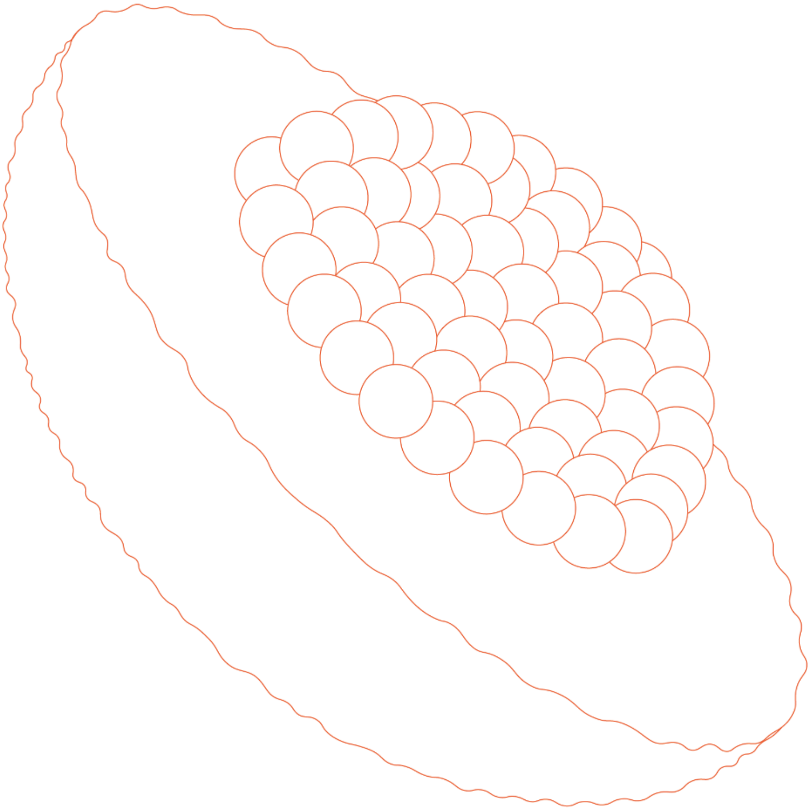
Molecular regulation of neural stem cell quiescence by FoxO transcription factors

Draijer, S.

Publication date
2022

Chapter 5

The circadian clock in adult neural stem cell maintenance



This chapter has been published in *Progess in Neurobiology*
Draijer S, Chaves I, Hoekman MFM. The circadian clock in adult neural stem cell maintenance. Prog Neurobiol. 2019 Feb;173:41-53.

The circadian clock in adult neural stem cell maintenance

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Abstract

Neural stem cells persist in the adult central nervous system as a continuing source of astrocytes, oligodendrocytes and neurons. Various signaling pathways and transcription factors actively maintain this population by regulating cell cycle entry and exit. Similarly, the circadian clock is interconnected with the cell cycle and actively maintains stem cell populations in various tissues. Here, we discuss emerging evidence for an important role of the circadian clock in neural stem cells maintenance. We propose that the NAD^+-dependent deacetylase SIRT1 exerts control over the circadian clock in adult neural stem cell function to limit exhaustion of their population. Conversely, disruption of the circadian clock may compromise neural stem cell quiescence resulting in a premature decline of the neural stem cell population. As such, energy metabolism and the circadian clock converge in adult neural stem cell maintenance.

Key words: circadian rhythms - neural stem cell – quiescence - SIRT1 – metabolism - aging

Abbreviations

BMAL1, brain and muscle ARNT-like protein 1; CLOCK, Circadian Locomotor Output Cycles Kaput; PER, period; CRY, cryptochrome; RORα/β, RAR-related orphan receptor alpha; DBP, D-box binding protein; qNSC, quiescent neural stem cell; aNSC, activated neural stem cell; SIRT1, NAD-dependent protein deacetylase sirtuin-1; HDAC, histone deacetylase; HAT, histone acetyltransferase; Nampt, nicotinamide phosphoribosyltransferase; Nmnat, nicotinamide/nicotinic acid mononucleotide adenylyl transferase; NMN, nicotinamidemononucleotide

1. Introduction

Circadian rhythms, driven by an internal oscillator with a near 24-hour periodicity, provide an excellent means to anticipate food processing and to sequestrate complex and often incompatible metabolic processes (Dibner et al., 2010; Mohawk *et al.*, 2012). Consequently, the circadian clock is vitally important for regulating metabolism, behavior, endocrine regulation and a large variety of cellular pathways, to the extent that it is estimated that about 10 to 20% of genes in any given cell is cyclically expressed (Sahar and Sassone-Corsi, 2012; Aguilar-Arnal and Sassone-Corsi 2013). Hence, various diseases are associated with disturbances of circadian rhythms, including cancer, type-2 diabetes and neurodegenerative disorders (Bechtold et al., 2010; Hood and Amir, 2017a). Throughout life, mammalian stem cells allow for continuous cell division in order to replenish bone, blood, epithelia, muscle, gametes and the nervous system, amongst others, with new cells. These cells, which may lie dormant until activation following injury or physiological changes, are controlled within restricted niches. Due to the importance of stem cells for regeneration in both health and disease, it is vital to understand the underlying control mechanisms.

The circadian clock modulates the function of adult stem cells in various tissues, including neural stem cells (NSCs) in the adult brain (Brown, 2014; Janich et al., 2014; Weger et al., 2017; Dierickx et al., 2017). NSCs have the ability to self-renew and give rise to neurons and glia via symmetric and asymmetric cell divisions in the embryonic, neonatal and adult brain (Merkle and Alvarez-Buylla 2006; Ponti et al., 2013). Whereas neurogenesis and gliogenesis are most extensive during embryonic development, a pool of quiescent neural stem cells continues to produce neurons and glia in the adult brain, predominantly in the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus and in the subventricular zone bordering the lateral ventricles (Taupin and Gage, 2002; Basak and Taylor, 2009). In recent years, a number of studies have reported a role of the circadian clock in adult NSC proliferation and differentiation. Here, we highlight and discuss the role of circadian rhythms in the maintenance of adult neural stem cells. The circadian clock and cell cycle are interconnected and converge on energy metabolism. By restricting entry of quiescent neural stem cells into the cell cycle when cellular energy levels are low, the circadian clock limits exhaustion of the stem cell population. Conversely, weakening of the circadian clock may remove these restrains on neural stem cell activation resulting in a depleted stem cell population. As such, circadian dysfunction accelerates the age-dependent decline of neural stem cells associated with cognitive impairments.

2. Circadian clock, cell cycle and stem cell homeostasis

2.1 Molecular basis of the circadian clock

Circadian rhythms are generated by a circadian oscillator based on feedback loops in transcription and translation of core clock genes (Buhr and Takahashi, 2013; Takahashi, 2016). In the positive limb, transcriptional complexes of basic helix-loop-helix transcription factors BMAL1 and CLOCK, or BMAL1 and NPAS2, activate transcription of clock-controlled genes (CCGs) by binding to E-box elements within their promoters (**Figure 1**).

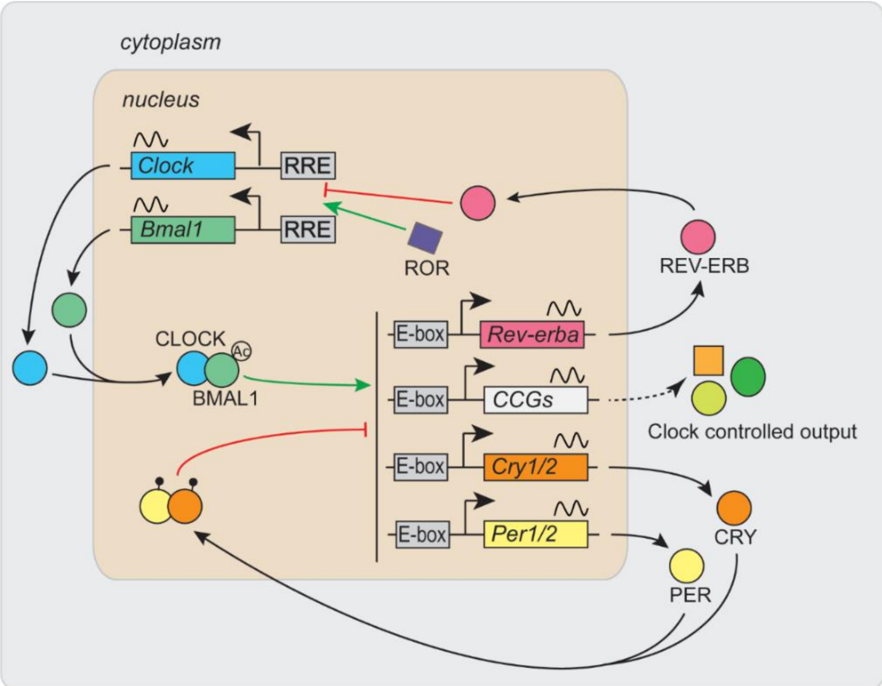

Figure 1. Molecular basis of the circadian clock.
Schematic representation of the molecular circadian oscillator. The primary negative feedback loop of the circadian oscillator involves Clock, Bmal1, Per1, Per2, Cry1, Cry2 genes. CLOCK/BMAL1 heterodimer activates E-box transcription of Per and Cry genes. Subsequently, PER and CRY proteins heterodimerize and translocate to the nucleus to inhibit CLOCK/BMAL1-driven transcription. A secondary feedback loop is composed of REV-ERBα mediated repression of Bmal1 transcription. Adapted from van den Berg et al., 2017.

Among these target genes are *Per1-3* and *Cry1-2*, the main components of the negative limb PER1-3 and CRY1-2, in turn, form heterodimers and translocate to the nucleus to inhibit CLOCK:BMAL1 transcriptional activity, repressing their own transcription (Buhr and Takahashi, 2013; Takahashi, 2016). Following phosphorylation of PER and CRY and subsequent degradation, PER-CRY complexes can no longer inhibit CLOCK:BMAL1 activity, starting a new cycle of *Per* and *Cry* transcription. In addition, CLOCK:BMAL1 activates transcription of orphan nuclear receptor genes *Rev-Erbα/β* and *RORα/β*. These genes encode for transcriptional repressors and activators, respectively, competing for RORE binding sites in the *Bmal1* promoter (Preitner et al., 2002). Moreover, a number of posttranslational modifications (e.g. phosphorylation, histone acetylation, methylation and sumoylation) and posttranscriptional modifications (e.g. RNA polyadenylation and methylation) have been found to control circadian clock dynamics (Lee et al., 2001; Gallego and Virshup, 2007; Kojima et al., 2012; Fustin et al., 2013).

These mechanisms are shared by virtually all mammalian cells and most tissues exhibit persistent circadian oscillations in gene expression and function (Dibner et al., 2010; Mohawk *et al.*, 2012). Further tissue-specific regulation of clock-controlled genes can result from interactions of core clock components with chromatin remodelers and local transcription factors (Masri and Sassone-Corsi, 2013). The period of the circadian clock, however, is not exactly 24 hours and needs daily resetting by light to prevent misalignment with the light-dark cycle (Dibner et al., 2010; Mohawk *et al.*, 2012). To this end, neurons in the suprachiasmatic nucleus (SCN) of the hypothalamus are reset by incoming light signals via the retinohypothalamic tract. The SCN then synchronizes cells in the rest of the body and brain, the peripheral oscillators, via the autonomic nervous system, hormones such as glucocorticoids, body temperature and feeding behavior. Alternatively, metabolic signals deriving from food intake can overrule signals imposed by the SCN and synchronize peripheral oscillators to feeding time. As a result, there is a close reciprocal relationship between metabolism and circadian rhythms, allowing the circadian clock to temporally restrict metabolic processes. Circadian rhythmicity is, in other words, vital for metabolic homeostasis. This becomes apparent when light signals and metabolic signals are not in phase (e.g. during shift work or jet lag) causing peripheral oscillators to be uncoupled from the SCN (Damiola et al., 2000). Such a misalignment between circadian rhythms and metabolic cues poses an increased risk for metabolic disease and cancer (Bechtold et al., 2010; Janich et al., 2014).

The mechanisms coupling metabolism to the circadian clock are rapidly being uncovered and clearly show their extensive crosstalk (Bass and Takahashi, 2010; Asher and Schibler, 2011; Sahar and Sassone-Corsi, 2012). Whereas the circadian clock controls a large range of metabolic processes, metabolic fluxes in glucose, oxygen levels, ATP, NAD^+ and glucocorticoids regulate circadian function via AMPK and SIRT1 activity (Bass and Takahashi, 2010). In addition, we have demonstrated that insulin directly modulates circadian rhythms by controlling *Clock* expression in the liver (Chaves et al., 2014). Transcription factor FOXO3, inactivated by insulin-PI3K signalling, was found to be necessary for circadian rhythmicity by binding directly to the *Clock* promoter. In other words, FOXO3 directly links metabolism to the circadian clock.

Moreover, the circadian clock and metabolism converge on epigenetic mechanisms (Bellet and Sassone-Corsi, 2010; Aguilar-Arnal and Sassone-Corsi, 2013). Chromatin remodelling induced by cellular metabolites can result in transcriptional activation or silencing of promoters of clock-controlled genes (Aguilar-Arnal and Sassone-Corsi, 2013). Importantly, the post-translational modifications of histones driving this plasticity (Cheung et al., 2000) are dynamically present on CCG promoters following a circadian rhythm (Doi et al., 2006; Etchegaray et al., 2003). For instance, CLOCK:BMAL1 is rhythmically recruited to the rhythmically acetylated *Dbp* promoter (Ripperger and Schibler, 2006). Importantly, CLOCK has intrinsic histone acetyl transferase (HAT) activity driving H3K14 acetylation at CCG promoters in a circadian manner (Doi et al., 2008). Therefore, the circadian clock regulates gene expression by controlling chromatin remodelling in response to metabolism (Aguilar-Arnal and Sassone-Corsi, 2013).

2.2 Circadian rhythms and the cell cycle

The cell cycle is divided into sequential stages known as G_1, S, G_2 and M phases. DNA is replicated in the S phase, mitosis occurs in the M phase and the G_1 and G_2 phases are intermediary growth periods terminating in cell cycle checkpoints. Cell cycle progression depends on the sequential and transient activation of cyclin-dependent kinase-cyclin complexes controlling these checkpoints (Satyanarayana and Kaldis, 2009). Since the activation and repression of these cell cycle regulators is periodic, the cell cycle can be considered as a biological oscillator coexisting with the circadian oscillator (Hunt and Sassone-Corsi, 2007). Cyclin-dependent kinase inhibitors p16Ink4A, $p21^{cip1/waf1}$ (p21) and $p27^{Kip1}$, for instance, are critical in halting progression of the cell cycle (Satyanarayana and Kaldis, 2009). On the other hand, phosphatases of the Cdc25 family promote cell cycle transition by activating the cyclin-dependent kinase complexes.

Interestingly, the circadian clock controls both transcription and direct protein-protein interactions of cell cycle regulators. Circadian expression of cell cycle inhibitor *p21*, for instance, is regulated by REV-ERBα and RORα/γ (Gréchez-Cassiau et al., 2008) whereas circadian transcription of *p16-Ink4A* depends on NONO, a partner of PER (Kowalska et al., 2013). Similarly, circadian transcription of *Wee1*, which encodes for the kinase controlling G_2/M transition, is regulated by the CLOCK:BMAL1 dimer (Matsuo et al., 2003). Core clock components CRY, PER and TIM, moreover, control G_1/S and G2/M transitions by interacting with the ATR-CHK1 and ATM-CHK2 DNA damage pathways (Kang and Leem, 2014; Yang et al., 2010). Among the clock-controlled cell cycle regulators are Sox9, Itga6, Wnt3, Smad7, Cdk4, LHx2, Tcf4, β-catenin as well as known oncogenes c-Myc and Mdm2, tumor suppressor p53 and cyclins Ccnd1 and Ccnd1b (Fu and Kettner, 2013).

The circadian clock is, therefore, commonly understood to gate cell cycle progression (Matsuo et al., 2003; Kowalska et al., 2010; Karpowicz et al., 2013; Plikus et al., 2013). However, two recent studies using single live cell imaging found that the cell cycle modulates the circadian clock (Feillet et al., 2014; Bieler et al., 2014). As such, it has been argued to reject the concept of a circadian clock gating the cell cycle and to consider a bidirectional relationship in which the cell cycle affects the circadian clock and vice versa instead (Feillet et al., 2015). Tumor suppressor p53 could be key in linking the cell cycle and circadian clock in a bidirectional way, as it was found to repress *Per2* transcription, preventing binding of CLOCK:BMAL1 (Miki et al., 2013). Importantly, coupling of the circadian clock to the cell cycle minimizes DNA damage during replication (Chen and McKnight, 2007; Brown, 2014). As metabolic processes cause the formation of mutagenic free radicals, the circadian clock could segregate DNA replication away from periods when metabolic rates are highest. As such, circadian rhythms, the cell cycle and metabolic cycles are strongly interconnected.

2.3 Circadian rhythms in stem cell homeostasis

The importance of circadian function in maintaining tissue homeostasis has emerged in recent years (Brown 2014; Janich et al., 2014; Weger et al., 2017; Dierickx et al., 2017). Circadian disruptions, for instance, have been found to cause tissue-specific pathologies in the liver, pancreas, adipose tissue, muscle, intestine, the hematopoietic system, the skin, cartilage and the brain (Janich et al., 2014). Amongst tissue-specific roles that promote homeostasis, the circadian clock has an important function in regulating stem cell homeostasis. Such a mechanism has been documented in stem cells within the skin, the regenerating intestine, hair follicle and adult hippocampus, amongst others (Geyfman et al., 2012; Janich et al., 2013; Plikus et al., 2013; Karpowicz et al., 2013; Bouchard-Cannon et al., 2013).

Another major role for the circadian clock could lie in the generation of heterogeneity within a stem cell population (Janich et al., 2011, 2013). Using a Per1-Venus mouse model as a circadian clock reporter, the hair follicle stem cell niche was shown to contain coexisting populations of dormant stem cells in different circadian phases. As a result, these stem cells express different receptors than their neighbours, making them either predisposed, or less prone, to activating signals. This circadian heterogeneity in epidermal stem cell function was further explored in a subsequent study (Janich et al., 2013). By determining clock gene expression in keratinocyte stem cells during the day, the authors were able to identify distinct stem cell populations. These populations also showed distinct transcriptional profiles related to proliferation and differentiation. Differentiation pathways were upregulated in the morning, whereas expression of genes involved in DNA replication was increased in the evening. As such, this heterogeneous stem cell population can be expected to have differential metabolic needs as well. Indeed, single epidermal stem cells differed in their metabolic activity during the day but also from their neighbours in a different circadian phase (Stringari et al., 2015).

These are interesting findings as they suggest a pivotal role for the circadian clock in stem cell biology. A stem cell niche with a plethora of circadian phases would continuously be able to offer an adequate response to external cues while never exhausting the whole population at once. As such, the circadian clock might create a tremendous complexity within the stem cell niche. Not only do stem cells differ in the response to a differentiation signal during the day

(Janich et al., 2013), their activation depends on the circadian phase which might be different from their neighbours. In turn, neighbouring cells might reciprocally inhibit the activation of surrounding cells via juxtacrine signalling. In the developing nervous system, for example, a salt-and-pepper pattern of Notch signalling results in lateral inhibition of neural progenitors preventing them from differentiating (Kageyama et al., 2008).

Conceptually, two stem cells in the same circadian phase might, therefore, still differ in their response to the same activating signal if these cells are surrounded by different neighbours. Similarly, stem cells in the same circadian phase could still function differently when their position towards incoming signals differs (i.e. next to a blood vessel or at opposing ends of a signalling gradient). Together, this would result in an extraordinary level of complexity within the stem cell population. However, this is speculative for now: it is unknown whether this mechanism of clock-mediated stem cell heterogeneity observed in the hair follicle is conserved in all adult stem cell niches.

3. Circadian rhythms in adult neurogenesis

3.1. Neural stem cells and their niches

Neural stem cells are the multipotent source of neurons, astrocytes and oligodendrocytes in the central nervous system (Taupin and Gage, 2002; Merkle and Alvarez-Buylla, 2006). Having the ability to self-renew or remain in a quiescent state outside of the cell cycle (i.e. G_0 phase), NSCs are capable of producing neurons and glia throughout life. In order to retain this ability, regulation of the cell cycle entry and exit dynamics of NSCs is vitally important. If NSCs lose the ability to remain quiescent and start to proliferate in an uncontrolled manner, their population could become exhausted leaving the adult and aging brain with diminished levels of neurogenesis (Encinas et al. 2012; Ro et al. 2013). Coupling of the circadian clock to the cell cycle could, conceptually, maintain this balance by regulating cell cycle entry and exit of neural stem cells.

In the adult brain, NSC reside in restricted niches, predominantly in the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus and in the subventricular zone bordering the lateral ventricles (Basak and Taylor, 2009). These niches have their own microenvironment and are highly vascularized (Scadden, 2014; Licht and Keshet, 2015). As a result, NSCs are well positioned to respond to external signals to remain quiescent or to re-enter the cell cycle (Scadden, 2014; Lugert et al., 2010). These signals largely derive from a variety of signalling pathways, notably Wnt, BMP, Notch and Shh, which control adult NSC fate and self-renewal in a context-dependent and often antagonistic manner (Seib et al., 2013; Mira et al., 2013; Ehm et al., 2010; Imayoshi et al., 2010; Ahn et al., 2005). WNT signalling, for example, promotes self-renewal and induces neuronal differentiation (Qu et al., 2010; Piccin and Morshead, 2011) whereas BMP signalling inhibits proliferation and promotes astrocytic fates in NSCs (Lim et al., 2000; Colak et al., 2008).

These signalling pathways, importantly, are thought to be regulated by the circadian clock (Brown, 2014). Genes encoding members of the Notch, Wnt, TGFβ and BMP pathways have been found to be expressed in a circadian manner in human hair follicle stem cells (Janich et al., 2011, 2013). For instance, Wnt pathway components and cell cycle regulators Sox9, Wnt3a, Tcf4, beta-catenin, Lhx2 and c-Myc are directly clock-regulated (Fu and Kettner, 2013) as well as Smad7, which is a BMP signalling inhibitor inhibiting NSC proliferation (Krampert et al., 2010). Interestingly, BMAL1 was found to rhythmically bind to the promoter of these genes (Janich et al., 2011; Rey et al., 2011). In myoblasts, BMAL1 positively regulates transcription of Wnt genes, the accumulation of ß-catenin - the key transducer of canonical Wnt signalling – and the expression of Wnt target genes (Guo et al., 2012; Chatterjee et al., 2013). As such, circadian activity of these signalling pathways could result in oscillatory NSC cell cycle entry and exit. A role for circadian rhythms in signalling pathways regulating NSC fates, however, has yet to be established.

In addition to these canonical signal transduction pathways, metabolism and oxidative stress are increasingly found to control proliferation of NSCs (Le Belle et al., 2011; Rafalski and Brunet, 2011; Knobloch and Jessberger, 2017). Importantly, regulation of metabolic processes and oxidative stress responses are intimately connected to the circadian clock (Sahar and Sassone-Corsi, 2012; Peek et al., 2013). Moreover, clock-regulated p53, Mdm2 and Cdk4 (Fu and Kettner, 2013) also have an important role in NSC cell cycle dynamics. P53, for instance, suppresses adult NSC self-renewal (Meletis et al., 2006) but its ubiquitin-dependent degradation is promoted by MDM2 (Kruse & Gu, 2009). Cdk4, conversely, promotes neural stem cell expansion in the adult brain at the expense of neurogenesis (Artegiani et al., 2011).

As such, it is conceivable that the coupling between metabolic cycles, circadian rhythms and the cell cycle is important for neural stem cell maintenance. This would temporally allow NSCs to leave and enter the cell cycle, resulting in rhythmic neurogenesis, while maintaining the stem cell population.

3.2. Circadian rhythms in adult neurogenesis

A number of studies have examined daily rhythms in hippocampal neurogenesis with varying outcomes (**Table 1**). In one of these studies, adult rats were injected with thymidine analog 5-Bromo-2′–deoxyuridine (BrdU) at four different time points across the light-dark cycle and sacrificed two hours later (Guzman-Marin et al., 2007). This revealed a circadian rhythm in the number of dividing, BrdU-positive cells in the subgranular zone (SGZ) of the dentate gyrus, but not in the hilus. This suggests that the presence of circadian rhythms in hippocampal cell proliferation may differ between anatomical regions in the dentate gyrus. Indeed, another study reported a circadian rhythm in BrdU incorporation in the granule cell layer (GCL) and in the hilus but not in the SGZ (Kochman et al., 2006). This is in line with a study in rats showing a decrease in cell proliferation in the hilus but not in the SGZ following sleep deprivation (Roman et al., 2005). Yet another study in rats did not report circadian proliferation in the GCL nor in the hilus or in the dentate gyrus (Ambrogini et al., 2003). However, the authors of this study examined BrdU incorporation at only four time points rather than six and waited for 24 hours past BrdU injections instead of the 2-hour pulses used by Kochman and co-workers. As such, methodological differences likely account for the different outcomes.

Nevertheless, circadian rhythms in mitotic cells have also been found in the SGZ of the dentate gyrus of adult Syrian hamsters, rats and mice (Tamai et al., 2008; Smith et al., 2010; Gilhooley et al., 2011; Matsumoto et al., 2011; Bouchard-Cannon et al., 2013; Schnell et al., 2014). Importantly, the increase in dividing $SOX2^+$ $GFAP^+$ hippocampal progenitors was accompanied by an increase of DCX^+ newborn neurons (Tamai et al., 2008; Bouchard-Cannon et al., 2013).

Interestingly, two studies report no circadian variation in the hippocampal cells positive for either BrdU (Holmes et al., 2004) or proliferation marker Ki67 (van der Borght et al., 2006). However, access to a running wheel in the middle of the dark period increased neurogenesis but not during other periods (Holmes et al., 2004). Similarly, mice housed with a running wheel for 9 days showed increased cell proliferation in the SGZ compared to sedentary controls (Van der Borght et al., 2004). This effect was most profound directly after the dark phase although the interaction was not statistically significant (Van der Borght et al., 2004). This suggests that the circadian clock, possibly via circadian regulation of neurogenic factors (Holmes et al., 2004), may enhance exercise-induced neurogenesis. However, it is also conceivable that circadian oscillation are more easily detected when levels of neurogenesis are elevated following running activity.

Table 1. Circadian rhythms in neural stem cell proliferation in the adult hippocampus and subventricular zone of the lateral ventricle.

Region		Circadian rhythm in proliferation	Period of maximum proliferation	Ref.
dentate gyrus	SGZ	Present	end of light phase – dark phase	[1 – 7]
		Absent	-	[8 – 11]
	GCL	Present	end of light phase	[8]
		Absent	-	[11]
	hilus	Present	light phase	[8]
		Absent	-	[1, 11]
SVZ of lateral ventricle		Absent	-	[4]

1, Guzman-Marin et al., 2007; 2, Smith et al., 2010; 3, Gilhooley et al., 2011; 4, Tamai et al., 2008; 5, Bouchard-Cannon et al., 2013; 6, Schnell et al., 2014; 7, Matsumoto et al., 2011; 8, Kochman et al., 2006; 9, van der Borght et al., 2006; 10, Holmes et al., 2004; 11, Ambrogini et al., 2006. SGZ, subgranular zone; GCL, granule cell layer; SVZ, subventricular zone; LV, lateral ventricle

In summary, adult hippocampal neurogenesis likely exhibits a circadian rhythm but results differ between regions and seem to depend on the proliferation markers and number of time points used. Perhaps circadian control of proliferation is limited to subsets of neural stem cells. Moreover, the variability in outcomes using different proliferation markers suggest a differential role of the circadian clock in the neural stem cell cycle. Hippocampal NSCs, for instance, have been found to lack daily variation in S-phase marker BrdU but did show a circadian rhythm in M-phase marker PH3 (Tamai et al., 2008; Matsumoto et al., 2011). This might also explain the absence of circadian rhythmicity in SGZ proliferation in some studies using BrdU (Kochman et al., 2008). As such, the circadian clock may differentially regulate cell cycle entry or cell cycle progression in different neural stem cells.

Alternatively, the effects of circadian disruptions on hippocampal proliferation have been examined. For instance, 6-hour phase advances every third day, mimicking jet lags, resulted in decreased neurogenesis in hamsters and impaired long-term learning and memory (Gibson et al., 2010). Similarly, weekly 6-hour phase shifts led to a reduced number of DCX^+ immature neurons in the rat dentate gyrus (Kott et al., 2012). This effect was enhanced with more weeks of phase shifts and was only true for a phase advance and not for a phase delay (Kott et al., 2012). Disruption of circadian rhythms, however, results in sleep deprivation and stress, both of which are known to suppress hippocampal neurogenesis (Lucassen et al., 2010). Indeed, levels of stress hormone cortisol were increased in 'jet-lagged' hamsters (Gibson et al., 2010). In addition, mice kept in a constant light environment showed a clear decrease in the number of BrdU-labelled βIII-tubulin-positive newborn neurons and had impaired hippocampus-dependent memory formation (Fujioka et al., 2011). A similar study in rats, however, found no significant difference in total cell survival or new neurons following 3 weeks of constant light (Mueller et al., 2011). Since running is known to enhance neurogenesis (van Praag et al., 1999), however, reduced running activity in a constant light may directly result in impaired neurogenesis.

3.3. Circadian clock in adult neural stem cell maintenance

Various knockout mice with deletions in clock genes have been used to directly study the effect of the circadian clock on neural stem cell proliferation (**Table 2**). Interestingly, mice exhibit a loss of a diurnal rhythm in hippocampal neurogenesis in the absence of either *Bmal1*, *Rev-erbα* or *Per2* (Bouchard-Cannon et al., 2013; Schnell et al., 2014; Borgs et al., 2009).

Table 2. Role of clock genes in adult neurogenesis.		
Gene	**Phenotype of mouse mutant**	**Ref.**
Bmal1	Arrhythmic Loss of circadian rhythm in hippocampal neurogenesis Increased hippocampal neurogenesis in young mice, no difference in adult mice, and decreased neurogenesis in old mice. Increased cell death in the dentate gyrus Impaired cognitive function	[1-6]
Per2	Shorter circadian period, gradually arrhythmic Loss of circadian rhythm in hippocampal neurogenesis Increased hippocampal neurogenesis in young mice Impaired cognitive function	[6,7,8]
Rev-Erbα	Rhythmic with shorter circadian period Loss of circadian rhythm in hippocampal neurogenesis Increased hippocampal neurogenesis in young mice Impaired cognitive function	[9,10]
Cry1 / Cry2	Arrhythmic Smaller SVZ and DG-derived primary neurospheres Impaired cognitive function	[5, 11, 12]
1, Rakai et al., 2014; 2, Ali et al., 2015; 3, Kondratov et al., 2006; 4, Kondratova et al., 2010; 5, Malik et al., 2015b; 6, Bouchard-Cannon et al., 2013; 7, Borgs et al., 2009; 8, Zheng et al., 1999; 9, Preitner et al., 2002; 10, Schnell et al., 2014; 11, van der Horst et al., 1999; 12, Vitaterna et al.¸1999		

Whereas the number of BrdU-positive cells was clearly increased in young *Bmal1*$^{-/-}$ mice, doubling the number found in controls (Bouchard-Cannon et al., 2013), adult *Bmal1*$^{-/-}$ mice exhibit striking decrease in proliferating cells, to half the number found in controls (Ali et al., 2015). No difference in hippocampal cell proliferation, however, was found in young adult Bmal1$^{-/-}$ mice of 60-days old (Rakai et al., 2014). Together, this suggests that the absence of *Bmal1* results in increased proliferation of NSCs, leading to a premature depletion of the stem cell population.

Young mice with a loss of *Per2* also exhibit an increased number of neural progenitors in the dentate gyrus (Bouchard-Cannon et al., 2013; Borgs et al., 2009) and both *Bmal1*$^{-/-}$ and *Per2*$^{-/-}$ mice show an increased cell cycle entry of SOX2^{+}GFAP^{+} qNSCs (Bouchard-Cannon et al., 2013). Unlike *Per2*$^{-/-}$ mice, *Bmal1*$^{-/-}$ mice also showed an increase in the number of SGZ cells leaving the cell cycle with an increase in newborn NeuN^{+} neurons in the SGZ. As such, Per2 and Bmal1 both likely restrain qNSCs from entering the cell cycle with Bmal1 also limiting the number of cell divisions occurring in aNSCs before they leave the cell cycle towards differentiation.

Rev-erbα$^{-/-}$ mice, moreover, showed constantly high levels of hippocampal neurogenesis and exhibited impaired hippocampus-dependent cognitive function (Schnell et al., 2014). Interestingly, REV-ERBα was found to repress expression of *Fabp7*, a marker of mitotically active NSCs, and may therefore limit activation of NSC (Schnell et al., 2014). This is in line with the putative function of BMAL1 in restraining NSC activation to prevent exhaustion of the NSC population (Bouchard-Cannon et al., 2013). REV-ERBα, however, is a negative transcriptional regulator of *Bmal1* expression and *Rev-erbα*$^{-/-}$ mice show increased *Bmal1* expression (Preitner et al., 2002). Also, *Bmal1*$^{-/-}$ are arrhythmic (Bunger et al., 2000) while *Rev-erbα* $^{-/-}$ mice are still rhythmic and exhibit a shorter circadian period in constant darkness. Therefore, it would be interesting to determine if a REV-ERBα deficiency also results in the depletion of NSCs in aged animals.

Five to eight months old *Cry1*$^{-/-}$*Cry2*$^{-/-}$ double knockout mice, moreover, show reduced numbers of SVZ and DG-derived neurospheres (Malik et al., 2015b). Although the authors argued that this resulted from suppressed proliferation or increased apoptosis, it seems more likely that the NSC population has become depleted in the absence of these two cryptochromes with a phenotype similar to that of *Bmal1*$^{-/-}$ mice. *Cry1*$^{-/-}$*Cry2*$^{-/-}$ knockout mice, for instance, show diminished *Bmal1* expression (Shearman et al., 2000) whereas loss of NSCs can already be observed in 3 month-old *Bmal1* KO mice (Bouchard-Cannon et al., 2013). Also, *Cry1*$^{-/-}$*Cry2*$^{-/-}$ show an impaired cognitive function arguably similar to the cognitive deficit observed in *Bmal1*$^{-/-}$, *Per2*$^{-/-}$ and *Rev-erbα*$^{-/-}$ mice (Kondratova et al., 2010; Bouchard-Cannon et al., 2013; Schnell et al., 2014).

This suggests that Bmal1, Per2, Rev-erbα, and Cry1/2 may similarly regulate hippocampal neurogenesis. This is striking since these core clock components act either as activators or repressors within the clockwork machinery and have different behavioral phenotypes. Considering the interconnecting feedback loops regulating clock gene expression, however, it seems likely that in the absence of any component, the circadian clock would be severely impaired. In these clock mutant mice, however, various other organs besides the brain were likely affected, which could have interfered with adult neurogenesis. For instance, insulin production and liver function rely on a functional circadian clock (Allaman-Pillet et al., 2004; Kornmann et al., 2007). In a clock gene mutant mouse, metabolic dysfunction could therefore have impaired neural stem cell behavior (Knobloch and Jessberger, 2017). Nevertheless, knockdown of *Bmal1* and *Clock* in neurospheres did also directly affect neurogenesis (Kimiwada et al., 2009). Moreover, Nestin-Cre transgenic mice with a brain-specific deletion of *Bmal1* developed severe age-dependent pathology in the cortex and hippocampus (Musiek et al., 2013). Together, this asserts that a functional circadian clock is essential to maintain the neural stem cell population throughout life.

This is functionally reminiscent of cell cycle inhibitor p21, tumor suppressor p53 and FOXO transcription factors, loss of which results in increased proliferation culminating in neural stem cell depletion (Kippin et al., 2005; Meletis, 2005; Ro et al., 2013). For instance, both *FoxO1/3/4* triple and *FoxO3* single knockout mice show an initial increase in NSC proliferation at young age and a reduced NSC population in the adult brain (Paik et al., 2009; Renault et al., 2009). Therefore, mechanisms governing the circadian clock and neural stem cell maintenance may converge. Indeed, p21 has been identified as a clock-controlled gene as it is rhythmically expressed following binding of the REV-ERB and ROR nuclear receptors (Gréchez-Cassiau et al., 2008). Moreover, p53 has been found to repress CLOCK:BMAL1-mediated activation of *Per2* expression (Miki et al., 2013) and we have found FOXO3 to regulate *Clock* transcription in the liver (Chaves et al., 2014). As such, these regulators of neural stem cell fates are likely interconnected with the circadian clock.

3.4. Coupling of circadian rhythms to the cell cycle in neural stem cells

The presence of circadian rhythms in hippocampal cell proliferation suggests that the cell cycle of neural stem cells is directly coupled to the circadian clock. Indeed, levels of phosphorylated CDK1, an initiator of G_2/M transitions, and the number of $PH3^+$ cells, residing in M-phase, both peaked at night in the dentate gyrus (Tamai et al., 2008). Moreover, BrdU incorporation, marking the S-phase, has been found at its highest at the end of the day (Bouchard-Cannon et al., 2013).

A recent study (Akle et al., 2017) further demonstrated that cell cycle progression and the circadian clock are coupled in the adult zebrafish brain. By examining cell cycle markers in various neurogenic niches, the authors observed G_1/S transition in the morning, progression through the S-phase during the day with G_2/M and mitosis occurring late at night. Moreover, the circadian expression of cell cycle regulators cyclin A2, cyclin B2, cyclin D and cyclin-dependent kinase inhibitor p20 accompanied these transitions. Interestingly, circadian phases differed between different neurogenic niches suggesting niche-specific regulation by the circadian clock. As such, this paper raises an intriguing question: is this niche-specific clock function conserved in the mammalian brain? Most studies examining circadian rhythms in neurogenesis, however, have focused on the dentate gyrus and little is known about clock function in other neurogenic niches. So far, the only study examining circadian proliferation in the SVZ did not detect a proliferation rhythm in this niche as opposed to the time-of-day dependent increase in proliferating cells found in the DG (Tamai et al., 2008). The complete absence of a diurnal rhythm in SVZ neurogenesis, however, seems unlikely. Whereas newborn olfactory bulb neurons generated from SVZ NSCs are thought to be important for odor discrimination (Gheusi et al., 2000; Breton-Provencher et al., 2009), olfactory discrimination is reportedly regulated by a circadian clock within the olfactory bulbs (Granados-Fuentes et al., 2011). Rather, in these 6-week old mice, the number of proliferating cells in the SVZ was about a 4-fold higher than in the DG. (Tamai et al., 2008). Possibly, any circadian restraints on neural stem cell maintenance are outweighed by the high rates of SVZ neurogenesis at this age.

Alternatively, Bouchard-Cannon et al. (2013) observed a circadian rhythm in cell cycle entry of quiescent NSCs. The authors found an increased proportion of active $BrdU^+SOX2^+GFAP^+$ neural stem cells in the dentate gyrus relative to the total population of $SOX2^+GFAP^+$ NSCs at the end of the day. These rhythms, interestingly, were absent in both *Bmal1*$^{-/-}$ and *Per2*$^{-/-}$ mice. As such, the age-related depletion of NSCs in *Bmal1*$^{-/-}$ is likely caused by loss of quiescence and increased cell cycle entry (Ali et al., 2015). Together, these studies suggest that the circadian clock may differentially regulate cell cycle entry and cell cycle progression in neural stem cells.

3.5. Circadian clock in neural stem cell differentiation

The circadian clock not only regulates NSC proliferation but likely controls neural stem cells differentiation as well. For instance, in the absence of *Bmal1* hippocampal NSCs increasingly differentiated into GFAP$^+$ astrocytes at the expense of neurons expressing NeuN, DCX and beta-III tubulin (Ali et al., 2015; Malik et al., 2015b). Similarly, knockdown of *Bmal1* and *Clock* in cultured NSCs both resulted in less Map2-positive (Kimiwada et al., 2009). Mice with a functional mutation in PER2, however, show an increase in DCX$^+$ and NeuroD$^+$ immature neurons in the SGZ but no differences in GFAP$^+$ astrocytes or O4$^+$ oligodendrocytes (Borgs et al., 2009). Additionally, in the absence of the *Cry1* and *Cry2* genes, mice exhibit normal percentages of neuronal cells but increased astrocyte proliferation (Malik et al., 2015b). Together, these studies suggest that Bmal1 and Clock promote NSCs to adopt neuronal fates at the expense of astroglial lineages, which is inhibited by repressors Per2, Cry1 and Cry2.

Mechanistically, BMAL1 and CLOCK could directly regulate neural stem cell fates by binding to an E-box element in the promoter region of neurogenic transcription factors and by chromatin remodeling caused by histone acetyltransferase (HAT) activity of the CLOCK protein (Doi et al., 2006; Nakahata et al., 2008; Kimiwada et al., 2009). Indeed, downregulation of *Bmal1* and *Clock* suppressed both gene expression of transcription factor *NeuroD1* and neuronal differentiation (Kimiwada et al., 2009). Expression of *Id2* and *Hey1*, conversely, increased following downregulation of *Clock*. Whereas NeuroD1 promotes neuronal differentiation (Gao et al., 2009), Id2 and Hey1 promote self-renewal of neural stem cells and inhibit proneuronal basic helix-loop-helix transcription factors such as NeuroD1 and Mash1 (Jung et al., 2010; Sakamoto et al., 2003). Similarly, CLOCK:BMAL1 was found to directly regulate *Pax6* expression by binding to an E-box element within its promoter (Morgan, 2004). Transcription factor Pax6, interestingly, was found to control the balance between neural stem cell self-renewal and neurogenesis in both the adult and developing brain (Curto et al., 2014; Sansom et al., 2009). Therefore, the circadian clock may exert control of neural stem cell fates by regulating expression of transcription factors.

Importantly, mouse embryonic (ES) stem cells have been found to lack circadian expression of clock genes in two independent studies (Yagita et al., 2010; Kowalska et al., 2010). Neuronal differentiation of ES cells, however, induced circadian oscillations in *Bmal1* expression (Yagita et al., 2010;

Kowalska et al., 2010). Interestingly, these neural stem cells were later dedifferentiated using reprogramming factors Oct3/4, Sox2, Klf4 and c-Myc. As a result, circadian oscillations disappeared again with gene expression *Cry1*, *Per2* and *Bmal1* returning to the levels observed in ES cells (Yagita et al., 2010). In other words, iPSCs match ES cells in both circadian rhythmicity and levels of clock gene expression (Yagita et al., 2010). Despite the apparent absence of a functional circadian clock in ES cells, circadian oscillations in glucose uptake and glucose transporter mRNA have been observed (Paulose et al., 2012). Therefore, it can be argued that differentiation from ES cells to NS cells induces a functional circadian clock.

Conversely, differentiation of activated neural stem cells may induce circadian rhythmicity. During differentiation, circadian rhythms in clock gene expression emerged in neurospheres (Kimiwada et al., 2009; Malik et al., 2015a). This was accompanied by a decrease in stem cell markers SOX2 and Nestin and an increase of cells expressing differentiation markers DCX, beta-III tubulin, NeuN and GFAP. Since neurospheres are mainly derived from activated neural stem cells rather than quiescent neural stem cells (Codega et al., 2014), qNSCs might lose their circadian rhythmicity upon activation and regain rhythmicity during subsequent differentiation. However, the putative absence of a circadian rhythm in activated NSCs is contradictory to the circadian control of cell cycle progression and exit observed in adult neural stem cells *in vivo* (Akle et al., 2017; Bouchard-Cannon et al., 2013). Nevertheless, these studies suggest that circadian rhythmicity may have a dual function in the neurogenic lineage: promoting maintenance of neural stem cells as well as cellular homeostasis of terminally differentiated neurons, for instance by regulating neuronal redox homeostasis (Musiek et al., 2013).

4. SIRT1 and circadian rhythms in neural stem cells

4.1. SIRT1 links circadian rhythms and metabolism

In recent years, NAD-dependent deacetylase SIRT1 has emerged as an important link between circadian rhythms and metabolism by connecting the enzymatic feedback loop regulating the NAD^+ salvage pathway and the circadian transcriptional-translational feedback loop (Nakahata et al., 2009; Bellet et al., 2011; Eckel-Mahan and Sassone-Corsi, 2013). Deacetylating both histones and transcriptional regulatory proteins, SIRT1 is involved in genome stability, transcriptional silencing, metabolism and longevity (Blander and

Guarente 2004; Dali-Youcef et al. 2007). Transcription factors known to be direct targets of SIRT1 include PGC1a (Rodgers et al., 2008), LXR (Li et al., 2007), p53 (Vaziri et al., 2001), Hes1 (Takata and Ishikawa 2003; Fusco et al., 2016) and FoxO family members (Motta et al., 2004; Brunet et al., 2004).

SIRT1 requires the breakdown of one NAD^+ molecule for its deacetylase activity and is, therefore, closely connected to the [NAD^+]/[NADH] ratio within a cell (Blander and Guarente 2004; Dali-Youcef et al. 2007). Metabolic activity during respiration results in oxidative stress and increases the ratio of [NAD^+] to [NADH] ratio. In low energy conditions, the [NAD^+]/[NADH] ratio is high, prompting SIRT1 activity to respond to the cellular energy status. Therefore, SIRT1 is both an important sensor of cellular energy and a mediator of metabolism and epigenetic regulation, mechanisms found critical in circadian regulation as well.

Importantly, SIRT1 regulates the circadian clock via rhythmic deacetylation of BMAL1 and histones in circadian promoters and is rhythmically recruited to the CLOCK:BMAL1 chromatin complex (Asher et al., 2008; Nakahata et al., 2008). Moreover, SIRT1 has been found promote the deacetylation and subsequent degradation of repressor PER2 (Asher et al., 2008). As such, SIRT1 regulates CLOCK:BMAL1 transcriptional activity and the expression of clock-controlled genes. Interestingly, SIRT1 was found to counteract CLOCK-mediated acetylation of BMAL1 at Lys537 and histone H3 in circadian promoters (Hirayama et al., 2007; Doi et al., 2006, Nakahata et al., 2008). As such, the resulting dynamic interplay between the NAD^+-dependent SIRT1 and CLOCK connects energy metabolism to the circadian clock machinery.

Rhythmic SIRT1 deacetylase activity, moreover, is the result of circadian control of the NAD^+ salvage pathway (Nakahata et al., 2009). Among the CCGs, CLOCK:BMAL1 induce expression of *Nampt,* which encodes for the rate-limiting enzyme in the NAD^+ salvage pathway (Revollo et al., 2004). In the NAD^+ salvage pathway, NAMPT converts nicotinamide to NMN, which is then converted to NAD^+ by Nmnat. The resulting oscillations in NAD^+ lead to rhythmic SIRT1 activity (Nakahata et al., 2009). In other words, NAD^+-dependent SIRT1 controls its own activity by regulating NAD^+ levels through modulation of transcription of the clock-controlled gene *Nampt*.

4.2. SIRT1 in adult neural stem cells

Importantly, SIRT1 and NAMPT are expressed in $SOX2^{+}$ neural stem cells of the adult SVZ and DG (Saharan et al., 2013; Ma et al., 2014; Rafalski et al., 2013; Stein and Imai, 2014). Since neural stem cell fates are modulated by metabolism (Knobloch and Jessberger, 2017) and reactive oxygen species (Le Belle et al., 2011; Vieira et al., 2011), it has been argued that the NAD^{+}-dependent SIRT1 may regulate NSC fates in response to their cellular redox state (Prozorovski et al., 2008; Saharan et al., 2013). Indeed, SIRT1 activity in adult NSCs increased in response to metabolic stress, coinciding with enrichment of SIRT1 responsive genes involved in metabolic pathways (Ma et al., 2014).

Although knockdown of *Sirt1* did not affect proliferation of neural progenitors in SVZ and hippocampal neurospheres (Saharan et al., 2013), both *Sirt1* KO and Nestin-Cre *Sirt1*$^{-/-}$ mice did show an increase in the numbers of both $Sox2^{+}$ NSCs and DCX^{+} neurons in the hippocampus (Ma et al., 2014). The absence of increase in proliferation in *Sirt1*$^{-/-}$ neurospheres could indicate a developmental defect following a *Sirt1* deletion. However, a tamoxifen-induced *Sirt1* deletion at one month after birth resulted in increased proliferation as well (Ma et al., 2014). Whereas SIRT1 overexpression suppressed proliferation of NSCs and directed their differentiation towards the astroglial lineage at the expense of the neuronal lineage, inhibition or loss of SIRT1 increased proliferation of NSCs and promoted neuronal fate decisions (Saharan et al., 2013). Similarly, repression of *Sirt1* was found to promote differentiation of mouse iPSCs into NSCs (Hu et al., 2014). Interestingly, this stands in contrast with the differentiation into neuronal lineages promoted by CLOCK:BMAL1 activity. As such, a combination of SIRT1-directed gliogenesis and a CLOCK:BMAL1-directed neurogenesis may maintain a balance between astrocytic and neural progenitors in the adult brain.

Together, these studies demonstrate that SIRT1 could act as gatekeeper to neural stem cells by mediating responses to metabolic stress. Interestingly, conditions that are known to affect hippocampal neurogenesis, such as caloric restriction and exercise, also affect metabolic stress (Knobloch and Jessberger, 2017). Since SIRT1 appears to be a key mediator between circadian rhythms and metabolism on the one hand and a regulator of neural stem cell fates on the other, it is conceivable that SIRT1 controls CLOCK in neural stem cells in order to regulate neurogenesis. Supporting this, adult *Bmal1*$^{-/-}$ mice showed increase SIRT1 immunoreactivity in the dentate gyrus as well as an upregulation of genes responding to oxidative stress *Prxdx1* and *Mt* (Ali et al., 2015). A direct relationship between SIRT1 and circadian function in neural stem cells, however, has yet to be established.

Importantly, both HES1 and FOXO transcription factors are directly modulated by SIRT1 and known for their key roles in adult neural stem cell homeostasis and energy metabolism (Fusco et al., 2016; Ro et al., 2013; Rafalski and Brunet, 2011). HES1, a downstream target of Notch signaling, directly represses the expression of proneural genes, such as Mash1 and Neurog2 (Imayoshi and Kageyama, 2014). SIRT1, importantly, binds to the *Hes1* promoter to represses *Hes1* expression in NPCs (Fusco et al., 2006; Hisahara et al., 2008) and was also found to associate with HES1 to modulate its transcriptional repression (Takata & Ishikawa, 2003). Using a γ-secretase inhibitor, Ma and colleagues (2014) demonstrated that the increase of NSC proliferation caused by a *Sirt1* deletion was largely abrogated when Notch signaling was inhibited (Ma et al., 2014). Conversely, inhibition of Notch signaling only increased the percentage of Tuj1^{+} neurons in neurospheres derived from wild-type mice but not when the neural progenitors were derived from *Sirt1* KO mice.

4.3 A possible SIRT1-FOXO axis in circadian rhythms and neural stem cell maintenance

SIRT1 is known to directly regulate the activity of FOXO transcription factors (van der Horst et al., 2004; Giannakou and Partridge, 2004; Brunet et al., 2004). For instance, SIRT1 was found to deacetylate FOXO3 in response to oxidative stress, resulting in increased cell cycle arrest (Brunet et al., 2004). Similarly, increased FOXO3 activity could restore maintenance of hematopoietic stem cells in the absence of SIRT1 (Matsui et al., 2012). This is in agreement with the prevailing notion that FOXO transcription factors are, arguably similar to SIRT1, sensors and regulators of redox signaling in order to control cell survival (Keizer et al.,, 2011; Rafalski and Brunet, 2011). Like SIRT1, FOXOs are also closely involved in aging and lifespan, and both link metabolism, oxidative stress and the circadian clock (Zheng et al., 2007; Chaves et al., 2014).

Direct SIRT1-FOXO interactions, however, have been scarcely studied in adult neurogenesis. In neuroblastoma cells, SIRT1 was found to induce neuronal differentiation via deacetylation of FOXO3a whereas SIRT1 activated FOXO3-

dependent transcription in the nucleus accumbens (Kim et al., 2009; Ferguson et al., 2015). Since FOXO3 has been recently found to regulate *Clock* transcription under the influence of insulin, such an interaction would be of special interest (Chaves et al., 2014). Conceivably, this could indicate the existence of an additional feedback loop in SIRT1's modulation of the circadian clock. If so, SIRT1 could regulate *Nampt* expression and hence its own activity in a two-fold way. Next to directly deacetylating CLOCK:BMAL1 complexes, SIRT1 might also regulate *Clock* expression by deacetylating FOXO3. Acetylated FOXO3 may then activate *Nampt* transcription resulting in an increase of Clock-mediated *Nampt* expression.

This is important as it suggests a model in which a SIRT1-FOXO axis is paramount to keeping neural stem cell maintenance in tune with circadian rhythms. In this model, FoxOs regulate neural stem cells by converging both circadian SIRT1 activity and metabolic signals via insulin signaling, possibly reflecting the interplay between peripheral oscillators and metabolic zeitgebers. Since SIRT1 activates FOXO3 and insulin inhibits FOXO3 activity, such a mechanism could alternatingly drive neural stem cells towards dividing or holding brakes on the cell cycle.

5. Circadian rhythms in the aging neural stem cell population

5.1. Circadian rhythms and aging

Circadian rhythms in physiology, endocrinology, behavior and metabolism are all subject to age-related changes (Hood and Amir, 2017b). In the aging brain, this is best reflected by attenuated circadian rhythms in both core clock gene expression and neuronal activity in the SCN, the master timekeeper (Nakamura et al., 2011). However, the age-related decline and altered rhythmicity in clock gene expression have also been found in the aging hippocampal neurogenic niche (Wyse and Coogan, 2010; Duncan et al., 2013). Perhaps altered clock gene expression in aging NSCs may impair their function.

Although circadian output generally shows an age-related decline, a set of stress-responsive genes was recently found to adopt *de novo* robust rhythmic expression in old flies (Kuintzle et al., 2017). Constant exposure to oxidative stress could induce rhythmicity of these genes in young flies as well, which suggests that these so-called 'late-life cyclers' could protect against oxidative damage (Kuintzle et al., 2017). This phenomenon appears to be conserved, as a post-mortem study on human prefrontal cortex also reported an age-related gain of rhythmicity in a number of genes (Chen et al., 2016).

This is reminiscent of two recent reports showing that rhythmic gene expression is reprogrammed to adapt to stress in, respectively, the liver and aging epidermal and muscle stem cells (Sato et al., 2017; Solanas et al., 2017). Importantly, caloric restriction, known to promote longevity, was found to restore the effects of aging on circadian function in all cell types. In other words, there may be a vital connection between aging, stress, circadian rhythms and metabolism (Orozco-Solis and Sassone-Corsi, 2014). Interestingly, *Bmal1* KO mice show a reduced lifespan, cognitive defects and tissue atrophy as well as an accumulation of ROS in various tissues, including the brain (Kondratov et al., 2006; Kondratova et al., 2010; Musiek et al., 2013). As such, BMAL1 is thought to have an important role in regulating neuronal redox homeostasis (Kondratov et al., 2006; Musiek et al., 2013). Whether the circadian clock has a similar function in neural stem cells needs yet to be confirmed. Since neural stem cell fates are modulated by reactive oxygen species (Le Belle et al., 2011; Vieira et al., 2011), this may be a mechanism for the circadian clock to regulate neural stem cell maintenance.

5.2. Age-related decline of adult neurogenesis

Neurogenesis persists through adulthood but shows a clear age-related decline in both the SVZ of the lateral ventricle (Maslov et al., 2004; Ahlenius et al., 2009) and the dentate gyrus of the hippocampus (Kuhn et al., 1996; Walter et al., 2011). Therefore, aging is considered to be one of the strongest negative regulators of adult NSC proliferation (Artegiani and Calegari, 2012).

The mechanism responsible for this continuous decline, however, remains controversial. Whereas the reduction in neurogenesis may reflect increased quiescence of NSCs during aging (Enwere et al., 2004; Lugert et al., 2010; Capilla-Gonzalez et al., 2014; Giachino et al., 2014; Leeman et al., 2018), others have argued that activated NSCs are lost following limited rounds of cell division, resulting in their depletion over time (Encinas et al., 2011; Bonaguidi et al., 2011; Calzolari et al., 2015; Obernier et al., 2018; Pilz et al., 2018). A recent study, for instance, found that defects in lysosomes impaired activation of aged qNSCs (Leeman et al., 2018) whereas recent lineage tracing studies observed the loss of activated NSCs as they were consumed by a limited number of cell divisions giving rise to progeny (Obernier et al., 2018; Pilz et al., 2018).

Surprisingly, one of these groups only observed symmetric cell divisions of adult V-SVZ NSCs (Obernier et al., 2018). This stands in contrast with the asymmetric cell divisions that have previously been reported for hippocampal NSCs (Encinas et al., 2011; Bonaguidi et al., 2011; Calzolari et al., 2015) and recently by Pilz et al. (2018), who report an irreversible switch from proliferative symmetric cell divisions to neurogenic asymmetric divisions in the adult hippocampus. Therefore, it is tempting to attribute these different observations to differences between the V-SVZ and DG niches. Perhaps signals originating from the cerebrospinal fluid or niche signals from the V-SVZ microenvironment and vasculature tend to promote symmetric cell divisions in subventricular NSCs. Moreover, activated NSCs have been thought to terminally differentiate into astrocytes (Encinas et al., 2011; Bonaguidi et al., 2011) but Pilz et al. (2018) only observed terminal differentiation of NSCs into neurons, not in astrocytes.

Another outstanding question is whether activated NSCs are able to return to quiescence (Bonaguidi et al., 2011; Urban et al., 2016; Obernier et al., 2018) or rapidly continue to divide after their activation (Encinas et al., 2011; Pilz et al., 2018). Therefore, interesting studies can be expected in the near future to reject or reconcile these hypotheses. Importantly, stem cell heterogeneity likely accounts for many of these differences as different neural precursors have self-renewal and differentiation properties and are differentially regulated (Bonaguidi et al., 2012; DeCarolis et al., 2013; Chaker et al., 2016). Nevertheless, the age-related decline in neurogenesis has been accepted and could contribute to an age-related decline in cognitive function (Gonçalves et al., 2016), although the presence of adult neurogenesis in humans has recently been contested (Sorrels et al., 2018). Circadian rhythms, therefore, could be important to prevent a premature drop in neurogenesis and, conversely, a disruption of the circadian clock may result in excessive activation leading towards neural stem cell exhaustion.

5.3. SIRT1 bridges the circadian clock in the aging brain

In the aging brain, including the hippocampus, both SIRT1 levels and activity decrease, as well as NAMPT and NAD^+ levels (Quintas et al., 2012; Chang and Guarente, 2013; Stein and Imai, 2014). For instance, loss of *Nampt* reduced neural progenitor proliferation in the SGZ whereas an increase of hippocampal NAD^+ levels could rescue the age-related decrease of neural progenitors in the SGZ (Stein and Imai, 2014).

Remarkably, young mice with a brain-specific deletion of *Sirt1* showed reduced levels of BMAL1 and PER2 in the SCN, similar to the levels observed in old mice (Chang and Guarente, 2013). This was also true for the fragmented circadian activity, longer circadian period and the inability to adapt to changes in the light schedule observed in both old wild-type and young *Sirt1* knockout mice. Conversely, overexpression of SIRT1 prevented these aging effects in young mice and reduced the severity in old mice. Similarly, a recent study demonstrated that mice lacking *Sirt1* have a shorter lifespan with increased levels of cellular senescence and DNA damage in the brain (Wang et al., 2016). Importantly, these *Sirt1* knockouts exhibited increased H4K16 acetylation of the *Per2* promoter resulting in overexpression of *Per2*. Per2, however, was found to negatively regulate *Sirt1* expression by inhibiting CLOCK:BMAL1 binding. During aging, interestingly, acetylation of the *Per2* promoter increased while *Sirt1* expression decreased (Wang et al., 2016). Together, these results fits the hypothesis of SIRT1 as an important link between the circadian clock and aging (Orozco-Solis and Sassone-Corsi, 2014). As such, it would be interesting to examine the effects of declining NAD^+ levels and SIRT1 activity on the circadian clock in aged neural stem cells.

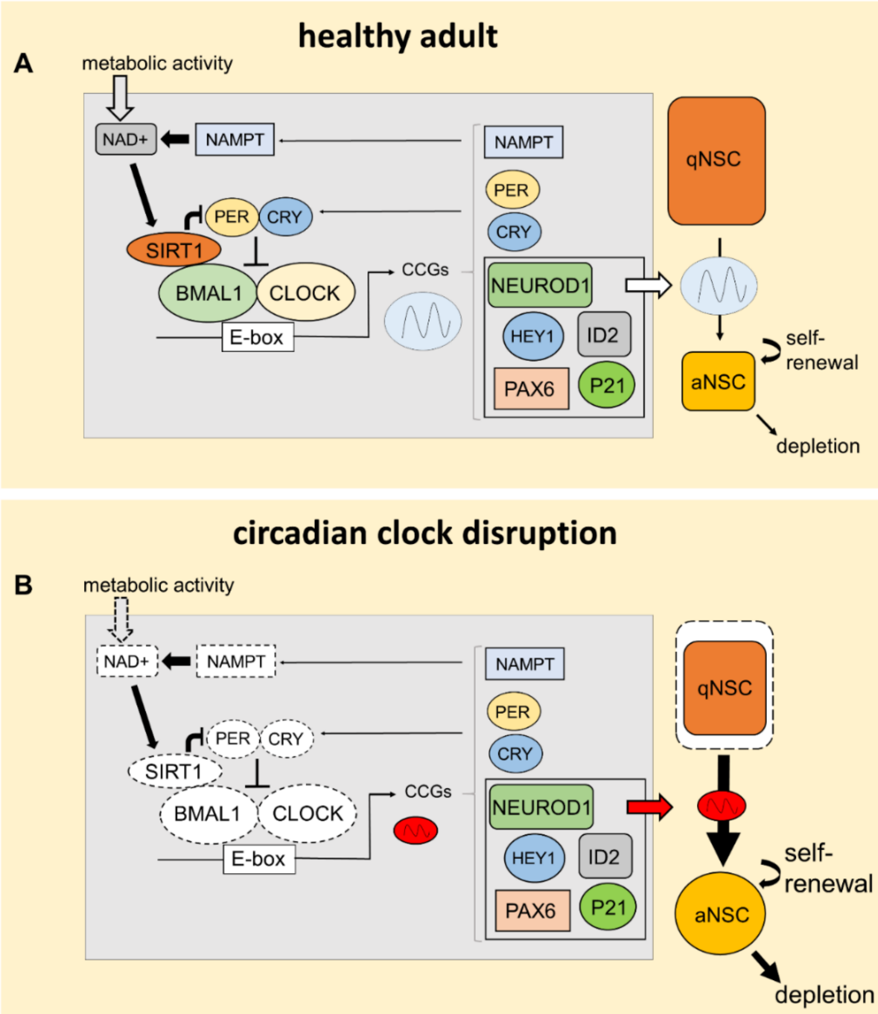

Figure 2. Circadian clock controls neural stem cell maintenance.
(A) Dormant quiescent neural stem cells (qNSCs) gradually enter the cell cycle in a circadian fashion. These activated neural stem cells (aNSCs) are able to self-renew but eventually leave the cell cycle and terminally differentiate. By limiting cell cycle entry and exit of qNSCs, the circadian clock minimises exhaustion of the neural stem cell population. The core circadian transcription factors BMAL1 and CLOCK regulate transcription of clock-controlled genes (CCGs) through binding of E-box elements within their promoters. Following the activation of the *Per* and *Cry*, PER and CRY proteins translocate to the nucleus as heterodimers and repress CLOCK:BMAL1 transcriptional activity. Among the CCGs, multiple transcriptional regulators including the *Neurod1*, *Hey1*, *Id2* and *Pax6* genes are activated as well as expression of *Cdkn1a*, the gene encoding for cell cycle regulator $p21^{cip1/waf1}$ (p21). Together, these regulators are involved in the cell cycle entry/exit and differentiation of neural stem cells. We propose that NAD^+-dependent deacetylase SIRT1 is important for circadian control of qNSC activation by promoting CLOCK:BMAL1 transcriptional activity.

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6. Conclusions and future directions

Adult NSCs continue to give rise to new neurons, oligodendrocytes and astrocytes throughout life. This is important for memory formation, mood regulation and regeneration following injury. To this end, the NSC population is relatively quiescent and needs active maintenance to prevent exhaustion. A variety of factors is involved in maintaining the NSC population, many of which are associated with energy metabolism and oxidative stress (Rafalski and Brunet, 2011; Knobloch and Jessberger, 2017). As such, the importance of the circadian clock in adult NSC biology has clearly emerged in recent years. By controlling proliferation and differentiation of NSCs in response to metabolic demands, the circadian clock could shape NSC cell fate decisions.

The circadian clock could temporally restrict activation of NSCs to maintain tissue homeostasis in the adult brain but minimizing depletion of the population. For instance, the circadian clock has also been found to regulate dendritic spine formation and adult neurogenesis via oscillations in glucocorticoids (Liston et al., 2013; Fitzsimons et al., 2016). Circadian regulation of adult hippocampal neurogenesis and synaptic plasticity could complement each other to allow a more efficient integration of new neurons into the adult brain (Janich et al., 2014). More than providing stem cells with a means to anticipate DNA damage and timed cell divisions, the circadian clock may be important to create heterogeneity within a stem cell population (Janich et al., 2011, 2013). Although this role has yet to be confirmed for other stem cells, such a mechanism may very well be relevant to NSC biology as there is

Figure legend continued from previous page.

SIRT1 is activated by a high [NAD^+] to [NADH] ratio, when energy availability is low, and induces CCG expression by associating with CLOCK:BMAL1 in a chromatin complex while promoting protein degradation of repressor PER2. The circadian clock controls cyclic synthesis of NAD^+, the coenzyme critical for SIRT1's deacetylase activity, by regulating expression of the gene encoding for the enzyme NAMPT, which is the rate-limiting step in the NAD^+ salvage pathway. As such, SIRT1 deacetylase activity promotes CLOCK:BMAL1 transcriptional activity and vice versa. Together, these mechanisms underlie a circadian clock that allows neural stem cells to make cell fate decisions based on energy availability.
(**B**) Disruption of the circadian clock may impair circadian control of adult neural stem cell maintenance. Pathologically altered circadian rhythmicity or metabolic demands that impact the circadian clock via NAD^+, Nampt and SIRT1 activity can disrupt clock-regulated transcription. We propose that this leads to a weakened circadian clock that can no longer control NSCs, resulting in excessive activation of qNSCs and, possibly, increased self-renewal of aNSCs. Whereas this causes an initial increase in neurogenesis, the exhaustion of the NSC population ultimately leads towards a premature decline in neurogenesis.

emerging evidence for a functionally heterogeneous NSC population (Alvarez-Buylla et al., 2008; Mich et al., 2014; Codega et al., 2014; Chaker et al., 2016; Dulken et al., 2017). Possibly circadian heterogeneity helps to create neural stem cell heterogeneity.

We hypothesize that the circadian control of neural stem cells is such that CLOCK:BMAL1 transcriptional activity maintains these cells in a quiescent state and that SIRT1 controls CLOCK:BMAL1 (**Figure 2**). Since SIRT1 activity depends on the availability of NAD^+ (Imai and Guarente, 2014), such a mechanism allows neural stem cells to make fate decisions by integrating signals of metabolism and oxidative stress with endogenous circadian rhythms. As such, neural stem cells are able to respond to external signals to maintain tissue homeostasis in the adult brain. Disruption of the circadian clock, however, can result in a weakened circadian clock that can no longer prevent loss of neural stem cell quiescence. The resulting excessive activation likely results in an initial increase in neurogenesis but would ultimately lead towards exhaustion of the neural stem cell population (**Figure 2**). As such, altered metabolic demands and circadian dysfunction may impair adult neurogenesis. Importantly, circadian disruptions following jet lag or shift work arise from a misalignment between metabolism and circadian rhythms (Schibler et al., 2003; Gachon et al., 2004; Damiola et al., 2000). As such, the proposed model may help to explain effects of jet lag, shift work or disease on neural stem cell function.

Importantly, aged neural stem cells show reduced NAD^+ levels, lowered SIRT1 activity as well as decreased *Nampt* expression (Quintas et al., 2012; Chang and Guarente, 2013; Stein and Imai, 2014). Perhaps this contributes to the decline in clock gene expression and rhythmicity in the aged dentate gyrus (Wyse and Coogan, 2010; Duncan et al., 2013). As such, it is tempting to speculate that this mechanism may impair neural stem cell function in the aging brain. Whereas an age-related decline in SIRT1 activity would enhance activation of qNSCs in our model, it is conceivable that other changes in aged qNSCs impairing the ability for activation, such as reduced EGFR expression (Enwere et al., 2014) or lysosomal defects (Leeman et al., 2018), could negate this effect.

Conflicts of interest

The authors declare no conflict of financial or commercial interest.

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