Different daily light and darkness signals regulate bone marrow leukocyte production and stem cell development

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Abstract

Blood forming stem cells are mostly retained in a quiescent, non-motile mode in the bone marrow (BM), shifting to a cycling, differentiating and migratory state to give rise to all mature leukocyte and blood cells as part of host defense and repair mechanisms. How murine BM stem cells replenish the blood with mature cells while maintaining their reservoir of undifferentiated cells, remains poorly understood. We report that stem cell levels and BM leukocyte production are regulated via light and darkness signals. We identified two different daily stem cell peaks: one following light initiation, which is accompanied by increased stem cell egress and differentiation and the other after darkness, which is associated with increased stem cell proliferation and reduced egress and differentiation. In both peaks stem cell begin to cycle via up-regulation of reactive oxygen species (ROS). The morning peak is initiated via norepinephrine (NE), leading to stem cell proliferation, differentiation and enhanced motility. Upon light termination TNFα/ S1P levels are increased, leading to ROS augmentation, but also induce COX2/PGE2 signaling in rare activated αSMA/Mac-1 macrophages, which restore low ROS levels, preventing stem cell differentiation and egress. Leukocytes differentiate in the BM towards noon with low egress until midnight, which is followed by mature leukocytes egress and blood replenishment. Mimicking bacterial infections, endotoxin-induced mortality depends on the time of its administration, with high mortality in mice treated in the afternoon and low mortality following midnight challenge. We found that LPS administration in the afternoon resulted in increased neutrophils and monocytes recruitment to the blood, in contrast to LPS injection at midnight, which induced low levels of myeloid cells in the blood. In summary, we identified two daily circadian peaks in BM stem cell levels which are regulated via light/darkness cues and concomitantly maintain dynamic host immunity and blood cell replenishment.