Diurnal cues metabolically regulate Hematopoietic Stem Cell maintenance and function

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PPrimitive hematopoietic stem cells (pHSC) are mostly maintained quiescent in the bone marrow (BM), preserving the stem cell reservoir. In response to hematopoietic stress, pHSC which are the only chemotherapy resistant HSC population, rapidly proliferate and differentiate to replenish the blood with new mature and immune cells in order to prevent lethal hematology failure and infections. For these tasks pHSC require new and tested mitochondria in order to accommodate the enhanced metabolic needs to fuel the emergency stressed hematopoiesis. How quiescent pHSC are metabolically regulated to rapidly be ready on demand and when their mitochondrial remodeling and turnover takes place is not fully understood.

In the current study we examined diurnal changes in BM retained pHSC and their metabolic regulation. We report that 5 hours following light onset the pHSC mitochondria reach peak activity as evident from higher mitochondria membrane potential (MMP). In contrast, five hours following darkness onset there were peak local BM melatonin levels, as a result pHSC mitochondria was least active with lowest MMP levels. At this time point there were high levels of HIF-1alpha, Wnt signaling, Glut-1 expression, leading to significantly higher glucose uptake in pHSC, providing them with higher long term competitive repopulation potential (LT-HSC).

Our study suggests higher mitochondrial activity in BM retained pHSC during daylight priming pHSC for migration and development in order to replenish the blood with new mature blood and immune cells. Higher glycolysis at night time suggests mitochondrial remodeling and turnover at night which is part of pHSC BM maintenance accompanied by increased LT-HSC competitive repopulation potential.

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