UW-Madison School of Medicine and Public Health: UW researchers discover essential protein for red blood cell regeneration and survival in anemia

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MADISON, Wis. – Researchers at the UW School of Medicine and Public Health have established a new mechanism that explains how red blood cells regenerate and survive in mice experiencing severe anemia.

The findings were recently published in the journal *Developmental Cell*.

Dr. Emery Bresnick, professor of Cell and Regenerative Biology at the UW School of Medicine and Public Health, and his collaborators, demonstrated that anemia increases activity of a gene that generates a protein implicated in controlling cellular communication, also called signalling.

Dr. Kyle Hewitt, an assistant scientist in Bresnick's research group, led the experimental effort.

This protein, Samd14, is involved in the process of sensing when the levels of red blood cells are dangerously low, also known as severe anemia. Under these

conditions, Samd14 promotes the regeneration of the red blood cells to ensure the delivery of oxygen to cells and tissues, which prevents cell and tissue damage or even death.

“While GATA-2 was known to promote the development of blood stem and progenitor cells, its role in anemia was not well understood,” Bresnick said. “Our deep knowledge of GATA-2, our unique multi-disciplinary team, and our innovative genetically engineered mouse model, led to this discovery.”

The protein production is controlled by a GATA-2-dependent non-coding DNA sequence called Samd14 Enhancer. This Samd14 Enhancer DNA sequence is a founding member of an ensemble of anemia-sensing enhancers required for red blood cell regeneration in severe anemia.

Bresnick and Hewitt previously collaborated with Dr. Sunduz Keles, professor of biostatistics and medical informatics at the UW School of Medicine and Public Health, to discover the Samd14 Enhancer during a study of non-coding DNA sequences in the genome. In the previous study they implicated the Samd14 Enhancer in the development and function of blood stem and progenitor cells. This discovery was published in *Molecular Cell* in 2015.

In the *Developmental Cell* study, Bresnick and his team examined genetically modified mice lacking the Samd14 Enhancer. They determined that Samd14 was not produced in the bone marrow and spleen during severe anemia unless the enhancer is present.

The enhancer was not necessary to maintain normal red blood cell levels, according to the study. But, in one of the tests described in the paper, when mice without the enhancer faced a severe loss of red blood cells, 15 of the 16 mice died.

Since anemia occurs in a diverse set of diseases, including myelodysplastic syndrome, kidney failure and chronic inflammatory conditions, Bresnick and his collaborators predict the enhancer could sense anemia in broader contexts and perhaps even modulate disease severity, in a similar way to the protection against anemia that they discovered in the mouse model.

Anemia is a debilitating medical condition affecting thousands of people in the United States, and in certain cases, anemia is non-responsive to the red blood cell stimulating agent erythropoietin.

To address this problem, fundamental scientific advances, like identifying the Samd14 Enhancer, are required to devise new methods for treating anemia, Bresnick said.

Advances related to GATA-2 are not limited to anemia, he said.

“GATA-2 deregulation causes myelodysplastic syndrome, leukemia and is linked to the progression of other cancers. Future studies may reveal that modulators of red blood cell regeneration have broader roles in human diseases and inform unrelated processes of cell and tissue regeneration,” Bresnick said.

Bresnick’s GATA-2 work is supported predominantly by two National Institutes of Health grants and support from the UW Carbone Cancer Center. Bresnick, who is also the director of UW-Madison Blood Research Program, and co-director of Genetic and Epigenetic Mechanisms Program of the Carbone Cancer Center, and his colleagues at UW-Madison and the UW School of Medicine and Public Health, collaborated on the study with researchers from Seoul National University, Seoul, South Korea; and Pennsylvania State University.