Circadian Regulation of Adult Stem Cell Homeostasis and Aging

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ABSTRACT

The circadian clock temporally organizes cellular physiology throughout the day, allowing daily environmental changes to be anticipated, and potentially harmful physiologic processes to be temporally separated. By synchronizing all cells at the tissue level, the circadian clock ensures a coherent temporal organismal physiology. Recent advances in our understanding of adult stem cell physiology suggest that aging and perturbations in circadian rhythmicity in stem cells are tightly intertwined. Here we discuss how circadian rhythms regulate and synchronize adult stem cell functions, and how alterations in clock function during aging modulate the extrinsic and intrinsic mechanisms that determine adult stem cell homeostasis.

INTRODUCTION

Life on earth is subjected to environmental changes affected by the 24-h cycle of the earth's rotation around its axis, which include variations in light (day and night), temperature, food availability, and predator activity. Organisms have evolved clock mechanisms that measure time and allow them to anticipate and adapt to these daily environmental changes. These molecular clocks follow certain principles: i) they are responsive to extrinsic signals that align organisms to the time of day, the so-called Zeitgeber ("time giver" in German) cues; ii) they establish circadian oscillations with periods of approximately 24 h ("circadian" derived from Latin *circa diem*, or "about a day"); and iii) they oscillate with a self-sustained rhythm that persists even in the absence of exogenous Zeitgeber cues, allowing them to anticipate the organism's physiology according to the time of day.

The mammalian circadian clock consists of a complex transcriptional oscillator network regulated by transcriptional/translational feedback loops. The circadian master transcription factor (TF) complex BMAL1 (brain and muscle ARNT-like 1) / CLOCK (circadian locomotor output cycles kaput) binds E-box elements to activate the transcription of their target clock-controlled genes (CCGs). CCGs include *period* (*Per*) and *cryptochrome* (*Cry*), whose protein products in turn inhibit the transcriptional activity of BMAL1 and CLOCK in the core loop (including their own transcription). Proteasome degradation of PER and CRY releases the BMAL1/CLOCK complex inhibition, triggering a new transcription cycle. Additionally, BMAL1/CLOCK transcriptionally promotes the expression of the nuclear receptor subfamily 1 group D member 1 (*Nr1d1* or *REV-ERB-α*) and member 2 (*Nr1d2* or *REV-ERBβ*) as well as of the RAR-related orphan receptor (ROR) group. REV-ERBα and REV-ERBβ, which inhibit *Bmal1* expression, and RORs, which activate *Bmal1* expression, compete for shared DNA binding sites (termed ROREs), thereby further regulating the BMAL1/CLOCK complex and CCGs. Together with other circadian clock–controlled TFs, such as D-box binding PAR BZIP transcription factor (DBP) (Takahashi, 2017), the circadian clockwork establishes transcriptional oscillations of CCGs with various phases of expression (reviewed in (Takahashi, 2017) (Figure 1).

The core clock machinery is expressed in most cells in mammals and generates circadian transcriptional oscillations in all peripheral tissues (Dibner et al., 2010, Zhang et al., 2014, Mure et al., 2018) except testis and thymus (Morse et al., 2003, Alvarez and Sehgal, 2005). A coherent circadian output at the tissue level is established by synchronizing the phase of all cells within the tissue, termed "entrainment". Environmental light sensed by the retina is the dominant entrainment cue. This photic input sets the circadian phase of a cluster of hypothalamic neurons termed suprachiasmatic nuclei (SCN), which in turn transmits the signal to peripheral tissues, thereby acting as a central clock or pacemaker (Dibner et al., 2010). Accordingly, damaging the SCN abolishes rhythmic locomotor activity, rhythmic feeding and drinking, and endocrine rhythms (Moore and Eichler, 1972, Nagai et al., 1978, Stephan and Zucker, 1972). The SCN provides organisms with circadian autonomy – e.g., the ability to anticipate rather than just respond to daily environmental changes. Specifically, it sustains circadian synchronization of peripheral tissue clocks under constant darkness conditions (Guo et al., 2005, Guo et al., 2006), through a combination of direct signals, such as humoral cues and neural signaling through the autonomic nervous system (Cailotto et al., 2009, Gamble et al., 2014, Terazono et al., 2003), as well as indirect signals that depend on rhythmic rest–activity, body temperature, oxygen levels, and/or feeding cycles (Brown et al., 2002, Stokkan et al., 2001, Damiola et al., 2000, Adamovich et al., 2017). Tissues show varying susceptibility and kinetics to different SCN-dependent entrainment cues (Guo et al., 2005, Guo et al., 2006, Damiola et al., 2000, Vujovic et al., 2008, Kiessling et al., 2010). Further, *in vivo* mouse models suggest that some tissues remain synchronized (albeit with a lower oscillatory amplitude) after the SCN is anatomically lesioned (Tahara et al., 2012, Yoo et al., 2004), after genetic disruption of a functional SCN clock (Husse et al., 2014, Izumo et al., 2014, Kolbe et al., 2019), or in absence of clocks in any tissue other than the tissue of interest (Koronowski et al., 2019, Welz et al., 2019). Thus, circadian entrainment of peripheral tissues might require not only dominant signals derived from the SCN (Dibner et al., 2010) but also fine-tuning systemic signals from the peripheral tissues themselves (which are largely still unidentified).

Once synchronized, peripheral tissues display a coherent and highly tissue-specific circadian output (Sato et al., 2017, Koronowski et al., 2019, Zhang et al., 2014, Mure

et al., 2018, Solanas et al., 2017). Tissue specificity is strongly determined by how the core circadian transcriptional machinery abides to the specific epigenetic landscape, and by TFs that define the lineage (Yeung et al., 2018, Papazyan et al., 2016, Takahashi, 2017). Post-transcriptional and post-translational regulatory mechanisms also contribute to establishing rhythmic gene expression even in the absence of rhythmic transcriptional changes (Mauvoisin et al., 2014, Reddy et al., 2006, Edgar et al., 2012, O'Neill and Reddy, 2011, O'Neill et al., 2011). Thus, circadian rhythmicity occurs at several regulatory layers, encompassing transcriptomic, proteomic, metabolomic, and even microbiome changes (Dyar et al., 2018, Mauvoisin, 2019, Zhang et al., 2014, Mure et al., 2018, Thaiss et al., 2016).

Circadian Rhythms in Adult Stem Cells and their Niche

Adult stem cells (SCs) are multipotent, self-renewing cells that can generate specialized cell types (Blanpain and Simons, 2013, Clevers and Watt, 2018). Here, we summarize the circadian physiology of selected adult SC compartments and the implication of the circadian clock in regulating SC homeostasis and aging (see Table 1).

Hematopoietic SCs

Hematopoietic SCs (HSCs) give rise to all the blood lineages (Spangrude et al., 1988) and are quiescent under steady-state conditions, while their offspring progenitor cells (HSPCs) maintain the high rate of new cells that are generated during hematopoiesis. Bone marrow HSCs express genes of the core clock machinery (Tsinkalovsky et al., 2006, Mendez-Ferrer et al., 2008). However, transcriptional oscillations of the core clock genes in HSCs seem to be largely absent (Tsinkalovsky et al., 2006).

Both HSCs and HSPCs first egress from the bone marrow into circulation in the resting phase of the day (as shown in mice and humans), and home back into the bone marrow on a daily basis (Pinho and Frenette, 2019, Mendez-Ferrer et al., 2008, Lucas et al., 2008). Mechanistically, their egression and homing depend on several factors. First, a gradient of C-X-C motif chemokine ligand 12 (CXCL12) expressed in bone marrow acts as a retention signal via the C-X-C motif chemokine receptor 4 (CXCR4) expressed in HSCs (Wright et al., 2002, Nagasawa et al., 1996, Peled et al., 1999, Mendez-Ferrer et al., 2008). This mechanism depends on circadian beta-adrenergic

signals activated by local noradrenalin released from sympathetic nervous system (SNS) neurons in bone marrow (Mendez-Ferrer et al., 2008), which activate the SP1 transcription factor in stromal cells, resulting in rhythmic expression of CXCL12 (Mendez-Ferrer et al., 2008). Fluctuations of CXCR4 on the surface of HSPCs are controlled by the core circadian clock machinery (Lucas et al., 2008). Once in circulation, neutrophils undergo a process of aging, which is regulated by the neutrophil circadian clock (Adrover et al., 2019). Aged neutrophils are then phagocytosed by macrophages in the bone marrow, thereby promoting HSPC egression (Casanova-Acebes et al., 2013).

Finally, systemic circadian oscillations of the stress hormone corticosterone regulate HSC/HSPC proliferation and migration through CXCL12 and Notch1 signaling (Kollet et al., 2013). However, the HSPC-intrinsic clock doesn't seem to contribute to the proliferation and differentiation potential of HSPCs (Ieyasu et al., 2014). The light and dark cycle, on the other hand, does regulate HSPC self-renewal and differentiation through TNF- and norepinephrine-mediated metabolic alterations within the HSPCs (Golan et al., 2018). Thus, although the circadian clock network is essential for the daily cycle of HSPC egression into circulation and homing back into the bone marrow (Mendez-Ferrer et al., 2008), the relevance of the circadian clock for HSPC maintenance and function is still enigmatic.

Interfollicular Epidermal SCs

Interfollicular epidermal SCs (EpSCs) exhibit a high level of self-renewal and differentiation that maintains the epidermal barrier function (Solanas and Benitah, 2013). The core clock machinery oscillates in EpSCs *in vivo* in mice (Solanas et al., 2017) and at least *in vitro* in human keratinocytes (Janich et al., 2013). Cell cycle regulation is one of the most prominent circadian-regulated functions in interfollicular EpSCs, with a peak of the highest percentage of basal cells in S-phase occurring at night in mice (Solanas et al., 2017, Geyfman et al., 2012, Gaddameedhi et al., 2011).

Epidermis is continuously exposed to potentially damaging factors, including UV radiation and infections. In mice, many genes related to DNA damage repair have a circadian expression, allowing protection from UV light during the correct time of the day; this is lost in *Bmal1*-KO mice (Janich et al., 2011, Solanas et al., 2017, Welz et

al., 2019, Geyfman et al., 2012). Further, exposure of skin to high levels of UV light when DNA repair gene expression is at its trough (e.g., jetlag) significantly increases DNA damage and the susceptibility of developing UV-mediated skin cancer (Geyfman et al., 2012, Plikus et al., 2015, Gaddameedhi et al., 2011).

The expression of many metabolic genes is also under clock control in the epidermis (Welz et al., 2019) and in EpSCs (Solanas et al., 2017). The ratio of NAD+ to NADH in murine EpSCs *in vivo* indicates that oxidative phosphorylation peaks in the light phase, while glycolysis peaks at night (when mice are active), in a BMAL1-dependent manner (Stringari et al., 2015). Importantly, increased rates of oxidative phosphorylation in the light phase correlate with increased levels of reactive oxygen species (ROS) and with fewer basal epidermal cells entering S-phase (Geyfman et al., 2012). This daily circadian shift from oxidative phosphorylation to glycolysis might allow EpSCs to temporally separate DNA replication from the period of maximum activity of oxidative phosphorylation and maximum UV light exposure, thereby minimizing the potentially harmful impact of these two processes on DNA replication (Geyfman et al., 2012, Solanas et al., 2017, Stringari et al., 2015, Gaddameedhi et al., 2011).

Hair Follicle SCs

Hair follicles undergo repetitive cycles of growth, rest, and degeneration, in a process is maintained by specialized hair follicle SCs (HFSCs) located in the so-called bulge region (Solanas and Benitah, 2013, Blanpain et al., 2004, Cotsarelis et al., 1990). Although the hair cycle is much longer than 24 h, HFSC functions are also under circadian control. For instance, whole body circadian arrhythmic mice show delays in the growth phase of hair follicles as they age (Lin et al., 2009, Plikus et al., 2013, Geyfman et al., 2012). This is likely either due to extrinsic regulatory cues or age-related accumulation of damage upon deletion of *Bmal1*, as hair follicle cycling is normal in young mice with an epidermal conditional deletion of *Bmal1* (Geyfman et al., 2012). Nonetheless, forced circadian arrhythmia in epidermis of young mice inhibits the circadian pattern of DNA replication in HFSCs and progenitor cells; this results in circadian-dependent susceptibility to genotoxic stress in hair follicles, with increased risk of damage in the morning and lower risk in the evening (Plikus et al., 2013).

Intriguingly, expression of components of the core clock machinery is homogenous in hair follicle progenitor cells but patchy in bulge HFSCs (in human and mouse) (Al-Nuaimi et al., 2014, Lin et al., 2009, Plikus et al., 2013). This patchy expression correlates with the susceptibility of bulge HFSCs to respond to signals that regulate proliferation and differentiation, suggesting that the circadian clock marks different HFSC states that are differentially predisposed to respond to proliferative and differentiation cues (Janich et al., 2011).

Intestinal Epithelial SCs

Lgr5+ intestinal epithelial SCs (IESCs) reside at the bottom of crypts (Barker et al., 2007). A transit-amplifying cell compartment in the lower crypt fuels the very high daily demand of differentiated cells of the tissue. Lgr5+ IESCs are interspersed with terminally differentiated secretory cells (called Paneth cells) that nurture them and form an important part of their SC niche (Sato et al., 2011).

The circadian clock regulates several essential physiological functions of the intestine, such as tissue regeneration (Stokes et al., 2017, Karpowicz et al., 2013), epithelium–microbiota communication (Mukherji et al., 2013), intestinal permeability (Summa et al., 2013), the immune response to infections and inflammatory processes (Summa et al., 2013, Rosselot et al., 2016), and body composition (Wang et al., 2017, Kuang et al., 2019). Strikingly, *in vitro* intestinal 3D organoids display synchronized circadian rhythms without external synchronizing cues (Moore et al., 2014, Matsu-Ura et al., 2016), even though their IESCs and progenitor cells show only a weak transcriptional oscillations of a *Per2*-reporter while their non-dividing cells exhibit robust circadian transcriptional cycles (Matsu-Ura et al., 2016). In IESCs, cell division is gated by the Paneth cell circadian clock, through intercellular WNT signals. Thus, intercellular coupling (through secreted factors) is likely to synchronize not only transcriptional oscillations of the circadian clock between different cells within an organoid and between different organoids, but also the timing of cell division cycles in SCs and progenitor cells (Matsu-Ura et al., 2016).

Whether IESCs lack a functional clockwork or in contrast show proliferative rhythms under homeostasis *in vivo* is still controversial. Nonetheless, during the regenerative

response to irradiation, intestinal epithelial proliferation occurs in *Bmal1*-dependent circadian cycles (Stokes et al., 2017). Discrepancies in results may be due to different regulation of proliferative cycles of cells *in vitro* or under homeostatic versus regenerative conditions *in vivo* (see extensive review (Parasram and Karpowicz, 2019)). Interestingly, IESCs in flies have transcriptional oscillations of the core clock components *in vivo* that seem to depend on communication with the niche (Karpowicz et al., 2013, Parasram et al., 2018).

Neural SCs

Distinct types of relatively quiescent neural stem and progenitor cells (NSPCs) reside in different brain regions (including the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG), and the subventricular zone (SVZ) bordering the lateral ventricles), with some intriguing differences in the circadian behaviour of their clock genes (Bouchard-Cannon et al., 2013, Borgs et al., 2009). For instance, *in vivo* in mice, some core clock proteins oscillate in quiescent NSPCs in the SGZ, stop cycling in proliferating NSPCs during neurogenesis, and become rhythmic again in mature neurons (Bouchard-Cannon et al., 2013). Furthermore, in neurosphere cultures from neural SCs from the SVZ or DG, reliable circadian rhythms of a *Per1*-reporter only appear upon differentiation (Malik et al., 2015a, Malik et al., 2015b). This suggests that the clock might function differently in different SC stages. Finally, circadian oscillations during NSPC proliferation occur in some brain regions but not others (reviewed in (Draijer et al., 2019). For example, although bromo-deoxyuridine–positive NSPCs are not in-sync in S-phase in the SGZ and SVZ (Tamai et al., 2008, Kochman et al., 2006), circadian rhythms of NSPCs in M-phase have been observed in the DG (Bouchard-Cannon et al., 2013, Tamai et al., 2008), suggesting that NSPCs enter mitosis in a circadian manner.

While still little is known about the transcriptional output and physiologic relevance of the NSPC-intrinsic circadian clock, several core clock genes have been implicated in neurogenesis regulation. For instance, BMAL1-deficiency increases NSPC proliferation in young mice, leading to SC exhaustion at later ages (Bouchard-Cannon et al., 2013, Rakai et al., 2014, Ali et al., 2015). Further, misalignment of the circadian clock with the external environment during jetlag inhibits adult neurogenesis (Gibson et al., 2010, Kott et al., 2012). Several questions remain open,

including whether jet lag–mediated inhibition of neurogenesis is NSPC–clock dependent, and what contributions do circadian signals from niches versus cues from the NSPC–intrinsic clockwork have on neurogenesis and NSPC physiology. Notably, several neurotransmitters and glucocorticoids in the NSPC niche (e.g., cortisol, dopamine, serotonin, GABA, and glutamate) exhibit diurnal concentration patterns (Dickmeis and Foulkes, 2011, Weger et al., 2017). Thus, it seems likely that the circadian clock in the niche also impacts neural SC physiology.

Skeletal Muscle SCs

Skeletal muscle SCs (also called satellite cells) are long-term quiescent cells closely associated with myofibers that become active mainly upon damage (Murphy et al., 2011). Satellite cells have a robust oscillation of the core clock machinery *in vivo* (Solanas et al., 2017). Importantly, the circadian rhythmic output involves pathways that are essential for satellite cell homeostasis, such as those related to regulation of quiescence and readiness for activation (including TGFβ/BMP and FGF signaling), cytoskeleton organization, and autophagy (Solanas et al., 2017, Garcia-Prat and Munoz-Canoves, 2017, Brack and Rando, 2012).

BMAL1 has also been implicated in myogenesis and satellite cell maintenance. In contrast to neurogenesis and EpSCs, in which BMAL1 deficiency promotes differentiation, BMAL1-deficient myoblasts are impaired for myogenic differentiation downstream of WNT signaling *in vitro* (Chatterjee et al., 2013). Furthermore, BMAL1 directly or indirectly seems to regulate the expression of *MyoD*, a central regulator of myogenesis, leading to disrupted myofilament architecture in skeletal muscle of *Bmal1*-KO mice (Andrews et al., 2010, Schiaffino et al., 2016).

In summary, the circadian clock likely impacts on satellite cell physiology and maintenance by aligning quiescence and activation potential of satellite cells with the appropriate time of the day.

Circadian Systemic Cues in the Adult SC Niche

Adult SCs receive signals from the local niche and systemic cues, including neural, humoral, and metabolic signals, that can all be regulated by the circadian clock

network. Here, we briefly summarize what is known about the circadian rhythms of systemic cues that are likely to regulate adult SC function.

Neural activity oscillates in a daily manner in the SCN (Colwell, 2011), and autonomic nervous system cues help to synchronize cellular clocks in peripheral organs (Mohawk et al., 2012, Cailotto et al., 2009, Terazono et al., 2003). SCN-dependent autonomic signals also regulate adrenal function and influence glucocorticoid secretion (Mohawk et al., 2012, Buijs et al., 1999, Ishida et al., 2005). Importantly, SCN-dependent neural signaling is implicated in several adult SC niches, such as those of hair follicles and the HSC compartment (Fan et al., 2018, Mendez-Ferrer et al., 2008). Thus, autonomic signals regulate adult SC clocks and daily SC physiology.

Several hormones, including melatonin and glucocorticoids, are under control of the circadian clock network and can contribute to synchronization of circadian clocks in peripheral tissues (Gamble et al., 2014). In concert with local peripheral clocks, the SCN mediates regulation of melatonin levels via the pineal gland (Hood and Amir, 2017) and of glucocorticoids (such as cortisol) via the hypothalamic pituitary adrenal axis (HPA) (Son et al., 2018). Melatonin transmits changes in environmental light to clocks in peripheral tissues and regulates sleep, affects vascular reactivity, and acts as an anti-oxidant (Gamble et al., 2014). Interestingly, melatonin affects the proliferation and differentiation of neural SCs (Yu et al., 2019, Mendivil-Perez et al., 2017), and regulates the differentiation of mesenchymal SCs (Luchetti et al., 2014).

Glucocorticoids are important for the body's stress response. Baseline glucocorticoid levels have a circadian rhythm, with maximum levels occurring during the active phase of the organism (Fitzsimons et al., 2016). Acting through both transcriptional and non-transcriptional pathways, glucocorticoids can impact energy metabolism, lipid metabolism, and inflammation (Joels et al., 2012). Glucocorticoid signaling has been implicated in regulation of SC and progenitor cell proliferation in several tissues, such as the small intestine, lung, and epidermis (Dickmeis and Foulkes, 2011). Importantly, circadian rhythms of glucocorticoids have been implicated in the regulation of neural SC activation and the maintenance of a quiescent neural SC pool in the hippocampal DG (Schouten et al., 2019).

Most metabolic pathways are under control of the circadian clock network (Greco and Sassone-Corsi, 2019). Recent advances in metabolomic studies suggest that the circadian clock network not only imposes circadian oscillations on many metabolites (Dyar and Eckel-Mahan, 2017, Skene et al., 2018, Kervezee et al., 2019, Dallmann et al., 2012, Koronowski et al., 2019) but also helps to temporally coordinate the tissue-intrinsic metabolome between the different organs (Dyar et al., 2018). Importantly, high fat diet and dietary restriction alter the transcriptional circadian output in adult SCs (Solanas et al., 2017) as well as at the whole organ level (Eckel-Mahan et al., 2013, Sato et al., 2017). Thus, the circadian clock network controls metabolism at both local and systemic levels and thereby impacts adult SC physiology.

Aging of Adult SCs and Circadian Rhythms

Throughout the aging process, loss of adult SC levels and function leads to a decline in regenerative capacities and contributes to the loss of tissue homeostasis (Lopez-Otin et al., 2013). The circadian clock and diurnal rhythmicity are not only implicated in adult SC homeostasis but are also interwoven with several other processes that contribute to the hallmarks of aging (Welz and Benitah, 2019), such as epigenetic regulation (Takahashi, 2017, Masri and Sassone-Corsi, 2013, Kim et al., 2018, Doi et al., 2006, Nakahata et al., 2008), nutrient sensing (Peek et al., 2012), mitochondrial function (Manella and Asher, 2016, Jacobi et al., 2015), and intercellular communication (Stenvers et al., 2019, Hood and Amir, 2017). Several of the hallmarks of aging in turn influence the correct functioning of the circadian clock. In mammals, disturbed circadian rhythmicity increases the risk of developing several pathologies that can shorten lifespan, including cancer (Filipski et al., 2003, Davis and Mirick, 2006, Penev et al., 1998, Roenneberg and Merrow, 2016). Further, experimentally-induced chronic “jet-lag” increases mortality in mice (Davidson et al., 2006, Inokawa et al., 2020). Here, we discuss how aging-related functional alterations of the circadian clock negatively impact adult SC function and contribute to several hallmarks of aging.

The Aged Systemic Circadian Clock Network

During aging, the central role of the SCN in synchronizing clocks in peripheral tissues is affected in several ways. For instance, the sensitivity for detecting and responding

to light as a synchronizing cue is reduced in aged animals due to reduced lens transmittance of light (Zhang et al., 1998, Kessel et al., 2010), a reduced number of intrinsically photoreceptive retinal ganglion cells (ipRGCs) that transmit the photic input to the SCN (Lupi et al., 2012, Semo et al., 2003), and a functional decline in the SCN itself. The total cell number in the SCN appears to be constant with age (Madeira et al., 1995, Roozendaal et al., 1987). However, aged SCNs in mice and humans contain fewer neurons that express the neurotransmitter vasoactive intestinal polypeptide (VIP) (Krajnak et al., 1998, Zhou et al., 1995), an important mediator of intercellular coupling between individual SCN neurons (Aton et al., 2005, Maywood et al., 2006). Aged SCNs also show a reduction of intercellular coupling between individual neurons (Farajnia et al., 2012, Nakamura et al., 2015) and a reduced number of synaptic terminals (Palomba et al., 2008). Thus, the cumulative reductions in i) sensitivity towards the photic input, ii) signal transmission, and iii) coupling within neural networks lead to a functional decline of light responses in aged SCN (reviewed in (Zhao et al., 2019). Notably, functional deterioration of an aged SCN greatly reduces longevity, as transplanting SCNs from young donors into aged hamsters increases their lifespan (by almost 20%) (Hurd and Ralph, 1998).

Core clock gene expression in the SCN is affected during aging in a gene-specific manner. For instance, while the overall protein levels of *Bmal1* and *Per2* are reduced in aged SCN (Chang and Guarente, 2013), no changes in expression or period lengthening occur for other clock genes (Zhao et al., 2019). Aged SCN neurons also have a reduced circadian amplitude of intracellular signaling (Farajnia et al., 2012, Zhao et al., 2019). Although the functional relevance of these distinct changes is largely unknown, they likely contribute to aging-related dampening of the circadian SCN-dependent output, such as reduced locomotor activity amplitudes and photoperiodic adaptation (Buijink et al., 2020), perturbed sleep-wake cycles (Mattis and Sehgal, 2016), reduced body temperature cycles (Kondratova and Kondratov, 2012), decreased neural activity rhythms (Nakamura et al., 2011), and impaired humoral rhythmicity (Hood and Amir, 2017).

Aging and Circadian Rhythmicity within SC Niches and Systemic Cues

Some aging-related alterations in the SC niche are either under regulation of the circadian clock network or affect circadian rhythmicity within the niche. Neural

signaling appears to be impaired in the aging adult SC niche (Maryanovich et al., 2018, Ho et al., 2019), with a weaker response to noradrenergic stimulation and downregulation of adrenergic receptor mRNA expression in aged peripheral tissues (Tahara et al., 2017). Loss of circadian oscillations of HSPC levels in blood of old mice, and HSPC aging, depends on a decrease in sympathetic neural innervation of the HSPC niche and β-adrenergic signaling (Maryanovich et al., 2018, Ho et al., 2019). Whether HSPC aging also is due to a decline in SCN-dependent circadian regulation of sympathetic activity remains to be shown.

Furthermore, light-dependent activation of HFSCs relies on SCN-controlled sympathetic innervation and release of norepinephrine in the skin, yet it seems to be independent of SCN-mediated alterations in physical activity rhythms (Fan et al., 2018). It is tempting to speculate that the age-related SCN functional decline and impaired signal transmissions downstream of the SCN might contribute to the aging process of HFSCs, possibly by modulating circadian rhythmicity in the HFSC niche.

Circadian oscillations of both melatonin and glucocorticoids (e.g., cortisol) have been reported to have a dampened amplitude with aging; however, this might not occur in healthy aging but only in unhealthy states of the aging process in humans (Hood and Amir, 2017). Melatonin is not only a strong synchronizing factor in the circadian system but also has important anti-aging properties (Hood and Amir, 2017, Majidinia et al., 2018), and pineal gland transplantation from young to old recipient mice prolongs lifespan (Lesnikov and Pierpaoli, 1994). Melatonin regulates the expression and activity of antioxidant enzymes and is a free-radical scavenger (Elkhenany et al., 2018, Orozco-Solis and Sassone-Corsi, 2014, Zhang et al., 2017). Melatonin also promotes hematopoiesis, protects the hematopoietic system from free radicals, radiation-induced damage, and cytotoxic drugs, and protects HSPCs from chemotherapeutic toxicity in culture (Greish et al., 2005, Anwar et al., 1998, Sharma et al., 2008, Maestroni and Conti, 1996). Finally, melatonin supplementation supports neurogenesis in aged mice (Ramirez-Rodriguez et al., 2012) and after spinal cord injury *in vivo* (Lee et al., 2014), and promotes NSPC proliferation and differentiation *in vitro* (Sotthibundhu et al., 2010, Moriya et al., 2007).

Increased glucocorticoid levels in aged rats have been linked to suppression of hippocampal neurogenesis and to contributing to age-related memory disorders (Montaron et al., 2006). Circadian glucocorticoid oscillations have been associated with the preservation of a hippocampal SC population (Schouten et al., 2019); however, whether and how dampened circadian oscillations of hormonal cues impact aging SC niches remain to be determined.

In addition to altered circadian control of systemic factors, age-related alterations in local niches can also negatively impact adult SC function. For instance, mechanosensing of the extracellular matrix (ECM) stiffness regulates the oscillation amplitude of the circadian clock in mammary epithelial SCs, epidermal keratinocytes, and lung epithelial cells *in vitro* (Yang et al., 2017, Williams et al., 2018). As ECM stiffness in breast tissue increases with age, the amplitude of circadian oscillations in the mammary epithelium is reduced in tissue explants from old mice (Yang et al., 2017). Whether this observation also translates into the regulation of the circadian clock *in vivo* remains to be shown.

Furthermore, signals generated by the circadian clock in cells within the local niche could impact the temporal organization of adult SC physiology. Alterations with aging have been reported for some oscillations (mainly in amplitude but also in phase) of core clock proteins, such as BMAL1 and CLOCK, in various non-SCN regions of the brain in mice (Wyse and Coogan, 2010), as well as of several core clock genes at the RNA level in the liver and pancreas (Novosadova et al., 2018, Bonaconsa et al., 2014). Strikingly, however, many aged tissues have few-to-no changes in oscillations of the circadian core clock machinery; these include liver, heart, pineal gland, paraventricular nucleus of the hypothalamus, lung, colon, kidney, submandibular gland, epidermis, and hair follicles (Tahara et al., 2017, Bonaconsa et al., 2014, Oishi et al., 2011, Asai et al., 2001, Novosadova et al., 2018, Sato et al., 2017, Yamaguchi et al., 2017). Thus, the circadian clockwork seems to be relatively robust throughout the aging process, at least under non-challenged conditions in most peripheral tissues. However, when challenged with phase shifts of light, liver explants from aged PER1::LUC reporter rats display altered phase-resetting responses as compared to those from young rats; however, this effect was not observed for young and aged SCN explants (Davidson et al., 2008). Thus, changes in the light phase might

desynchronize clocks between different tissues of aged individuals. Notably, several explanted aged peripheral tissues (including kidney, liver, and submandibular gland) display phase shifts of PER2::LUC reporter oscillations as compared to young tissues when harvested in the absence of synchronizing light cues (Tahara et al., 2017). These results imply that aging diminishes the ability of the circadian clock network to respond to dynamic changes emanating from environmental cues at the tissue level.

Aging and Circadian Rhythms in Adult SCs

A recent study has shed some light onto the outstanding question of how the circadian clockwork functions in adult SCs during physiological aging *in vivo*. Intriguingly, the core circadian machinery remains perfectly rhythmic in aged EpSCs and skeletal muscle satellite cells (Solanas et al., 2017). However, only a small set of clock-controlled genes maintain their daily oscillations at the transcriptional level in aged EpSCs and satellite cells, while a new gene set becomes expressed in a daily rhythmic manner (Solanas et al., 2017). Such a reprogrammed circadian transcriptome has also been described in aged murine liver, human prefrontal cortex, and heads of *Drosophila melanogaster* (Sato et al., 2017, Chen et al., 2016, Kuintzle et al., 2017). Thus, these studies establish circadian reprogramming of the transcriptome as a new paradigm for how aging impacts circadian clock function at the tissue and adult SC levels (see Figure 2). Central to this aging-related circadian reprogramming is the observation that, in all aged tissues and SCs studied to date, the newly-oscillating rhythmic output is always related to tissue-specific stresses.

EpSCs are highly proliferative and mainly replicating their DNA during the night, when genotoxic stress induced by oxidative phosphorylation is low (Stringari et al., 2015, Geyfman et al., 2012, Solanas et al., 2017). In line with that, oscillatory transcripts in EpSCs from adult mice are largely involved in homeostatic functions, such as DNA replication, differentiation, and barrier function (Solanas et al., 2017). On the other hand, EpSCs from old mice enter S-phase with a delay of about 8–12 h, coinciding with the time of maximal oxidative phosphorylation. Thus, in aged EpSCs, unwound DNA is likely exposed to increased levels of genotoxic stress, which might contribute to their elevated levels of oxidized DNA (Solanas et al., 2017). Accordingly, the oscillatory transcriptome of EpSCs from aged mice relates to DNA repair, ROS response, and inflammatory processes (Solanas et al., 2017).

In contrast to EpSCs, satellite cells in skeletal muscle are normally in a quiescent state and therefore do not experience replicative stress. However, many transcripts involved in functions regulating satellite cell quiescence, such as myotube differentiation or TGFβ/BMP and FGF signaling, oscillate in satellite cells from adult mice (Solanas et al., 2017). Aged satellite cells remain quiescent and maintain the rhythmicity of transcripts involved in regulating their interactions with their niche. However, newly-oscillating transcripts in satellite cells from aged mice are implicated in the regulation of inflammation and mitochondrial DNA repair (Solanas et al., 2017). Importantly, aged satellite cells show a decline in overall autophagy, a process that is essential for their proper functioning (Garcia-Prat et al., 2016), and they lose the rhythmic expression of transcripts involved in autophagy regulation (Solanas et al., 2017).

In summary, aging leads to a reprogrammed rhythmic output in adult SCs that reflects the aging-related, tissue-specific conditions within individual SC compartments. Additionally, systemic or niche-related signals change in aged SCs, which likely contributes to aging-related reprogramming of the circadian transcriptome. This is further supported by the finding that caloric restriction, which also entrains the clock of the SCN (reviewed in (Froy, 2013)), largely prevents aging-related circadian reprogramming (Solanas et al., 2017).

Circadian Clock Disruption and Adult SC Aging

Disruption of the circadian clockwork in genetically manipulated animal models has been linked to development of pathologic conditions in several tissues and adult SC compartments throughout the aging process. For instance, PER2 is a negative regulator of the aging-related DNA damage response specifically in lymphoid-biased HSPCs; in contrast to wildtype mice, *Per2*-deficient mice show no defects in HSC differentiation in response to DNA damage, which might contribute to an elongated lifespan (Wang et al., 2016).

Full-body *Bmal1*-knockout (KO) and epidermis-specific *Bmal1* deficiency lead to a progressive increase in the number of differentiated keratinocytes and a phenotype that resembles aging (Janich et al., 2011, Welz et al., 2019). EpSCs from full-body

Bmal1-KO mice express higher levels of differentiation markers, which are partially reverted to the wildtype expression patterns in mice that express BMAL1 exclusively in the epidermis (Welz et al., 2019). Thus, epidermis-intrinsic as well as non-epidermal BMAL1 prevents increased differentiation of EpSCs. Interestingly, mice expressing epidermis-only BMAL1 that are kept for one week in complete darkness lose epidermal circadian transcriptional cycles but still largely maintain a reduced expression of differentiation markers as compared to the full-body *Bmal1*-KO mice (Welz et al., 2019). Therefore, BMAL1 might prevent EpSC differentiation at least partially independently of its function in the circadian clockwork. Notably, the epidermis of *Bmal1*-KO mice has also a reduced capacity for wound closure after injury (Kowalska et al., 2013). In addition, *Bmal1* ablation in hair follicles results in increased levels of label-retaining bulge SCs and reduced numbers of proliferative cells in aged mice (Janich et al., 2011), while *Per1/Per2* deficiency has the opposite phenotype (Janich et al., 2011). This suggests that the circadian clockwork determines EpSC activation and maintenance throughout the aging process.

Satellite cell numbers are reduced in middle-aged *Bmal1*-KO mice, but not in muscle-specific BMAL1-deficient mice when *Bmal1*-depletion is induced in adulthood (Schroder et al., 2015), suggesting that either skeletal muscle–extrinsic BMAL1 is required for regulating satellite cell levels, and/or that BMAL1 regulation of satellite cell maintenance is determined at earlier developmental stages. In line with this, regeneration through satellite cell expansion after injury is impaired in *Bmal1*-KO mice (Chatterjee et al., 2015). Interestingly, REV-ERBα (an inhibitor of *Bmal1* gene transcription) has the opposite effect on myogenesis than BMAL1, as it suppresses myogenesis in myoblasts by inhibiting both proliferation and differentiation; additionally, loss of REV-ERBα promotes muscle regeneration by increasing proliferative satellite cell expansion after injury (Chatterjee et al., 2019). REV-ERBα also regulates WNT signaling and other pathways involved in SC proliferation (Chatterjee et al., 2019). The opposing effects of BMAL1 and REV-ERBα deficiency on satellite cell numbers indicate that they regulate satellite cell maintenance through their opposite functions in the circadian clockwork.

Several core clock genes have been implicated in neurogenesis. *Bmal1*-KO mice show increased neurogenesis at 5–6 weeks of age, no changes in NSPC proliferation

at 8 weeks of age, and decreased NSPC proliferation in the DG at 10–15 weeks of age (Bouchard-Cannon et al., 2013, Rakai et al., 2014, Ali et al., 2015), suggesting that BMAL1 is required to prevent excessive NSPC proliferation at young ages and following SC exhaustion in adult mice. Notably, brain-specific *Bmal1* depletion (using Nestin-Cre) causes neuropathology, and siRNA-mediated *Bmal1* knockdown in neurosphere culture *in vitro* alters neural differentiation (Musiek et al., 2013, Kimiwada et al., 2009), arguing that BMAL1 regulates neurogenesis in the NSPCs or in the local niche. Furthermore, BMAL1 promotes migratory behaviour of NSPCs and prevents increased ROS levels in NSPC cultures (Ali et al., 2019). Similar to *Bmal1*-KO mice, *Per2*-KO mice exhibit increased neurogenesis (Borgs et al., 2009), with increased numbers of proliferative type 1 neural progenitors; however, only *Bmal1*-KO mice contain increased numbers of proliferative type 2b, post-mitotic 3 neural progenitors, and new neurons in the SGZ (Bouchard-Cannon et al., 2013). Thus, both PER2 and BMAL1 prevent excessive amounts of otherwise quiescent NSPCs from entering the cell cycle, but only *Bmal1*-deficiency further promotes extended numbers of NSPCs to exit the cell cycle and to generate new neurons in the SGZ. Increased numbers of proliferative NSPCs have also been described for *Rev-erbα*-KO mice, and *Cry1/Cry2*-double-KO mice show reduced numbers of DG- and SVZ-derived neurospheres (Schnell et al., 2014, Malik et al., 2015b). While *Bmal1*-KO, *Per2*-KO, and *Rev-erbα*-KO mice all lack diurnal rhythmicity in neurogenesis, it is difficult to ascribe these deficiencies to the function of the depleted genes in the clock. As it is still controversial whether an oscillating clockwork exists in NSPCs, it cannot be excluded that some of the observed phenotypes are non–clock-related or depend on niche cues. Furthermore, *Bmal1*- or *Rev-erbα*-deficiency each causes an increase in NSPC proliferation, even though REV-ERBα is a negative regulator of BMAL1 expression (with upregulated BMAL1 expression in *Rev-erbα*–deficient animals) (Preitner et al., 2002). Thus, it is conceivable that the different clock-related genes might impact neurogenesis in a manner independent of their role in the circadian clockwork and through different mechanistic means, even if the outcome—that is, an increase in NSPC proliferation—is the same.

In conclusion, core clock genes play an important role in the maintenance of adult SC pools throughout the aging process in several tissues. Generally, while BMAL1 seems to prevent SC exhaustion (with the exception of HFSCs) by reducing their

proliferation during youth, negative regulators of BMAL1 in the circadian clockwork often (but not always) have opposite functions. It is therefore possible that genes of the circadian core clockwork regulate adult SC physiology not only through clock-dependent mechanisms, but also through non–clock-related functions. The impact of disruption of circadian clock gene regulation has tissue-specific effects on adult SC physiology, which have been attributed to cell cycle (mis)regulation (Plikus et al., 2013, Boucher et al., 2016), to regulation of SC signaling pathway components that are related to differentiation and proliferation (Janich et al., 2011, Plikus et al., 2013, Welz et al., 2019), and to increases in cellular damage (Kondratov et al., 2006, Kondratov et al., 2009, Jacobi et al., 2015, Ali et al., 2019, Musiek et al., 2013). How each mechanism contributes to the overall aging process of adult SCs requires further investigation.

Aging-Related Signaling Pathways that Regulate the Circadian Clock

Three signaling pathways that are involved in regulating the aging process—mammalian target of rapamycin (mTOR) signaling, sirtuin-dependent cues, and adenosine monophosphate-activated protein kinase (AMPK) signaling—have been implicated in regulating clock function (Khapre et al., 2014, Orozco-Solis and Sassone-Corsi, 2014, Nakahata et al., 2008, Ramanathan et al., 2018, Lamia et al., 2009) (see Figure 1).

The nicotinamide adenine dinucleotide (NAD+)-dependent deacylase SIRT1 regulates clock function both at the level of the core clockwork, by deacetylating PER2 and BMAL1, and at the output level, by deacetylating histone H3 at promoters of clock-controlled genes (Nakahata et al., 2008, Nakahata et al., 2009, Asher et al., 2008). The age-related decrease of BMAL1 and PER2 expression in the SCN (which leads to a decline of circadian function in the SCN) is SIRT1-dependent (Chang and Guarente, 2013). BMAL1 in turn regulates the expression of the rate-limiting enzyme nicotinamide phosphoribosyl-transferase (NAMPT) in the NAD+ salvage pathway, resulting in circadian regulation of SIRT1 activity (Ramsey et al., 2009, Nakahata et al., 2009). Importantly, both SIRT1 activity and the levels of its cofactor NAD^+ decrease with age (Gomes et al., 2013), and both have been implicated in the aging process of adult SCs (Igarashi et al., 2019, Ma et al., 2014, Zhang et al., 2016).

mTOR signaling regulates the aging process by impacting on nutrient sensing, maintenance of proteostasis, autophagy, mitochondrial dysfunction, cellular senescence, and adult SC function (reviewed in (Papadopoli et al., 2019). mTOR regulates translation of the intercellular coupling factor VIP in the SCN, thereby affecting the capability of the SCN to entrain to shifted light/dark cycles (Cao et al., 2013). Additionally, the mTOR-signaling component ribosomal protein S6 kinase beta-1 (S6K1) phosphorylates BMAL1, leading to rhythmic association of BMAL1 with the translation machinery (Lipton et al., 2015). mTOR signaling also controls BMAL1 proteostasis (Lipton et al., 2017) and period length of the circadian clock in peripheral tissues (Ramanathan et al., 2018). Intriguingly, *Bmal1* deficiency increases mTOR signaling, while inhibition of mTOR signaling prolongs lifespan of the short-lived *Bmal1*-deficient mice (Khapre et al., 2014), arguing for a bidirectional relationship between mTOR-related signaling and BMAL1.

AMPK acts as a sensor of low-energy states in cells and activates several aging-related pathways, including mTOR and sirtuin pathways (reviewed in (Burkewitz et al., 2014). AMPK can promote CRY degradation directly (Lamia et al., 2009) and PER degradation through the activation of casein kinase I epsilon (CKIε) (Um et al., 2007), thereby directly affecting the regulation of the circadian clockwork.

Additionally, aging-related metabolic alterations are likely to impact clock function in SCs. For example, polyamines regulate the interactions between clock components. Polyamine levels decline with age thereby contributing to a lengthening of the circadian period in constant darkness (Zwighaft et al., 2015). Also, given the role of HIF1α in mediating oxygen-dependent clock resetting (Adamovich et al., 2017) and regulation of circadian transcription (Peek et al., 2017), the accumulation of HIF1α in aged tissues (Gomes et al., 2013) could impact on circadian clock function.

Future Perspectives

Recent progress in circadian SC research has shed light on the importance of circadian rhythms for SC function and strongly suggests that the temporal organization of adult SC physiology by the circadian clockwork is critical for maintaining tissue and SC homeostasis. Both the transcriptional/translational oscillator system and the circadian output appear to adapt to the specific homeostatic

needs of each adult SC compartment in the young organism; in contrast, in the aged adult SCs, the circadian functions shift towards a stress-dominated program.

Intriguingly, it appears as if not all adult SC compartments establish transcriptional oscillations of the core clock machinery, even though the circadian clock components are expressed in most SCs (if not all). Specifically, embryonic SCs and some adult SC compartments, including IESCs, HSCs, and probably also some NSPC populations, do not establish robust transcriptional oscillations of the core clockwork, but rather only develop circadian transcriptional oscillations during their differentiation processes (Yagita et al., 2010, Malik et al., 2015a, Malik et al., 2015b). Neither the mechanistic background nor the physiological reason for this disparity is currently clear. Posttranscriptional suppression of CLOCK protein expression in ESCs and fetal heart has been linked to the absence of circadian clock function in these undifferentiated cells (Umemura et al., 2017), and release of this suppression might be linked to the differentiation process (Umemura and Yagita, 2020). Interestingly, inducing circadian clock oscillations in pluripotent SCs during *in vitro* beta cell differentiation also triggers epigenetic changes that promote maturation of the engineered pancreatic islets (Alvarez-Dominguez et al., 2020), suggesting that the establishment of a functional clock in SCs could be an important step in the differentiation and maturation process. Future work will have to unravel the physiological significance of either having a functional clock or not in the different adult SC compartments, and identify which cell intrinsic or extrinsic signals determine clock function and circadian output.

Importantly, however, daily physiological rhythms have been observed even in SC populations lacking an oscillatory clock (Stokes et al., 2017, Paulose et al., 2012, Lucas et al., 2008, Mendez-Ferrer et al., 2008), suggesting that in these cells, circadian rhythms are established by the niche (Matsu-Ura et al., 2016), non-transcriptional cues (Mauvoisin et al., 2014, Wang et al., 2018), and/or circadian clock–independent cues (Edgar et al., 2012, O'Neill and Reddy, 2011). An example of circadian clock–independent rhythmicity is found in epidermis, where the diurnal light cycle is sufficient to maintain daily oscillations of transcription of genes involved in the regulation of translation and oxidative phosphorylation (Welz et al.,

2019). It still remains to be determined if adult SC physiology and aging are affected by circadian clockwork–independent regulation of daily rhythms.

In peripheral tissues, the circadian clockwork appears to act as an oscillator that allows the incorporation of upstream synchronizing environmental cues—both extrinsic (such as light or food intake) and intrinsic ones (such as metabolic, temperature or mechanical cues)—to coordinate downstream temporal tissue physiology accordingly. In healthy young organisms, unperturbed upstream signal transduction of synchronization cues leads to a robustly oscillating clockwork. Deterioration of signal transduction during the aging process, for example by reduced autonomic innervation (Maryanovich et al., 2018, Tahara et al., 2017), altered humoral cues (Hood and Amir, 2017), and increased ECM stiffness (Yang et al., 2017, Williams et al., 2018), could lead to reduced robustness of the clock oscillator in peripheral tissues and adult SCs (see Figure 3). This in turn might reduce the capacity of the clockwork to react to changes in environmental conditions, and potentially to detrimental desynchronisation between clocks in different peripheral tissues and adult SCs (Davidson et al., 2006, Davidson et al., 2008, Tahara et al., 2017). Future work is also required here to clarify the impact of these aging-related disruptions.

Circadian output is paramount for adult SC homeostasis and proper daily tissue function. Critically, while the circadian clock output in young mice mainly deals with homeostatic functions of the specific tissue or adult SC compartments, new sets of genes become rhythmic in aged mice that are usually involved in tissue-specific, stress-related responses. How this age-related circadian reprogramming is regulated is still unknown, although epigenetic factors as well as stress/aging-induced transcriptional and posttranscriptional regulators are good candidates for altering clock output.

Finally, circadian rhythmicity has historically mostly been measured either by single gene reporter systems or at the transcriptomic level. Given the complex posttranscriptional regulation of the circadian clockwork, assessment of the core clock status at the protein level and protein-modification level, as well as measurement of circadian rhythmicity of both the metabolome and microbiome, will be important to

further improving our understanding of how the circadian clock impacts tissue and adult SC function during aging.

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FIGURE LEGENDS

Figure 1. Molecular Connections Between the Circadian Clock and Aging-related Signaling Pathways

BMAL1 and CLOCK form the central transcription factor complex of the circadian clock. Several positive and negative feedback loops, involving PER, CRY, REV-ERB and ROR proteins, establish daily rhythmicity of the circadian clock. Several aging-related signaling pathways have been linked to the circadian clock, these include nutrient sensing pathways (involving mTOR, SIRT1, AMPK), mechanosensing, and transcription factors (HIF1α) (see text for details). In yellow – central activating signaling complex of the circadian clock; in red – negative regulators of BMAL1/CLOCK; in green – positive regulators of BMAL1/CLOCK; in purple – proteins linking ageing-related signaling with regulation of the circadian clock.

Figure 2. Aging-Related Changes that Impact on Circadian Rhythmicity in Adult Stem Cells

Reduced light transmittance and intrinsically photoreceptive retinal ganglion cell (ipRGC) degeneration reduces the photic input signal to the SCN. Functional decline in the SCN further weakens the SCN output, which includes less robust sleep–wake cycles, altered metabolic cycles, and a reduced neural and humoral output. Less robust transmission of synchronization cues in aged peripheral tissues and adult stem cell compartments also is due to reduced overall physical activity and reduced innervation as well as altered mechanical properties of the adult stem cell niche. While the core clockwork seems to remain rather robustly oscillating in most aged peripheral tissues, the reduced robustness of synchronizing cues might lower the

capability of peripheral tissues to respond to changes in environmental conditions. Finally, reprogramming of the circadian transcriptome and altered circadian rhythmicity in adult SCs of old mice might also depend on altered niche-related cues.

Table 1. The Circadian Clockwork and Circadian Functions in Young and Old Stem Cells

Summary of functions of circadian rhythmicity and outcome of circadian clock disruption in different young and old SC compartments.

Declaration of Interests

The authors declare no competing interests.

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