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Daily light-and-darkness onset regulates mouse hematopoietic stem cells

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Abstract

Hematopoietic stem and progenitor cells (HSPCs) replenish the blood daily with new mature cells with a finite lifespan while maintaining the bone marrow (BM) stem cell reservoir. Currently, it is not clear how these opposite roles are regulated and synchronized. Preclinical mouse studies revealed that daily onset of light and darkness differentially regulates HSPC differentiation and blood replenishment with maintenance of the BM reservoir. Light onset transiently increases BM HSPC reactive oxygen species levels, initiated by bursts of norepinephrine (NE) and tumor necrosis factor (TNF), leading to HSPC migration and differentiation for blood replenishment. Darkness onset induces a lower peak of BM HSPC reactive oxygen species levels, initiated by lower bursts of NE and TNF, leading to high BM melatonin levels at night. Melatonin maintains BM HSPCs directly and indirectly by changing their metabolic state, cell-surface markers, function, and BM microenvironment. Bone-forming stromal precursors are also regulated by daily light-and-darkness onset. These results suggest that NE and TNF in the morning metabolically program HSPCs for their migration and differentiation, replenishing the blood. In contrast, lower TNF levels and melatonin at night metabolically reprogram BM HSPCs back to their undifferentiated state endowed with higher repopulation potential. Because mice are nocturnal, blood replenishment occurs at opposite times compared with humans due to metabolic differences in circadian rhythms. However, BM melatonin treatment similarly regulates mouse and human HSPCs in chimeric immune-deficient mice, suggesting its clinical potential. The relevance of these findings to clinical BM transplantation, aging decline, cancer, osteoporosis, anemia, and host immunity will be discussed.

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