irregular practice of physical exercise (Riley & Esser 2017, Duglan & Lamia 2019).

Concluding remarks

In modern 24/7 societies, the prevalence of circadian rhythm disruption is rising as more and more people have adopted nocturnal lifestyles. Nonetheless, circadian rhythm disruption is yet to be recognised as a major public health issue; and the circadian modulation of physiology

has been largely overlooked in clinical research and practice.

Over the last decade or so, several lines of evidence have shed light onto the complex interactions between the circadian clock and the skeletal system (Fig. 3). Genome-wide expression studies have established molecular clocks as pivotal modulators of the temporal segregation of metabolism in bone and cartilage cells. Studies in transgenic mouse models have linked the disruption of the molecular clock machinery to imbalances in processes such as cartilage matrix synthesis/degradation and bone formation/resorption, which often predispose the tissue to pathophysiological changes. In addition, epidemiological studies have also associated circadian rhythm disruption with a greater risk of developing skeletal disorders such as arthritis and osteoporosis.

Despite these recent advances, our understanding of the multiple levels of circadian regulation of skeletal metabolism and physiology remains largely unexplored. Future work will require conditional tissue-specific and cell-type-specific inactivation or overexpression of different molecular clock components to distinguish between gene-specific (e.g. during development) and post-natal clock-related functions. In addition, epidemiological studies should account for individual chronotype variability by including stratification approaches. Although the translational applications of circadian biology are only beginning to be explored, the clinical implementation of chronotherapy to treat RA resulted in significant benefits

Figure 3

The circadian control of skeletal homeostasis. The central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus modulates the rhythmicity of physiological processes, such as sleep-wake and feeding-fasting cycles, fluctuations of core body temperature and physical activity. These processes also serve as circadian time cues that can entrain the peripheral clocks present in the skeletal system, such as in articular cartilage and bone. Molecular clocks control a spectrum of genes and pathways that are essential for the maintenance of skeletal homeostasis: in cartilage and bone they are involved in the temporal regulation of chondrocyte and osteoblast/osteoclast metabolism, respectively. Ultimately, circadian rhythm dysregulation can result in pathophysiological changes and the development of skeletal disorders such as arthritis and osteoporosis.

for patients. By taking into consideration the multifaceted role of the circadian clock in skeletal homeostasis, new therapies could be developed that will greatly enhance therapeutic index and bring us one step closer to precision medicine.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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