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Study results promise faster recovery from life-threatening blood cell shortages

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A key compound resupplies bone marrow with fast-acting stem cells that can more quickly rekindle blood cell production, according to a study published online today in the journal *Blood*. While the study was in mice, in the study authors say it has the potential to increase survival among patients with life-threatening blood cell shortages.

Thanks to stem cells, humans develop from one cell into a complex being with as many as 400 cell types. As the fetus develops, successive generations of stem cells specialize (differentiate), with each round becoming more specific until they become the end-stage functional cells of the body. Some human tissues, including bone marrow, keep a stem cell pool on reserve into adulthood, ready to differentiate into replacement parts when called upon. For instance, the marrow houses the hematopoietic system that turns stem cells into red blood cells, white blood cells and platelets.

In leukemia patients, cancer cells have invaded the bone marrow and physicians must kill with radiation and chemotherapy all cells in the marrow in hopes of saving the patient's life. In other cases, infections have damaged the marrow or genetic blood disorders have resulted in too few, or abnormal, cells. Injuries to the marrow are often addressed with stem cell transplants from healthy donors that restore the marrow's ability to supply blood cells. While the transplants have helped tens of thousands, they leave patients at risk for severe infections (too few white blood cells), anemia (too few red blood cells) and internal bleeding (too few platelets) for about six weeks as the marrow recovers.

In the current study, researchers found that a key compound, prostaglandin E2 (PGE2), can dramatically increase the number of fast-acting stem cells most useful in the rapid recovery of the bone marrow's hematopoietic capability.

"Our results show that PGE2 more quickly restores blood cell production, and continues to do so for the exact period, six to eight weeks, when patients are most at risk," said Laura M. Calvi, M.D., assistant professor of Medicine in the Endocrine/Metabolism Division at the University of Rochester Medical Center. "Currently stem cell treatments used for the restoration of bone marrow function are often unable to produce enough stem cells, or throw off the balance between stem cells and mature blood cells. PGE2 treatment could represent a precise way to accelerate recovery from bone marrow injury," said Calvi, corresponding author for the study.

Bone Deep

To maintain pools of potential replacement cells throughout adult life but still be able to react quickly to a blood cell shortage, hematopoietic stem cells (HSCs) have evolved into three sub- types.

These include long term-HSCs that self-renew for life, short-term-HSCs that self-renew for four to eight weeks and multi-potent progenitors that (MPPs) self-renew for less than two weeks. Past studies have suggested that long term-HSCs, while ensuring a steady lifetime supply of blood cells, do not differentiate fast enough into mature blood cells to be useful immediately after bone marrow destruction. Short term-HSCs and MPPs do, if there are enough of them around.

Bodily functions, including stem cell behavior, are regulated by hormones. The parathyroid gland, for instance, releases parathyroid hormone (PTH), which is known to increase the number and action of

cells neighboring HSCs: the bone-building osteoblasts. In a paper published six years ago in the journal *Nature* (2003;425:841-5), Calvi and colleagues established that PTH signals for a greater supply of hematopoietic stem cells along with osteoblasts. Based on the hunch that PTH somehow regulated HSCs through osteoblasts, the team was able to genetically engineer mice that were nearly four times as likely to survive bone marrow transplant as control mice, with their marrow densely packed with blood cells.

Since then studies by others have found that PTH stimulates osteoblasts to produce prostaglandin E2 (PGE2), and the current research team focused on the effects of PGE2 treatment on the number of a key type of hematopoietic stem cells compared to control-treated mice. PGE2 was found to preferentially expand fast-acting, shortlived stem cell populations (ST-HSCs and MPPs) in mice, but not Long Term-HSCs. Because the cell types increased in number act quickly to expand blood cell supply, but do not reproduce for very long, researchers were not surprised to see that the effect in live animals of PGE2 had disappeared by 16 weeks post stem cell transplant. This study represents the first time a single factor has been shown to expand a specific HSC subset.

Further experiments found that mice with PGE2 administered to their HSCs cells saw "superior" rebuilding of white blood cell supply versus control mice. Three weeks after transplantation, PGE2-treated mice saw an approximately 30 percent greater reconstitution of bone marrow white blood cell supply over control mice, as determined by flow cytometry, which fluorescently tags, then counts, cell types. Studies already underway in Calvi's lab seek to clarify the molecular mechanisms responsible for the regulation of ST-HSCs by PGE2, and whether existing drugs known to encourage the PGE2 signal can make a difference in blood marrow transplant recovery.

Regis J. O'Keefe, M.D., Ph.D., chair of the Medical Center's

Department of Orthopaedics and Rehabilitation, and Craig Jordan, Ph.D., professor of Biomedical Genetics in the James P. Wilmot Cancer Center, collaborated with Calvi on the work. Key student contributors were Benjamin Frisch, Rebecca Porter, Benjamin Gigliotti, Adam Olm-Shipman and Jonathan Weber. The work was supported by the National Institute of Diabetes, Digestive and Kidney Diseases, the Wilmot Cancer Research Fellowship Program and the Pew Charitable Trusts.

"Also important for leukemia patients, this work places new importance on the discovery that PTH stimulates PGE2 production by turning up the action of COX 2, the enzyme targeted by a widely used anti-inflammatory pain medications like Celebrex," Calvi said. "Could painkillers used by patients recovering from stem cell transplants be hampering their ability to re-start blood cell production? Beyond leukemia, an emerging theory holds that cancer stem cells resemble normal stem cells and explain how cancer can be spread by a single cell. If this is true, then osteoblasts, PTH and PGE may regulate cancer growth, as they do HSC numbers, and might be manipulated to stop breast and prostate cancer cells from spreading to bone."

Source: University of Rochester Medical Center (news : web)