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The circadian clock and extracellular matrix homeostasis in ageing and age-related diseases

Michal Dudek, Joe Swift and Qing-Jun Meng*

Wellcome Centre for Cell Matrix Research, Division of Cell Matrix Biology and Regenerative Medicine, Faculty of Biology, Medicine and Health, University of Manchester, Oxford Road, Manchester, UK

*Corresponding author: Email: Qing-Jun.Meng@manchester.ac.uk

Abstract: The extracellular matrix (ECM) is the non-cellular scaffolding component present within all tissues and organs. It provides crucial biochemical and biomechanical cues to instruct cellular behaviour and has been shown to be under circadian clock regulation, a highly conserved cell-intrinsic time keeping mechanism that has evolved with the 24-hour rhythmic environment. Ageing is a major risk factor for many diseases, including cancer, fibrosis and neurodegenerative disorders. Both ageing and our modern 24/7 society disrupt circadian rhythms, which could contribute to altered ECM homeostasis. Understanding the daily dynamics of ECM and how this mechanism changes with age will have profound impact on tissue health, disease prevention and improving treatments**.** Maintaining rhythmic oscillations has been proposed as a hallmark of health. On the other hand, many hallmarks of ageing turn out to be key regulators of circadian timekeeping mechanisms. In this review, we summarise new work linking the ECM with circadian clocks and tissue ageing. We discuss how the changes in the biomechanical and biochemical properties of ECM during ageing may contribute to circadian clock dysregulation. We also consider how dampening of clocks with age could compromise daily dynamic regulation of ECM homeostasis in matrix rich tissues. This review aims to encourage new concepts and testable hypotheses about the two-way interactions between circadian clocks and ECM in the context of ageing.

The extracellular matrix and ageing

The evolution of multi-cellular organisms from single cell organisms was one of the most significant transitions in the evolution of life on Earth. This evolutionary step was critical to enabling organisms to escape predation, colonize new environments and store and share oxygen and food. A key mediator of metazoan multi-cellularity is the extracellular matrix (ECM), which is required to bridge between cells to form specialised functional tissues and organs, for communication, and to support cell survival and differentiation (1, 2). The ECM is an intricate network of multi-domain macromolecules forming a biochemical and biomechanical local cellular microenvironment for cells to function within. Broadly speaking, animals have two types of ECM: the specialised basement membrane for epithelial tissues, and the interstitial matrix. Major components of the ECM are collagens, elastin, proteoglycans and cell-binding glycoproteins. The composition, structure and mechanical properties of the ECM maintain the size, shape and function of tissues and organs (3). In addition to being important structural components, the ECM also contains a reservoir of growth factors and bioactive molecules that are critical regulators of cell signalling. Through direct interactions between cells and matrix components and through the effects of adhesion signalling receptors, the ECM is critical for physiological tissue functioning. The ECM is a highly dynamic entity and vital to control the most fundamental behaviours of cells, instructing cells how to orient themselves (adhesion and polarity), whether and when to divide (proliferation), move (migration) and die (apoptosis), where to deposit molecules (secretion), what cells to develop into (differentiation) and how to respond to external cues. Abnormal functioning of the ECM underpins many of the pathologies associated with advancing age and therefore represents a promising therapeutic avenue for the treatment of fibrosis, cancer and wound healing (4–9).

During ageing, the integrity of the ECM declines through the accumulation of fragmented collagens, oxidation, glycation, and protein aggregates, resulting in the deterioration of ECM dynamics and subsequent tissue fibrosis (10–14). ECM stiffness increases with age due to the progressive increase of enzymatic and stochastic non-enzymatic intra-intermolecular covalent bonds (crosslinks) between molecules with slow rates of turnover, such as fibrillar collagens and elastin (15). Interestingly, dual inhibition of crosslinking enzymes lysyl oxidase like 2 and 3 (LOXL2 and LOXL3) was sufficient to normalise collagen fibrillogenesis, reducing tissue stiffness. Thus, inhibition of collagen crosslinking can maintain mechano-homeostasis to limit the self-sustaining effects of ECM on progressive fibrosis and aging (16). Of note, while increased ECM stiffness might drive the senescent phenotype in aging and chronic fibrotic diseases, ECM derived from young human fibroblasts induces a youthful state in aged senescent cells (17, 18). The fibrotic process is promoted by excessive secretion of transforming growth factor beta (TGFβ) and nuclear translocation of the transcription factor yes-associated protein 1 (YAP1) and its paralog WW domain-containing transcription regulator protein 1 (TAZ) with an increase of matrix stiffness (19). The YAP/TAZ molecules act as mechano-transducers and trigger the expression of pro-fibrotic genes such as transglutaminase-2 and lysyl oxidases (17). However, the link between ageing and the YAP/TAZ signalling is not as straightforward and may be dependent on tissue context as genetic inactivation of YAP/TAZ in stromal cells causes accelerated aging, while sustaining YAP function rejuvenates old cells and prevents the emergence of aging features by controlling “inflammaging” (20)

Circadian biology

Circadian (‘circa’, about; ‘dia’, day) clocks are molecular mechanisms that allow organisms to synchronize their internal biological processes with the external day-night cycles of their environment. These clocks are evolutionarily conserved and found in virtually all organisms, ranging from bacteria, fungi, plants to mammals including humans. The circadian clocks operate through a cell-intrinsic and permissive biochemical mechanism that enable the adaptation and anticipation of environmental changes (21). The circadian system is composed of a network of central and peripheral clocks, which respond to rhythmic input pathways (zeitgeber, or time cue) and control diverse targets by rhythmic regulation of clock-controlled genes (CCGs). Peripheral clocks are synchronized by a master clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus, which receives light input from the retina. The peripheral clocks in various tissues and organs also receive input from other cues such as food, body temperature, and hormones. The output from the circadian clocks is complex and tissue-specific, regulating a wide range of physiological processes including metabolism, hormone secretion, and immune function (22, 23). The circadian clock is comprised of a transcriptional-translational feedback loop (Figure 1). This loop involves a set of core clock genes, including Period (*Per*), Cryptochrome (*Cry*), *Clock* and *Bmal1*. These genes form a regulatory network that oscillates over a 24-hour period and drives the expression of CCGs. The transcriptional-translational feedback loop is tightly regulated by post-translational modifications, including phosphorylation, acetylation, and ubiquitination (24–27).

Circadian clock and ageing, reciprocal regulation

Ageing is associated with a number of changes in the circadian clock system. Phase advance and amplitude dampening are well-established changes during human ageing, which can be observed in melatonin secretion, body temperature, and fibroblast rhythms (28). Studies in animals have also demonstrated a decline in the robustness of behavioural rhythmicity, dampening of the amplitude and changes in circadian phase of various tissue clocks with age (29–32). This age-related decline in circadian rhythm leads to impaired sleep, altered metabolic processes and increased susceptibility to disease (28). Ageing also leads to a profound reprogramming of the circadian targets in skin and muscle stem cells to cope with the different needs of aged cells. In aged mice, epidermal and muscle stem cells retain a robustly rhythmic core circadian machinery, but the rhythmic transcriptome is extensively reprogrammed, switching from genes involved in homeostasis to those involved in tissue-specific stresses, such as DNA damage or inefficient autophagy (33). Similarly, liver from aged mice also showed genome-wide reprogramming, which was proposed to contribute to the progression of age-related diseases, such as cancer and neurodegeneration (33–35). Several well-established hallmarks of ageing (36) are known to regulate the circadian clock and are themselves under circadian clock control, forming feedback loops. For instance, the enzyme sirtuin 1 (Sirt1) has been implicated in regulating the circadian clock through deacetylation of key clock proteins (24, 37), while nicotinamide phosphoribosyl transferase (NAMPT), the rate-limiting enzyme for NAD+ salvage pathway, is a rhythmically expressed protein under clock transcriptional control (38). The protein complex mechanistic target of rapamycin complex 1 (mTORC1) regulates the circadian clock through phosphorylation of BMAL1 by its effector kinase S6K1, while its activity is also affected by circadian clock dampening in aging (39, 40). The nutrient sensing/AMPK pathway has been shown to affect the circadian clock through degradation of PERs and CRYs (41, 42). The circadian clock undergoes significant alterations in both cell-intrinsic mechanisms such as senescence, autophagy, and the unfolded protein response, as well as systemic changes in hormone levels, temperature regulation, and neuroendocrine signalling (28, 43).

Studies in various clock knockout and mutant models have demonstrated accelerated tissue ageing and reduced lifespan. Most notably, *Bmal1* knock-out mice are extremely short lived and display conditions related to ageing, e.g., sarcopenia, cataracts, cornea inflammation, osteoporosis, ectopic calcification of joints and premature hair loss (44). Mice with mutations in *Clock*, *Per1* and *Per2* also show reduced lifespan and age-related diseases such as cataracts, hypoinsulinaemia and diabetes, early decline in fertility, kyphosis and increased tumour incidence (45–47). Disruptions to circadian clocks in mice have also been associated with fibrotic diseases in tissues such as lung, kidney, heart and adipose (48–51). Rotating shift work (and by extension chronic jet lag) that disrupts circadian rhythms has been proposed as risk factors for a wide range of human conditions (52–54). Most notably, epidemiological studies of shift workers revealed increased prevalence of breast cancer, metabolic syndrome, cardiovascular disease, osteoporosis, and bone fractures (55–59). This effect is recapitulated in animal experiments by prolonged environmental disruption of the circadian rhythm through frequent shifting of the light/dark phases or misalignment of feeding with normal activity phase. Animals with rhythm disruptions showed increased incidences of metabolic syndrome, premature cellular ageing, immune senescence, shortened lifespan, increased cancer risk and osteoarthritis (60–64). In humans, even short experimental protocols of circadian misalignment result in decreased leptin, increased arterial mean pressure and glucose level and post-prandial response resembling pre-diabetic state (65). While chronic misalignment caused by exposure to artificial light at night or residency in polar regions was also found to be deleterious to human health (66, 67). On the other hand, circadian clock disruption may be part of the disease process. For example, disrupted circadian rhythms and sleep are an early warning sign for a range of age-related neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's (68). Expression of circadian clock genes was found to be dysregulated in mouse model of induced osteoarthritis and in human cartilage from osteoarthritis patients undergoing joint replacement (69–71). Severity of human intervertebral disc degeneration is correlated with downregulation of clock genes, while experimental approaches suggest that abnormal mechanical load negatively affects the clock which may contribute to loss of tissue homeostasis (72, 73). A range of pulmonary diseases, including age related pulmonary fibrosis, show time of day dependent symptoms, response to treatment and a striking correlation with dysregulated clock gene expression (74). However, it is still challenging to disentangle the cause and effect relationship between circadian clock disruption and age-related diseases.

Circadian control of ECM homeostasis in matrix-rich tissues

As an integral temporal regulator of tissue physiology throughout the 24-hour day, the circadian regulation of ECM homeostasis is especially salient in matrix-rich tissues (Figure 2). In the skin, cutaneous circadian clocks have been shown to control cell migration and proliferation, stem cell differentiation and susceptibility to oxidative stress or UV damage (75). Of note, dermal fibroblasts, the main ECM-synthesising cell type in the skin, have been widely used as a model of peripheral circadian clocks (76). The cell-autonomous clock in fibroblasts was shown to drive a temporal proteomic program that imposed rhythmic regulation upon the actin cytoskeleton, such as cytoskeletal regulators, such as cofilin 2 and RhoA (76). Critically, the fibroblast circadian clock modulates the efficiency of actin-dependent processes, including cell migration and adhesion, leading to a time-of-day dependent wound healing response in cells, skin explants and in patients with burns (76). In collagen-rich tendon tissue, the circadian clock was shown to control endoplasmic reticulum-to-plasma membrane procollagen transport by the sequential rhythmic expression of SEC61, TANGO1, PDE4D and VPS33B. In addition, collagen degradation also appears to be rhythmic, attributed to the rhythmic levels of the enzyme cathepsin K (77). It was proposed that the daily homeostasis of persistent collagen network in tendon is maintained by a rhythmic sacrificial pool of dynamic and newly synthesized collagen I (77). Moreover, tendon-derived fibroblasts exhibit a circadian rhythm in composition of released extracellular vesicles with notable circadian control of matrix metalloproteinase 14 (MT1-MMP) (78).

Articular cartilage is a highly specialised connective tissue that lines the surface of long bones in the joints. It consists of a dense ECM and sparsely populated chondrocytes. The circadian rhythm in articular cartilage acts to temporally segregate the activities of ECM-related anabolic and catabolic molecules to optimal times of the day, as revealed by time series transcriptomics profiling (31, 70). Most rhythmic genes peaked during subjective daytime (resting phase in mice), including processes related to extracellular matrix and proteolysis e.g., Mmp14 and Adamts4 proteinases, Timp4 proteinase inhibitor, key chondrocyte transcription factor Sox9, and genes encoding two major cartilage structural components Acan (the proteoglycan aggrecan) and Col2a1 (collagen type II alpha I), among others). At protein level, time-resolved proteomics revealed a circadian rhythm in adhesion related molecules and matrisome proteins such as growth factors CTGF and CYR61 which are essential in cartilage homeostasis, SERPINE1 (a protease involved in regulation of inflammatory response), as well as enzymes PLOD1 and PLOD2 (responsible for hydroxylation of lysine during collagen synthesis) (79). These findings are consistent with circadian control of ECM molecules in human chondrocytes, where knocking down of BMAL1 led to an increase in the expression of catabolic genes (such as MMP1, MMP3, MMP13, ADAMTS5 proteinase genes) and dysregulated TGFB signalling (71, 80–82). Interestingly, environmental disruption or chondrocyte-specific genetic deletion of the circadian clock mechanism resulted in impaired cartilage homeostasis, disorganisation of the matrix structure and progressive degeneration (31, 63). Similar findings were also reported in another ECM-rich tissue of the skeletal system, the intervertebral disc (IVD), with rhythmic regulation of genes relating to ECM turnover (e.g. Adamts1, Timp4, Itgb1) and ER stress (e.g. Pak1, Atf6) (30). Col2a1-*Bmal1* knockout mice show age-related ECM phenotypes in the IVD, including collagen fibril thinning, disorganisation and ossification (83).

ECM regulation of circadian clocks

Recent studies have shown that biochemical and biomechanical cues from the ECM can regulate circadian clocks in a manner specific to cell and tissue type, and that these cues may contribute to tissue ageing and age-related diseases (Figure 2). Biochemical matrix-derived signalling pathways, such as those mediated by TGFβ, have been implicated as peripheral coupling factors that mediate paracrine phase adjustment of molecular clocks through transcriptional regulation of core-clock genes (84). Disruption of TGFβ signalling leads to desynchronization of oscillator networks among cells, with reduced amplitude and increased sensitivity toward external time cues (84).

Biomechanical regulation of circadian clocks is an emerging area of research that has potential implications for understanding tissue ageing (Figure 2). Recent studies have shown that the biomechanical properties of the ECM can influence circadian pacemaking of cells in a tissue and cell type specific manner. The circadian clock and the mechanical properties of the microenvironment both play critical roles in mammary gland ageing. Aged mammary gland was shown to have a less robust circadian clock and a stiffer mechano-microenvironment, as measured by atomic force microscopy. Mammary epithelial cells cultured in a soft environment had a stronger circadian rhythm in expression of clock genes compared to those in stiffer, while stromal fibroblasts from the same tissue showed an inverse response (32). This inverse relationship between epithelial and stromal cells was also demonstrated in other tissues such as lung and skin (32). Thus, it appears that cell-intrinsic clocks are regulated through the biophysics of the cellular microenvironment and local cell-matrix interactions. The stiffness of the cellular microenvironment seems to have a much bigger impact on circadian clock activity than the composition of the ECM (32). The effect of matrix stiffness on the clock is largely mediated by the cytoskeleton. Vinculin knockdown, disruption of the cytoskeleton, and Rho/ROCK-mediated activation of actomyosin contractility all influenced core clock transcription factors. A ROCK inhibitor improved the circadian rhythm amplitude in mammary epithelial cells cultured within a stiff environment in a dose-dependent manner, and increased clock amplitude in older mammary tissue (32, 85). Actin polymerization in response to external signals released MRTF from G-actin sequester, which activated SRF-mediated transcription of clock genes *Per1*, *Per2*, *Nr1d1* and *Nfil3*. By altering actin dynamics using Cytochalasin D and Latrunculin B (inhibitors of actin polymerization) or Jasplakinolide (actin stabilizer), or by blockade of integrin (which provides anchoring of the cells to the ECM and transmits stiffness information to the cytoskeleton), it was possible to modulate the expression of clock genes and regulate the circadian clock (86). These findings suggest that the mechanical properties of the ECM may play an important role in regulating circadian clocks, dysregulation of which could contribute to age-related disease.

Conclusions and future directions

The 24-hour rest/activity rhythm puts time-of-day dependent demands on most organs, tissues, cells, all the way down to cellular organelles and molecular pathways in the body. As a result, many metabolic processes are controlled by the circadian clock and temporally separated allowing segregation of often opposing biochemical reactions. Considering the dynamic nature of ECM remodelling, it is reasonable to predict that some of the involved processes will be separated in circadian time. This may be the case particularly in tissues which are subject to diurnal mechanical loading, and where the ECM comprises a large proportion of the volume of the tissue, such as in cartilage, IVD or tendons. For these ECM-rich tissues, separating clean-up of damaged matrix from assembly and deposition of new matrix could be beneficial.

Disruptions of clock mechanisms are linked to an increased risk of diseases, especially those associated with ageing. In light of these findings, it is highly likely that chronic circadian disruption as experienced by long term rotating shift work or in ageing could contribute to loss of ECM structural integrity and homeostasis, accelerate ageing and predispose to disease. Despite prominent circadian regulation, the roles of the microenvironments in which cells reside have been largely neglected in mammalian circadian biology, partly attributable to the common practice of culturing cells on stiff plastics which have limited physiological relevance. The recent discovery of ECM-dependent clocks highlights the need to consider the niche and cell type-dependent circadian functions. The biomechanical properties of different tissues range from soft (brain, bone marrow and adipose tissue) to stiff tissues (tendon, cartilage and bone) (87). One intriguing question that remains is whether the clock mechanism has evolved to adapt to their specific microenvironment. When the tissue stiffness starts changing, for instance during ageing, fibrosis or cancer, the circadian clock system may lose precision and compromise its rhythmic regulation, further exacerbating the diseases. The cell-specific regulation of circadian timing mechanism by the ECM also highlights the need to investigate clocks in a cell-specific manner and not to generalise findings. Future work should aim to address the scale and extent of ECM-dependent circadian clocks in other tissues and cell types and their implications for disease. The ECM is a dynamic and constantly remodelling structure, and the fragmentation of ECM proteins can result in the release of peptide cytokines, or matrikines, that can have diverse effects on cellular function. These matrikines have been implicated in regulating inflammation, tissue remodelling, and wound healing. However, their potential effects on the circadian clock have not been extensively studied (88). Given age-related changes in ECM composition and remodelling, further research is necessary to test whether matrikines could influence circadian clock functions, a new effector of ECM signalling that could contribute to age-related disease.

Delineating the complexities of how the biophysical and biochemical properties of the ECM influence cellular clocks and the underlying intracellular molecular mechanisms are clearly warranted and will aid our understanding of how disrupted clocks contribute to disease processes and ageing. In addition to rhythmic changes in gene and protein expression, future work should aim to better characterise diurnal changes in ECM physiology at tissue level. Although many rhythmic matrix genes and proteins have been found (by time-resolved RNA-seq and mass spectrometry proteomics experiments, respectively), the correlation between the two is limited, suggesting post-transcriptional or even post-translational circadian control. Indeed, as mentioned earlier, collagen I synthesis and secretion is under circadian control, so is the composition of extracellular vesicles, suggesting multiple levels of rhythmic control over ECM homeostasis. Importantly, recent work has suggested that post-transcriptional and post-translational mechanisms of regulating protein levels are abrogated in ageing and senescent cells (89, 90). Pulse-chase heavy-isotope labelled mass spectrometry experiments could help accurately quantify rates of accumulation and degradation of proteins according to circadian time (91). Moreover, zymography and degradomic studies utilising N-terminal labelling of proteins before tryptic digest, which distinguishes peptides cleaved by proteases *in situ* from tryptic peptides, performed as a circadian time-series experiments could reveal the dynamics of ECM proteases. Inclusion of tissue specific circadian clock knockout samples may help determine the extent to which the local circadian clock mechanism is involved in daily maintenance of the tissues and how much tissue physiology revolves around the diurnal rest/activity cycle. Live imaging approaches of fluorescently-tagged individual ECM molecules could shine light on circadian processes within the matrix. There is also opportunity to investigate whether clock targeting using small molecules could be a new way of modulating the ECM dynamics. Finally, it is imperative to take into account the time-of-day for experimental design and standardization of biomarker detections that involves ECM (e.g., matrikines). Answering these questions will not only reveal new aspects of ECM tissue biology, but also help us understand how disrupted clocks contribute to illness and to ageing. It is the intention of the authors to stimulate efforts to address these new ideas, which will provide new avenues of research into the crossover between extracellular microenvironment and intracellular time-keeping mechanisms throughout the life course.

Figure legends:

Figure 1. The molecular mechanism driving the circadian clock. The circadian clock mechanism is composed of a transcriptional-translational negative feedback loop (TTFL). BMAL1 and CLOCK constitute the positive arm of the clock. The BMAL1/CLOCK complex bind to E-box sequences in promoter regions of target genes to drive rhythmic expression of other clock components (*e.g.,Pers* and *Crys*). PERs and CRYs form the negative arm of the feedback loop. After being synthesised in the cytoplasm, they form a heterodimer and translocate back to the nucleus at night to suppress the transcriptional activity of BMAL1/CLOCK. The cellular localisation and stability of PERs and CRYs are controlled by post-translational modifications via CK1δ/ε, GSK-3β and AMPK kinases. Among the clock target genes, RORs and REV-ERBs regulate the transcription of *Bmal1* gene by competing for ROR Response Elements (RRE) to make the oscillator more robust. RORs are transcriptional activators, while REV-ERBs are transcriptional repressors. PERs and CRYs are subsequently ubiquitinated and degraded by the 26S proteasome, allowing the new cycle to start again. The whole process takes roughly 24 hours to complete.

Figure 2. Processes involved in reciprocal regulation between the circadian clock and the ECM are affected by aging. The circadian clock controls aspects of matrix homeostasis including rhythmic secretion and degradation of collagen, expression of signalling molecules, proteases and their inhibitors. Conversely, the biochemical and biomechanical properties of the ECM influence the strength of circadian rhythm in a cell type specific manner. During aging, the ECM properties are altered and the circadian clocks are dampened, leading to irregular sleep/wake cycle, dampening and misalignment of circadian rhythms in body temperature and hormone levels. On the molecular level, ageing reprograms global rhythmic gene expression patterns to cope with changing needs. This will inevitably affect expression of ECM genes and further propel degenerative changes in ECM composition.

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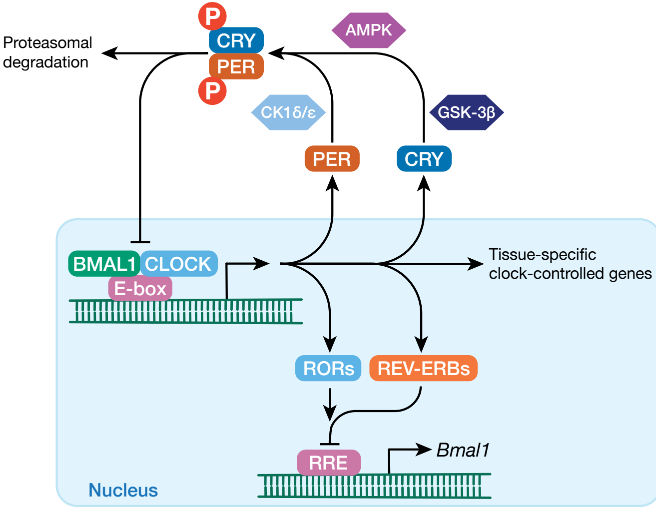

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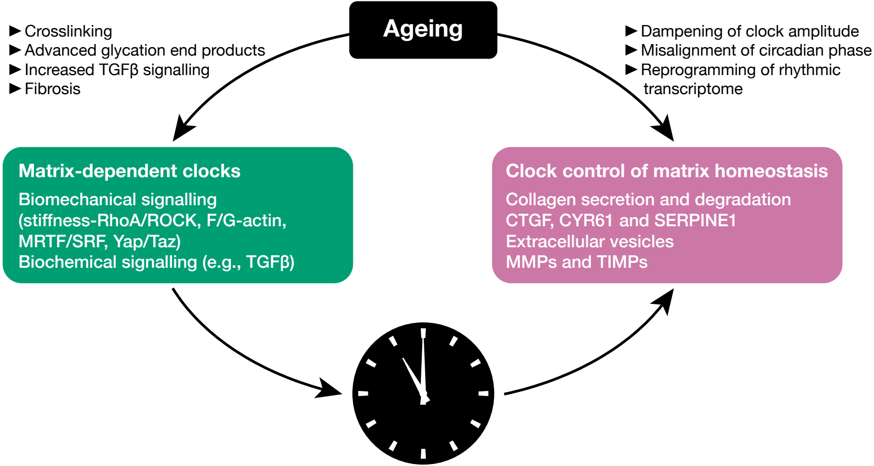
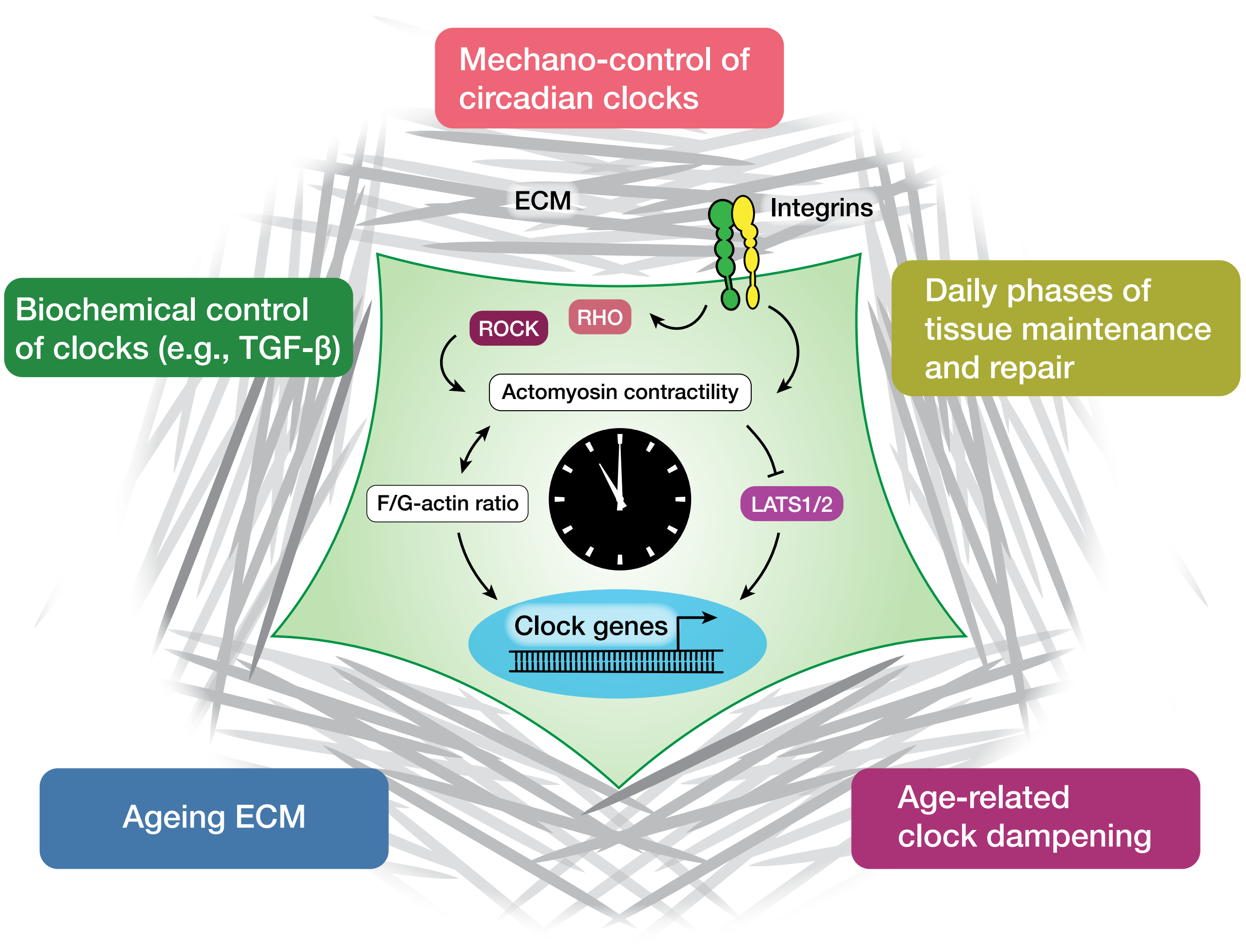

Ageing
► Crosslinking
► Advanced glycation end products
► Increased TGFβ signalling
► Fibrosis
► Dampening of clock amplitude
► Misalignment of circadian phase
► Reprogramming of rhythmic transcriptome
Matrix-dependent clocks
Biomechanical signalling (stiffness-RhoA/ROCK, F/G-actin, MRTF/SRF, Yap/Taz)
Biochemical signalling (e.g., TGFβ)
Clock control of matrix homeostasis
Collagen secretion and degradation
CTGF, CYR61 and SERPINE1
Extracellular vesicles
MMPs and TIMPs


Mechano-control of circadian clocks
Biochemical control of clocks (e.g., TGF-β)
Daily phases of tissue maintenance and repair
Ageing ECM
Age-related clock dampening
ECM
Integrins
ROCK
RHO
Actomyosin contractility
F/G-actin ratio
LATS1/2
Clock genes