

Time of day influences yield for pharmacologically stimulated stem cell mobilization

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A new study uncovers a previously unrecognized, species-specific impact of circadian rhythms on the production of mobilized stem cells. The research, published by Cell Press in the October 9th issue of the journal *Cell Stem Cell*, suggests that when it comes to collecting human stem cells for clinical transplantation, picking the right time of day to harvest cells may result in a greater yield.

A variety of organisms have evolved an endogenous timing system, called a circadian clock, to regulate metabolic activities in a day/night cycle. In mice, the cells that give rise to mature blood cells, called hematopoietic stem cells (HSC), are regulated under the influence of rhythmic circadian signals that influence expression of *Cxcl12*, a gene involved in white blood cell migration.

"Previous research has shown that the "sympathetic" branch of the nervous system, which is involved in stress responses, tightly regulates the amount of *Cxcl12* expressed in the bone marrow by circadian oscillation of noradrenaline release. Blood stem cell patterns are basically the mirror image of *Cxcl12* expression in bone marrow," says lead study author, Dr. Paul S. Frenette from the Mount Sinai School of Medicine.

Dr. Frenette and colleagues were interested in examining whether circadian time continues to influence mobilization of HSCs when mice

are treated with granulocyte-colony-stimulating factor (G-CSF), the most common stem cell mobilizer used in the clinic. The researchers found that after stimulations with G-CSF, synchronization of blood collection with the peak circadian time produced greater HSC recovery. Therefore, even when pharmacological manipulation is used to stimulate HSC mobilization, circadian clock genes continue to influence yield.

The researchers also demonstrated the existence of significant oscillations in the number of human HSCs and found that the circadian rhythm in humans is inverted when compared to that of the mouse. An examination of healthy donors who were contributing HSCs for bone marrow transplantation at Mount Sinai Medical Center between the years of 2000 and 2006 revealed that the average yield was greater for those who underwent the procedure in the afternoon compared with those who were harvested in the morning.

"Our results suggest that the human HSC yield for clinical transplantation might be greater if patients were harvested during the evening compared to the morning," explains Dr. Frenette. "Although prospective clinical studies are needed to ascertain the optimal time for HSC collection, it is possible that a simple adjustment in the collection time may have a significant clinical impact. Further, the maximum release of HSCs at the beginning of the rest period for both species (early night for humans, early morning for mice), supports the intriguing possibility that this phenomenon may contribute to regeneration."

Source: Cell Press

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