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INVITED REVIEW

Daily light and darkness onset and circadian rhythms metabolically synchronize hematopoietic stem cell differentiation and maintenance: The role of bone marrow norepinephrine, tumor necrosis factor, and melatonin cycles

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Hematopoietic stem and progenitor cells (HSPCs) are essential for daily mature blood cell production, host immunity, and osteoclast-mediated bone turnover. The timing at which stem cells give rise to mature blood and immune cells while maintaining the bone marrow (BM) reservoir of undifferentiated HSPCs and how these opposite tasks are synchronized are poorly understood. Previous studies revealed that daily light onset activates norepinephrine (NE)-induced BM CXCL12 downregulation, followed by CXCR4$^+$ HSPC release to the circulation. Recently, we reported that daily light onset induces transient elevations of BM NE and tumor necrosis factor (TNF), which metabolically program BM HSPC differentiation and recruitment to replenish the blood. In contrast, darkness onset induces lower elevations of BM NE and TNF, activating melatonin production, which metabolically reprograms HSPCs, increasing their short- and long-term repopulation potential, and BM maintenance. How the functions of BM-retained HSPCs are influenced by daily light and darkness cycles and their clinical potential are further discussed.

Hematopoietic stem and progenitor cells (HSPCs) dynamically replenish the blood with new mature blood and immune cells with a finite life span, while maintaining and renewing the undifferentiated HSPC bone marrow (BM) reservoir. Long-term repopulating hematopoietic stem cells (LT-HSCs) are identified and characterized in preclinical experimental transplantation assays, based on their functional ability to home and to durably repopulate the BM and blood with high levels of both myeloid and lymphoid cells. Short-term repopulating HSPCs are metabolically active with high levels of reactive oxygen species (ROS^{high}), giving rise to myeloid-biased differentiation and repopulation, while LT-HSCs are mostly retained in the BM in a nonmotile, quiescent, low-reactive-oxygen-species (ROS^{low}) metabolic state [1,2]. These low metabolic features are induced by adhesion interactions with niche-supporting CXCL12$^+$ BM stromal cells, which metabolically protect quiescent, CXCR4$^+$/EPCR$^+$, reserved LT-HSCs from DNA-damaging agents including radiation and chemotherapy insult, which preferentially kill cycling cells [1,3–6]. Chemotherapy-resistant CD73-expressing BM mesenchymal stem cells (MSCs) are spatially located at the endosteum and bone fraction, being pivotal for BM engraftment and hematopoietic recovery [7]. In line, chemotherapy-resistant LT-HSCs (reserved) are mainly maintained in the endosteum [6]. The chemotherapy resistance of BM LT-HSCs involves excess ROS transfer from chemotherapy-activated hematopoietic stem cells to their niche-supporting BM stromal cells [8]. Our preliminary results suggest that this ROS transfer is actually due to mitochondria transfer [9]. Several

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studies revealed that BM-retained primitive LT-HSCs are dormant, hibernating, quiescent stem cells, which rarely engage in cell cycle and make only minor contributions to hematopoiesis during steady-state homeostasis [10−14]. In contrast, other studies have found that some LT-HSCs also actively participate in steady-state hematopoiesis and durably contribute to multilineage cell production [15−17]. Future studies will resolve this controversy and will reveal how and when LT-HSCs play an active role in replenishing the circulation. The most primitive BM-retained LT-HSCs play a major role in durable long-term repopulation following BM transplantation. These primitive, quiescent HSCs are rapidly activated during alarm situations caused by infections, injury, bleeding, and DNA damage, to prevent lethal hematology and immune failure. We therefore hypothesize that their need to be immediately and ongoing ready for activation on demand during alarm situations requires their daily dynamic metabolic "exercise and training" circadian rhythms. These are induced by light and darkness onset also independently of cell division.

BM-retained, quiescent HSCs are maintained undifferentiated until they are activated by local signals originating from the stem cell niche microenvironment and by bone-degrading osteoclast activity [18]. Other cues activating HSCs are peripheral signals originating from the nervous, immune, and hemostatic systems [19−21]. Leukocyte trafficking and BM HSPC maintenance are also regulated by distinct BM blood vessel types, with the less permeable arterioles and capillaries, maintaining primitive HSPCs in an ROS^{low} state, whereas the more permeable sinusoids predominantly promote ROS^{high} HSPC activation and trafficking [22,23]. In line, BM imaging showed that quiescent HSCs preferentially localize near endosteal arterioles [24].

Bone cavities are formed by osteoclast-mediated bone turnover and are another component of the HSC niche microenvironment. Osteoclast activity also promotes HSPC mobilization, and osteopetrotic mice lacking bone cavities because of defective osteoclasts are not protected from chemotherapy insult. As a result, these mice rapidly die following chemotherapy treatment, which kills cycling cells [18,25]. Peripheral signals leading to neurotransmitter secretion in the BM regulate mature leukocytes as well as immature HSPCs. Inhibition of the sympathetic nervous system (SNS) resulted in increased myelopoiesis and reduced lymphopoiesis following BM transplantation [26]. Norepinephrine, the sympathetic neurotransmitter, rescued hematopoiesis and mouse survival following chemotherapy and irradiation [27]. In addition, both human and murine HSPCs functionally express dopamine and B2 adrenergic receptors with higher levels of expression in the more primitive human $CD34^+/CD38^-$ stem cells [28]. Adrenergic signals regulate human and murine HSPC retention, egress, and mobilization via direct and indirect effects through the BM microenvironment [19,28−30]. Nonmyelinating Schwann cells are hematopoietic niche glial cells ensheathed by autonomic nerves, which induce HSC quiescence via transforming growth factor (TGF)-β activation and signaling [31]. Interestingly these stem cell niche nerve cells are also shielded from the ROS^{high} circulating blood cells and are located near bone and the less permeable BM blood vessels, most probably because of their ROS sensitivity [22]. Osteoclast activity involves TGF-β activation via its release from the degraded bone, which in turn recruits Sca-1^+ bone-forming osteoblast precursors to the bone remodeling cite [32]. Human bone metabolism, including bone remodeling, is regulated by the SNS, thus affecting HSPC maintenance, trafficking, and blood replenishment [33,34]. The dynamic and complex interplay between the hemostatic, immune and nervous systems, bone remodeling (osteoblasts and osteoclasts), and the BM microenvironment regulate both blood and immune cell production as well as bone turnover [19,21,35,36].

An important and essential regulator of the body is melatonin, the darkness hormone. Melatonin is produced in the pineal gland during darkness and is evolutionarily conserved and found in almost all living organisms [37]. Its pineal synthesis is timed by the suprachiasmatic nucleus (SCN) via nocturnal sympathetic input via noradrenaline and ATP activation of β2 adrenoceptors and P2Y1 purinergic receptors, respectively. The production of the darkness hormone is negatively regulated by the pro-inflammatory cytokines and pathogen-associated molecular patterns via NF-κB in pinealocytes, and positively regulated in monocytes/macrophages and dendritic cells [38−40]. Melatonin regulates circadian rhythms, body temperature cycles, and immune responses, and is involved in different pathological disorders including cancer and cardiovascular diseases [41,42]. Interestingly, extra-pineal production of melatonin has been reported for different cells including myeloid cells [43]. In the human and murine BM, there is also local production of melatonin by bone-forming stromal precursors, and preconditioning of mesenchymal cells with melatonin increases their survival and therapeutic efficiency [44-46]. The facts that melatonin can be locally secreted in the BM and melatonin receptors are expressed on leukocytes as well as on BM stromal cells suggest that melatonin may play a role in BM stem cell regulation. As both the SNS and melatonin undergo daily regulation by light and darkness, and BM $CXCR4^+$ HSPC release and their niche supporting chemokine CXCL12 also undergo circadian rhythms [47,48], we investigated the potential role of all these factors in the physiological daily regulation of BM HSPC function and maintenance.

This review, overviews recent advances in the light of previous insights, to provide an updated and current understanding of how daily light and darkness onset and circadian rhythms regulate BM HSC differentiation and maintenance.

Light and darkness onset regulates BM HSPCs

Physiological and biological functions of all mammals are regulated by the changing surrounding environmental cues, and in particular daily light and darkness cycles, which are defined as circadian rhythms. Adjustment to light/dark cycles is governed by the brain pacemaker, the SCN, which daily synchronizes peripheral organs via the autonomous nervous system [19]. One of the peripheral organs regulated by light/darkness cues is the BM, the major origin of adult hematopoiesis. Hematopoiesis and host immunity follow daily rhythms in cell proliferation and function including BM production of blood cells and various leukocytes, which were all augmented during daytime both in humans and in mice [49–55]. Mature neutrophil turnover in mice is also regulated by circadian rhythms [56,57]. Homeostatic leukocyte recruitment to different organs exhibits circadian oscillations orchestrated by adrenergic nerves [58], and variations in transplanted BM cell engraftment potential were observed upon changes in time of transplantation [59,60].

Not only the BM compartment undergoes circadian variations but also the profile of circulating blood cells. Circulating human myeloid progenitor cells, polymorphonuclear (PMN) leukocytes, and endothelial progenitors demonstrate diurnal variations, with higher levels during the day [61–64]. Interestingly, daily HSPC release and the yield of G-CSF mobilized PBL follow circadian rhythms [47,48]. The highest levels of mouse and human circulating HSPC are found in the resting phase, morning for mice and night for humans [48,65].

Recently, by applying functional, preclinical murine stem cell models, we revealed that light onset and darkness onset differentially regulate BM HSPC differentiation and blood replenishment, while maintaining the BM reservoir of undifferentiated LT-HSCs. We identified two daily peaks in the levels of BM HSPCs, one 5 hours following light initiation and the other, 5 hours following darkness onset. Deeper investigations revealed that the morning peak involves differentiation, migration, increased vascular permeability, egress, and blood replenishment. The night peak involves decreased BM vascular permeability and renewal of the BM LT-HSC reservoir. The levels and BM repopulation potential of HSPC are elevated during the night (Figure 1). Overall, the two major HSPC peaks are phenotypically and functionally different [66]. The fluctuations observed in BM HSPC repopulation potential, including short-term and long-term repopulating HSCs, between day and night cannot be explained solely by increased proliferation. Our data suggest that BM HSPCs are metabolically primed by light and darkness cues that dynamically change their phenotype and function, as reflected by dynamic changes in cell surface receptor expression, for example, increased surface expression of the LT-HSC SLAM marker CD150 and reduced expression of c-Kit at night [66]. In line, previous reports showed reduced c-Kit expression by LT-HSCs, while HSCs with higher c-Kit expression display more limited expansion capacities and have impaired self-renewal and major reductions in their repopulation potential [67,68].

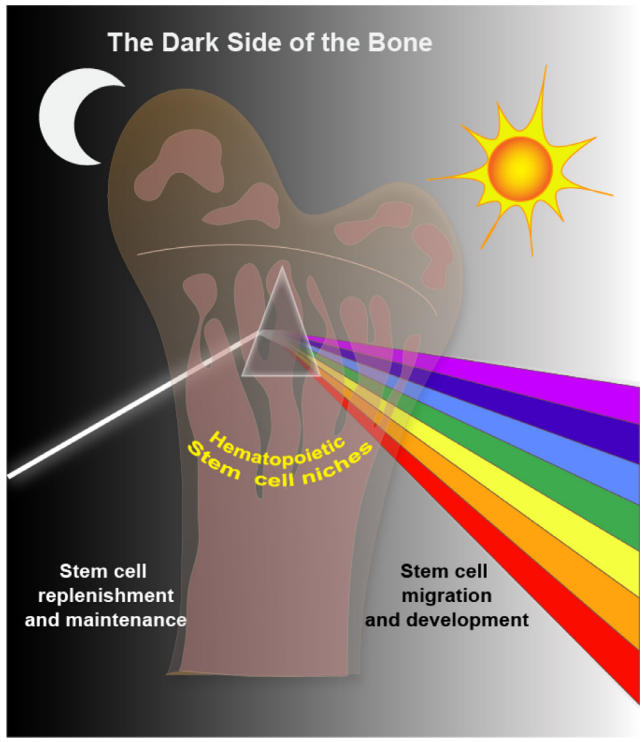

Figure 1. The dark side of the bone (the title and picture of the figure pay homage to the Pink Floyd album *The Dark Side of the Moon*). A model illustrating the role of BM hematopoietic stem cell niches as a prism. Light-onset signals program HSPCs for differentiation and migration, leading to maturing and mature leukocyte egress for blood and immune cell replenishment. Darkness-onset signals and melatonin induce renewal of the BM LT-HSC reservoir reprogramming HSPCs with a low metabolic state and enhanced stem cell surface profile endowed with high short and long-term repopulation potential.

Circadian rhythms regulate not only the hematopoietic and immune systems but also the bone and BM microenvironment of stromal cells. Bone remodeling mediated by osteoclasts and osteoblasts is essential for bone maintenance and for balanced mature blood and immune cell production throughout adult life. New bone formation also occurs in a diurnal manner in mice, with the greatest remodeling occurring 1 hour following light initiation [69], a process known to be enhanced by inflammation [70]. Mice with disturbed clock gene expression in osteoblasts display differences in their bone mass [64,71]. Moreover, sleep and circadian rhythms also influence osteogenic and adipogenic differentiation of stromal precursor cells [72]. Altogether, these results suggest that bone turnover synchronizes new bone formation with blood replenishment and renewal of host immunity while maintaining the BM blood and bone-forming stem cell reservoirs.

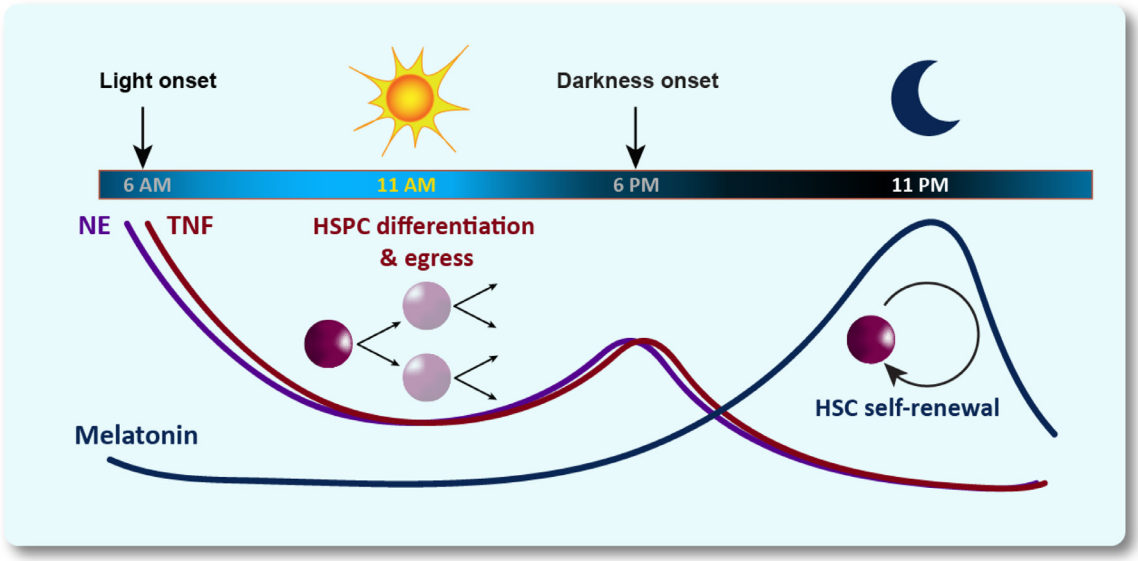

Figure 2. Daily onsets of light and darkness differentially control hematopoietic stem cell differentiation and maintenance. Adjusted from the review by Paatela et al. [119]. Light onset triggers a high rise in BM NE and TNF levels, which metabolically program HSPC migration and development to replenish the blood with new mature cells with a finite life span. Darkness-induced BM melatonin metabolically reprograms HSPC self-renewal, increasing their BM homing and both short- and long-term repopulation potential.

The molecular mechanism synchronizing light and darkness regulation of BM HSPCs

Metabolic HSPC regulation by daily light and darkness onset operates via different molecular pathways comprising many factors that are all tightly synchronized to induce a very precise outcome. Studies indicate that clock gene oscillation in peripheral blood cells and in bone remodeling cells both in humans and in mice [64,71,73–76] can be attributed to the daily variations in BM function. However, not all the oscillations in BM activity can be attributed to clock genes. The SCN via light signals was found to regulate also the SNS, where diurnal patterns of epinephrine (EPI) and norepinephrine (NE) levels in the blood and urine were reported [19]. Activation of SNS-mediated β-adrenergic signaling following light induction leads to degradation of the transcription factor Sp1 in stromal cells, which, in turn, reduces the expression of CXCL12 in the BM during the morning peak and induces release of $CXCR4^+$ HSPCs [19,47]. The chemokine CXCL12 and its major receptor CXCR4 are implicated in regulation of HSPC survival, homing, retention, development, and recruitment to the circulation [35]. In vivo NE treatment rapidly induces secretion of CXCL12 from the BM to the blood accompanied by rapid CXCR4-mediated HSPC mobilization [30]. Dynamic HSPC CXCR4 expression levels were reported to be regulated by the circadian clock in a pattern synchronized with its ligand, CXCL12 [48].

Interestingly, we identified two daily bursts in BM NE and tumor necrosis factor (TNF) levels induced by light and darkness onset. The first burst is higher and appears 1 hour following light initiation, accompanied by a transient elevation in BM HSPC reactive oxygen species (ROS) levels. The second burst takes place 1 hour after light termination, is more moderate, and is accompanied by a moderate increase in HSPC ROS levels. Inhibition of TNF or NE abolished HSPC ROS elevation and the morning BM HSPC peak and blood replenishment (Figure 2). We identified a regulatory cross-talk between NE and TNF. BM NE bursts were essential for the TNF bursts, and mice lacking TNF had abnormally high levels of BM NE and did not mobilize following NE injection. Light/dark induction elevated BM NE, which acts directly on BM leukocytes (most probably myeloid cells) to increase TNF levels via tumor necrosis factor-a–converting enzyme (TACE)-mediated membrane-bound TNF cleavage [66]. Consistent with our observations, circulating levels of hematopoietic growth factors including TNF display circadian oscillations [77]. Augmentation of BM TNF levels decodes the information of environmental light transition on or off, which may serve as a transient, moderate physiological stress, activating BM HSPCs for the rapid responses required for blood replenishment and HSPC maintenance. LT-HSCs are regulated by pro-inflammatory cytokines such as TNF [20,78] and functionally express its receptors [79]. Nevertheless, regulation of HSCs by TNF has been controversial over the years, with studies showing TNF suppresses HSC functions and others showing HSC support and activation [80–82]. A recent study revealed that TNF

has diverse and selective effects with respect to myeloid progenitor cells compared with primitive HSCs. While TNF induces apoptosis of myeloid progenitor cells, it promotes primitive HSC survival and their myeloid differentiation by activating the p65-nuclear factor pathway [83]. Moreover, TNF-mediated activation of NF-κB signaling increased surface CXCR4 expression by human HSPCs, enhancing their homing and engraftment [84]. Our data revealed high BM HSPC activation of the p65 and RelB pathways following light onset-induced morning TNF burst, preceding the time of HSPC differentiation and blood replenishment [66]. Another signaling cascade downstream of TNF, caspase-8, was shown to support HSPC function and differentiation of the myelomonocytic lineage; thus, caspase-8 signaling also has anti-apoptotic roles in BM HSPCs [85].

Both light- and darkness-induced NE and TNF bursts lead to transient elevated BM HSPC ROS levels. Augmented light-induced BM HSPC ROS levels facilitate proliferation, differentiation, increased BM endothelial permeability, and recruitment during the morning peak, replenishing the blood with new immature and mature blood and immune cells with a finite life span. While at night HSPC ROS elevation is more moderate, there is need for other factors to reduce it to prevent HSPC differentiation and recruitment and to facilitate BM HSPC maintenance and retention, including LT-HSC, and to replenish the stem cell pool.

We found that the night peak 5 hours post-darkness onset is driven predominantly by elevation of BM melatonin, which facilitates retention signals by both direct and indirect mechanisms. BM HSPCs functionally express MT1 and MT2 melatonin receptors, and its high levels at the time of the BM HSPC night peak diminish their ROS levels as well as their recruitment to the blood both directly and indirectly by reducing BM endothelial permeability [66]. BM melatonin also increases rare COX-2$^+$ monocyte/macrophage populations in the BM, which support HSPC BM maintenance and reduce their ROS levels by PGE2 secretion [66,86]. Retention signals may also be facilitated by melatonin by promoting osteoblast differentiation and new bone formation [87–89]. Melatonin protected circulating human HSPCs from chemotherapy insult via ROS downregulation [42] and human BM stromal cells from toxicity [90]. Murine LT-HSC levels during the night peak were elevated by melatonin, leading to increased CD150 expression, reduced c-Kit expression, and higher short- and long-term, competitive repopulation potential [66].

As mice are nocturnal and humans are active during the day, release of mature human leukocytes from the BM of immune deficient chimeric mice occurred at a different time compared with mouse leukocyte release, because of interspecies differences in ROS and CXCR4 regulation [91,92]. Importantly, melatonin injection in the morning to immune deficient chimeric mice pre-engrafted with human stem and progenitor cells induced elevation of human LT-HSC surface markers similar to mouse HSPCs. Thus, human stem cell regulation by melatonin and its secretion by BM stromal cells and by myeloid cells suggest that melatonin similarly regulates human and mouse BM HSPCs [44,66,86].

The peak of BM melatonin levels at night was threefold higher than that in plasma, most probably because of local melatonin production in the BM and the selective blood–BM endothelial barrier [22]. Melatonin levels were not elevated at night in mice treated with a TNF inhibitor, suggesting that the darkness-onset TNF burst induces melatonin production in the BM. Hence, melatonin-mediated anti-inflammatory activities are important for the balanced daily regulation of LT-HSC and blood/immune cell production; however, melatonin plays a crucial role during inflammation as well. Melatonin exerts its anti-inflammatory effects by blocking NF-kB activation, which is essential for antagonizing TNF- and LPS-induced pro-inflammatory responses [93,94]. Human BM mesenchymal stem cells (MSCs), which are part of the HSC niche, are protected by melatonin from H_2O_2 toxicity, therefore increasing cell viability and reducing TNF secretion and ROS production [90]. Our study demonstrates that a tightly synchronized balance of BM NE, TNF, COX-2, and melatonin maintains immature and mature leukocyte homeostasis. Basal inflammatory signals are required for steady-state HSPC function [20]. However, longer exposure to LPS impaired HSC competitive self-renewal and repopulation [95], demonstrating the need for robust short pulses of pro-inflammatory signals rather than chronic stimulations, which impairs stem cell function.

Additional factors such as diurnal corticosterone (in humans, cortisol) oscillations are part of the direct regulation of BM CXCR4$^+$ HSPC proliferation by low levels of corticosterone via notch signaling and indirectly through modulation of BM CXCL12 expression and expansion of stromal cells [96,97]. TNF and corticosterone are also involved in the switch of melatonin production from the pineal gland to activated myeloid cells during inflammation and immune activation by TNF, which is linked to the induction of the innate immune response and is switched back to pinealocytes during the time of immune resolution by corticosterone [40]. Nuclear translocation of specific NF-κB dimers in each cell type respectively is the basis for this switch. The cholinergic nervous system as well plays a role in orchestrating the daily HSPCs and leukocyte traffic. At night, the central parasympathetic cholinergic signals inhibit the noradrenergic tone to reduce BM HSPCs and leukocyte egress, while during daylight, via β3

receptor-NE signaling enhanced BM HSPC and leukocyte egress together with light-induced sympathetic cholinergic activity, which also reduces BM vascular cell adhesion and homing [98]. The parasympathetic cholinergic pathway have anti-inflammatory effects [60,99] that limit the continued secretion of cytokines such as TNF and NF-κB activation [60]. Finally, the murine complement cascade is also diurnally activated to regulate circulating HSPCs via a complex interplay with CXCL12 and sphingosine 1-phosphate (S1P) [100,101], both essential for HSPC egress and mobilization [66,100,102].

Altogether (summarized in the model in Figure 1 illustrating the role of the BM hematopoietic stem cell niches as a prism), the dynamic oscillations of the BM homeostatic milieu of cytokines, hormones, and neurotransmitters are crucial for metabolically programming HSPC migration and development for blood replenishment with mature blood and immune cells during the day while metabolically reprogramming BM HSPC maintenance with a high repopulation potential at night. Although daylight is important for blood replenishment and vitamin D synthesis, which is important for bone growth and integrity and myeloid cell host immunity, the darkness hormone melatonin is important for BM HSPC maintenance and renewal of the stem cell pool including LT-HSCs (schematically summarized and illustrated in Figure 2).

Clinical aspects related to disturbed light and darkness cycles

Daily oscillations and diurnal variations of many physiological parameters such as body temperature, blood pressure, and levels of soluble TNF receptor, cortisol, and other hormones and cytokines, as well as circulating leukocyte counts, have long been documented. Disruptions of the daily physiological regulation may result in homeostasis disorders with consequences that have been linked to several pathologies. Interestingly, a significant increase in patients' myocardial infarction onset was recorded early in the morning, with a threefold difference between the incidence of onset at 9 AM versus 11 PM [103]. The link between rhythmic leukocyte function and rhythmicity in the symptoms of various diseases, including asthma, chronic pulmonary disease, rheumatoid arthritis, allergic rhinitis, myocardial infarction, and ischemic stroke, has been extensively reviewed, suggesting consideration of treatment timing [104]. Circadian disruption caused by prolonged night shift work and sleep disorders have been associated with increased incidences of various cancers, including breast and prostate cancers. Moreover, circadian rhythms play an important role in regulating the metabolic features of cancer cells as well as their tumor microenvironment [105]. Mice with mutated clock genes or after subjection to chronic jet lag have increased growth of osteosarcoma, lymphoma, and hepatocellular carcinoma [106–109]. Interestingly, night shift workers have substantially reduced melatonin levels during night work and daytime sleep [110]. Several studies therefore suggest melatonin as a promising adjuvant molecule with many potential beneficial consequences when included in chemotherapy or radiotherapy protocols designed to treat endocrine-responsive tumors [111].

Disrupted circadian regulation may also impair HSC normal function and lead to the development of blood cell malignancies and imbalanced blood cell production. Sleep disruption impairs HSC transplantation in mice [112] and increases biased myelopoiesis damaging blood vessels by inducing atherosclerosis [113]. Interestingly, Clock and Bmal1 genes are required for the growth of acute myeloid leukemia (AML), and disruption of the canonical circadian molecular machinery depletes leukemic stem cells [114].

Aging-related alterations in the BM microenvironment substantially impair HSPC function. Some studies suggest that the first domino effect in aging-induced osteoporosis is the reduction in the quality of BM–blood barrier integrity and defective blood vessels [36]. Other alterations in the aging BM caused by deterioration of the nervous system have also been associated with the defective BM HSPCs and their niches, anemia, and reduced immune cell function. Age-related biased denervation and BM-niche remodeling lead to premature aging-like changes in murine HSCs [115]. The aging BM harbors not only reduced β3-AR signaling, but importantly also contains reduced endosteal HSC niches, which all lead to the aging-typical biased myelopoiesis [116]. Aging is also associated with a sharp decline in sex hormones and melatonin synthesis, accompanied by osteoporosis, anemia, and a major reduction in host immunity [37,117]. Thus, considering the local production of melatonin in the BM [44,46], the age-related reduction in melatonin synthesis and the lack of its antioxidant activity [117] may indicate the presence of an "age clock." Aging is also associated with increased risk for cancer, including leukemias [118].

Conclusion and future directions

The results of our study [66] present the potential of melatonin treatment to improve the outcome of clinical stem cell transplantation and BM engraftment. Thus, melatonin treatment of healthy donors before HSPC harvest or of collected cells ex vivo prior to their transplantation, and also of transplanted recipients, may facilitate stem cell-favoring conditions, which can potentially improve HSPC repopulation potential, enhance mature blood cell production, as well as reduce preconditioning-induced recipient BM toxicity

and side effects. Future investigations are needed to study the role of light and darkness cues in regulation of the human BM for the development of improved clinical BM transplantation protocols combined with melatonin treatment.

In summary, studying the circadian physiological rhythms of BM HSPC function is important to better understand and manipulate these cells for clinical procedures such as BM transplantation, ex vivo expansion, future development of protocols for ex vivo blood production, and immunotherapy. Understanding what can switch HSPC function from differentiation to increased repopulation capacity and quiescence is a key for future BM therapies.

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