Circulation

CARDIOLOGY NEWS

From the Literature

Tracy Hampton

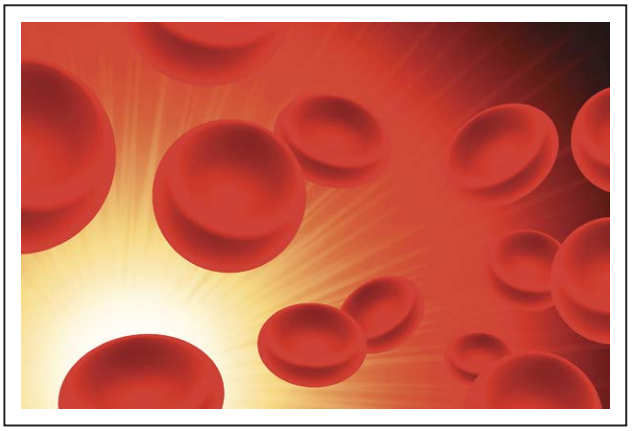
Vasopressin Improves Recovery From Anemia

New research reveals that, in addition to maintaining fluid balance by regulating water reabsorption in the kidneys, the hormone arginine vasopressin (AVP) also stimulates red blood cell production, and it does so on a shorter time scale than erythropoietin.

In a *Science Translational Medicine* study, a team led by investigators at the National Institutes of Health, in Bethesda, Maryland, found that mouse and human hematopoietic stem and progenitor cells express AVP receptors and rapidly respond to vasopressin by proliferating and differentiating into red blood cells. One particular vasopressin receptor (AVPR1B) played a predominant role in red blood cell production, and treating mice with AVP or an AVPR1B activator following injury- or radiation-induced blood loss increased the number of circulating red blood cells and sped up recovery from anemia.

The investigators also found that among 92 patients with central diabetes insipidus, which is caused by a lack of AVP, 87% of males and 51% of females had anemia. These rates compare with prevalence rates of 1.5% to 6% for males and 4.4% to 12% for females in the general population of the United States.

By accelerating proliferation and differentiation of bone marrow erythroid precursors in anemia, AVP may help jump-start the replenishment of blood cells until erythropoietin can take effect.



New research reveals that the hormone arginine vasopressin stimulates red blood cell production and aids in anemia recovery.

"We believe that an AVPR1B agonist may help people with anemia due to chemotherapy, radiation, or blood loss," said senior author Éva Mezey, MD, PhD, DSci. "Vasopressin is already routinely used in emergency rooms to fight shock. An AVPR1B agonist would induce red cell production quickly without affecting water balance, and it should be safe to administer."

Mayer B et al. Vasopressin stimulates the proliferation and differentiation of red blood cell precursors and improves recovery from anemia. Sci Transl Med. 2017;9:eaao1632. doi: 10.1126/scitranslmed.aao1632.

Modified CRISPR-Cas9 Technique Epigenetically Treats Diseases in Mice

Scientists have developed a modified CRISPR-Cas9 technique that alters the activity, rather than the underlying sequence, of disease-associated genes. The advance may help overcome concerns that the CRISPR-Cas9 gene-editing approach could cause unwanted mutations with potentially deleterious effects.

The CRISPR (clustered, regularly interspaced, palindromic repeats) technology is adapted from a bacterial defense system and uses the DNA-cutting enzyme Cas9 bound to a guide RNA molecule that targets a specific genetic sequence. To reduce the likelihood of off-target cuts, researchers have used a dead form of Cas9 (dCas9) that still targets specific sequences but no longer cuts DNA. In these systems, dCas9 is coupled with transcriptional activation complexes that turn on targeted genes epigenetically (without altering the DNA sequence); however, dCas9 bound to these complexes is too large to fit into the adeno-associated viruses (AAVs) that are used as delivery vehicles into cells in living organisms.

In this latest work, which is published in *Cell*, researchers at the Salk Institute for Biological Studies, in La Jolla, CA, and their colleagues discovered combinations of dCas9 and transcriptional activation complexes that worked even when they were not fused together but instead were delivered via 2 different AAVs.

The investigators used this technology to treat several mouse models of human diseases. In a model of acute kidney injury, they activated 2 genes involved in kidney function and observed increased levels of the proteins associated with those genes, and improved kidney function, as well. In a model of type 1 diabetes mellitus, treatment boosted the activity of genes that generate insulin-producing cells, leading to lower blood glucose levels. Finally, in a model of muscular dystrophy, the scientists expressed genes known to reverse disease symptoms, including a large gene that cannot easily be delivered via traditional virus-mediated gene therapies.

"We have been able to show that this technique could be used for many cell types and organs. Eventually, our epigenetic approach could be used to develop treatments and cures for a wide range of human diseases that would be difficult to achieve by standard gene therapy approaches," said senior author Juan Carlos Izpisua Belmonte, PhD. "We will extend these initial observations after we have improved several aspects of this technology, including efficiency and immune-related responses."

Liao H-K et al. In vivo target gene activation via CRISPR/Cas9-mediated trans-epigenetic modulation. Cell. 2017;171:1495–1507.e15. doi: 10.1016/j.cell.2017.10.025

Researchers Identify Gene Repressed During Heart Failure

Responses to cardiac injury and stress in the failing heart lead to changes in gene expression that cause cells to revert to a fetal-like state. Now investigators have identified a target to potentially prevent this process.

"Using this concept of fetal reprogramming we identified OPLAH, an enzyme that converts 5-oxoproline to glutamate," said senior author Peter van der Meer, MD, PhD, of the University of Groningen, in the Netherlands.

The research, which is published in *Science Translational Medicine*, involved profiling RNA in mouse hearts during embryonic development and after heart failure, revealing 68 genes that changed expression. The scientists identified decreased expression of the *Oplah* gene as a new characteristic of heart failure when they considered genes that were specific to the heart, also expressed in humans, and not previously described in the context of cardiac problems.

Repression of the gene was closely tied to poor cardiac outcomes, and boosting the gene's expression in mice lessened cardiac injury after myocardial infarction. Also, elevated bloods levels of 5-oxoproline were associated with worse outcomes in a cohort of 535 patients who had been hospitalized for heart failure.

By converting 5-oxoproline into glutamate, the OPLAH protein contributes to cellular antioxidant defenses. Indeed, OPLAH depletion in mice that occurred as a result of cardiac injury led to elevated 5-oxoproline and oxidative stress.

The study's findings suggest that OPLAH could serve as a therapeutic target, and a predictive marker for cardiac injuries, as well. Dr van der Meer noted that additional targets and markers may be identified as researchers continue to dissect the cardiac fetal-like gene program associated with heart failure.

van der Pol A et al. Accumulation of 5-oxoproline in myocardial dysfunction and the protective effects of OPLAH. Sci Transl Med. 2017;9:eaam8574. doi: 10.1126/scitranslmed.aam8574.

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Circulation. 2018;137:1285-1286
doi: 10.1161/CIRCULATIONAHA.118.034310
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539