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Discarded Immune Cells Induce the Relocation of Stem Cells

May 23, 2013 — CNIC researchers have discovered that the daily clearance of neutrophils from the body stimulates the release of hematopoietic stem cells from the bone marrow into the bloodstream, according to a report published today in the journal *Cell*.

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Neutrophils are leukocytes (white blood cells) that defend the body against attack from bacteria and other disease organisms. To perform their function, these cells release toxic substances when they come into contact with microorganisms. However, release of these substances in the wrong place by damaged neutrophils can result in severe injury to blood vessels and tissues. Evolution appears to have resolved this conflict by ensuring that neutrophils are renewed much more rapidly than most other cells in the body: approximately 10¹¹ neutrophils are eliminated every day and an equivalent number of stem cells are released into the bloodstream. This in turn generates a second problem: what to do with all these cells that have to be eliminated.

Dr. Andrés Hidalgo and his team in the Department of Epidemiology, Atherosclerosis and Cardiovascular Imaging, led by Dr. Valentín Fuster, have discovered the function of these neutrophils expelled every day by the body.

Graduate student María Casanova Acebes (Universidad Autónoma de Madrid), found that when additional apoptotic neutrophils were injected into mice, there was an increase in the number of circulating hematopoietic stem cells, the cells that generate all blood cells.

Using a wide variety of experimental approaches, including imaging assays, pharmacological treatments and genetic analysis, the team showed that when neutrophils in the blood get old, they migrate to the bone marrow to be eliminated by specialized phagocytotic cells called macrophages. The act of phagocytosing the neutrophils alters these macrophages' genetic properties and functions, and these changes in turn alter the function of specialized cells whose job it is to retain hematopoietic stem cells in the bone marrow. "As a consequence, the stem cells are released into the blood," explains María Casanova, first author of the study.

According to Dr. Hidalgo, "Key questions that arise from our study relate to the role of the hematopoietic stem cells expelled from the bone marrow, and how the elimination of neutrophils might affect other important stem cell populations, for example those that produce tumors."

The research also reveals that the aging of neutrophils follows a day/night, or circadian, cycle, suggesting possible implications for disease processes -- for instance heart attack -- that occur more frequently at certain times of day.

"Our study shows that stem cells are affected by day/night cycles thanks to this cell recycling. It is possible that the malign stem cells that cause cancer use this mechanism to relocate, for example during metastasis," Hidalgo emphasizes.

But this finding could have more direct implications for cardiovascular health. According to the authors, the daily changes in the function of neutrophils could be responsible for the tendency of acute cardiovascular and inflammatory events, such as heart attack, sepsis or stroke, to occur at certain times of day.

Dr. Hidalgo concludes, "Given that this new discovery describes fundamental processes in the body that were unknown before, it will now be possible to interpret the alterations to certain physiological patterns that occur in many diseases."

