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UC San Diego
University Archives. RSS 6020

Key Finding by UC-San Diego Scientists May Improve Treatment of Anemia

June 20, 2007

Debra Kain

Scientists at the University of California, San Diego (UCSD) have determined a key mechanism by which the body regulates iron metabolism, a discovery that may provide new approaches for the treatment of anemia.

The findings, which are reported this week in the online publication of *The Journal of Clinical Investigation*, represent a collaborative effort between the laboratories of Randall Johnson, Ph.D., UCSD professor of biology and Victor Nizet, M.D., professor of pediatrics and pharmacy at the UCSD School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences.

Iron is essential for many normal biological processes including the production red blood cells that deliver oxygen to the body's tissues. By studying the regulation of iron and production of red blood cells in mice, the researchers established the relationship between a pair of proteins that play a central role in monitoring a hormone called hepcidin.

The hepcidin hormone is a peptide, or small protein, that is synthesized in the liver and regulates the levels of iron in the body. It prevents the body from absorbing more iron than is needed from food or supplements, and blocks the export of iron from cells.

Patients with cancer, chronic inflammatory diseases or infections often develop high levels of hepcidin, which reduces the amount of iron available to support the production of new red blood cells. Consequently, such patients suffer from low red blood cell production, or anemia.

To properly respond to anemia, the body must somehow reduce hepcidin in order to increase the iron that is needed for red blood cell production. Until now, scientists didn't clearly understand the mechanisms by which hepcidin itself is regulated.

The UCSD research team discovered that a protein known as hypoxia-inducible transcription factor (HIF) is critical in orchestrating the proper hepcidin response in the liver. In turn, HIF levels are controlled on a minute-by-minute basis by the action of another protein known as von-Hippel Lindau factor (vHL.)

"The vHL factor works to lower HIF levels whenever oxygen is high or iron is abundant," said Johnson. "When iron levels and oxygen delivery to the tissues drop, as is the case in anemia, vHL ceases its action and HIF is preserved."

Previous research had shown that HIF is responsible for stimulating erythropoietin (EPO), a hormone that instructs the bone marrow to produce new red blood cells. The UCSD team made the critical and novel observation that HIF also strongly inhibits the production of hepcidin in the liver. "Our findings show that the vHL and HIF proteins play a central role in sensing and regulating iron levels," said lead author Carole Peyssonnaux, Ph.D., a former researcher with Nizet and Johnson who has now joined the faculty of the Institut Cochin in Paris, France. "In anemia, the body responds to low iron and oxygen levels by increasing HIF, which in turn suppresses hepcidin and boosts EPO to provide the iron and new red blood cells required to correct the problem."

Importantly, the researchers found that HIF was capable of suppressing hepcidin even in mice suffering inflammatory changes in their bodies.

"This key finding suggests that new drug treatment strategies to boost HIF or inhibit vHL could reverse the abnormally high hepcidin levels seen in the anemia that affects the majority of patients suffering from chronic infections or inflammatory disease," said Nizet.

Media Contacts: Debra Kain, Health Sciences, 619-543-6163 Kim McDonald, Biological Sciences, 619-543-6163