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STEM CELLS

Harvest in the right season

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Understanding the release of haematopoietic stem cells (HSCs) from the bone marrow into the bloodstream is the basis for bone marrow transplantation procedures. However, the molecular mechanisms that regulate this process are not well understood. A study in *Nature* now shows that the mobilization of HSCs follows a physiologically regulated circadian rhythm.

> “…the mobilization of HSCs follows a physiologically regulated circadian rhythm.”

While investigating the mechanism of enforced HSC mobilization by the growth factor granulocyte colony-stimulating factor (G–CSF), Paul Frenette and colleagues observed that the continuous exposure of mice to light could significantly affect HSC mobilization. Thus, a light-induced signal could influence the release of HSCs from the bone marrow. This unexpected finding led the authors to investigate the circadian pattern of HSC release and its role in homeostasis. Under normal conditions, HSCs do not circulate steadily or randomly but undergo precise circadian fluctuations, which can be altered by changes in the light–dark cycle, such as a ‘jet lag’ or the exposure of animals to continuous light. The authors also observed that expression of the *Cxcl12* gene, which encodes a chemokine that attracts HSCs to the bone marrow, mirrored the oscillations in HSCs. These findings suggest that the decrease in *Cxcl12* expression could be necessary for the rhythmic mobilization of HSCs.

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How is the light–dark cycle converted into fluctuations of *Cxcl12* expression and release of HSCs into the bloodstream? By performing chemical and surgical ablation experiments, Frenette and colleagues showed that local signals from the sympathetic nervous system (SNS), mediated by the β3-adrenergic receptor, regulate the rhythmic expression of *Cxcl12* and mediate the circadian exit of stem cells from bone marrow.

Next, the authors showed that core genes of the circadian clock, such as *Bmal1, Per1* and *Per2*, orchestrate *Cxcl12* expression and the trafficking of stem cells, probably by regulating the rhythmic secretion of noradrenaline (which activates the β3-adrenergic receptor) from the nerve terminals. But what is the molecule that regulates *Cxcl12* expression in response to SNS stimuli? Previous studies have shown that the transcription factor SP1 can bind to the promoter of *Cxcl12*. SP1 phosphorylation by the cAMP-dependent protein kinase (PKA) enhanced its DNA-binding activity. Furthermore, PKA is activated in response to β3-adrenergic signalling. Using specific inhibitors, Frenette and colleagues showed that local stimulation of β3-adrenergic signalling causes the degradation of SP1 and a reduction in *Cxcl12* expression, which results in increased HSC release.

These findings suggest that choosing the right time for harvesting HSCs could increase the yields of stem cells for clinical applications.

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ORIGINAL RESEARCH PAPER Méndez-Ferrer, S., Lucas, D., Battista, M. & Frenette, P. S. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature* 6 Feb 2008 (doi:10.1038/nature06685)
FURTHER READING Roenneberg, T. & Merrow, M. Circadian clocks — the fall and rise of physiology. *Nature Rev. Mol. Cell Biol.* **6**, 965–971 (2005)