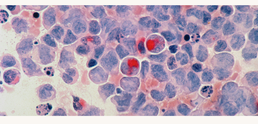
There's a new threat to our cells...

March 17, 2024



Welcome to Issue 81 of Science Says! Our weekly newsletter where you'll learn the latest healthy aging and C15:0 research news that our team of doctors, scientists, and experts are most excited about—without having to go search for it.

Eric and Steph
Co-Founders, Doctors, Nerds

What Dr. Stephanie Venn-Watson, our co-founder and author of over 80 peer-reviewed scientific publications, is reading.

HEALTHY AGING

...but we have a hypothesis that may protect them

In this Whole Body Health Series, we are sharing the latest science on our whole body, from our cells on up.

In our last issue, we talked about the rising importance of strong cells. This week, we're continuing our coverage of a new threat to our cellular health. It's called ferroptosis.

Well, that sounds ominous. What exactly is ferroptosis, again?

As we shared last week, ferroptosis is a newly found way that our cells are dying. This process was discovered by a research team at Columbia University back in 2012.

As described by Dixon et al., ferroptosis involves three basic steps:

- **Step 1: Fragile cell membranes.** Ferroptosis starts when fragile fatty acids (aka polyunsaturated fatty acids) in our cell membranes incite lipid peroxidation.
- **Step 2: Lipid peroxidation + intracellular iron.** Lipid peroxidation then combines with unwanted iron inside our cells to induce high levels of reactive oxygen species (ROS).
- **Step 3: Reactive oxygen species (ROS) that attack mitochondria.** In turn, ROS knocks out our cells' powerhouses (aka our mitochondria)... and our cells altogether.

The result? Thousands of studies have shown that ferroptosis is an emerging problem that negatively impacts our metabolic, heart and liver health.

Wait, how is iron involved in ferroptosis?

For our fellow nerds, you probably already picked up that "ferro" in ferroptosis stands for "iron". While we are used to hearing about the need to fix iron deficiencies, iron also has a naughty side when it is running free and gets into our cells.

In fact, there is a name for renegade iron in our bodies. It's called dysmetabolic iron overload syndrome (or DIOS). As described by Sachinidis et al., DIOS is directly linked to poor metabolic, heart and liver health. While DIOS used to be rare, Deugnier et al. share that this condition has been on the rise globally, right along with ferroptosis.

I think I understand, but how does "bad" iron get into our cells in the first place?

There are many hypotheses, but the following pathway has gained traction, including from our own discoveries while caring for older dolphins with DIOS and impressive insights from Otogawa et al.

- **Red blood cells become more fragile** due to unstable cell membranes.
- These **weak red blood cells are engulfed** by cells in the liver, called Kupffer cells.
- Red blood **cell corpses leave behind iron deposits in our liver,** which impair liver function.
- When enough iron accumulates in the liver, this **excess iron spills over into the bloodstream** and other organs.

Over time, the combination of fragile cells with excess iron can lead to ferroptosis.

Detecting the precursors of ferroptosis.

Given all the above, there are tests that can detect various precursors and components of DIOS and ferroptosis, including the following:

Red Blood Cell Fragility Tests

- **The Osmotic Fragility Test** directly measures the strength of our red blood cells.
- **The Saturation (aka Stability) Index** measures the ratio of selected unstable versus stable fatty acids in red blood cell membranes.
- **Hemoglobin** measures normal or low amounts of functioning red blood cells. Low hemoglobin can occur if red blood cell loss (including due to fragility) is higher than new red blood cell production.
- **Red Blood Cell Distribution Width (RDW)** measures the variability of red blood cell sizes. A high RDW may indicate premature loss of fragile red blood cells.

Lipid Peroxidation & Iron Overload Tests

- **Lipid Peroxidation** levels measure the amount of lipid peroxidation in blood or urine.
- **Ferritin** measurements can help detect potential iron overload in tissues, including the liver.

It is important to note that none of these tests are specific for DIOS and ferroptosis. As such, you need to work with your doctor to help guide which tests are appropriate and how to interpret the results.

Why is ferroptosis happening now?

Chances are, ferroptosis has been around longer than its discovery 12 years ago. That said, there is a real trend happening with more people having impaired red blood cell function, impaired iron handling, and impaired metabolic, heart and liver health.

These trends have coincided with population-wide declines in our C15:0 levels, caused both by diets containing less C15:0 and declining C15:0 with age.

For the past 10 years, we have been pursuing the hypothesis that nutritional C15:0 deficiencies may be driving the rise in cellular fragility and abnormal iron handling. Importantly, our studies and others, using relevant models, have shown that C15:0 can restore healthy cells. Here's how:

- As a stable fatty acid, C15:0 effectively strengthens cells by 80%
- C15:0 lowers lipid peroxidation levels in the liver by 40%
- C15:0 lowers intracellular iron deposition by 64%
- C15:0 directly repairs mitochondrial function and lowers ROS by 50%.

Research is still underway, so stay tuned here at *Science Says!* for the most recent advances in C15:0 science. Next week, we'll move from our general cellular health to our whole body health, starting with our metabolism. In the meantime, have a great week, everyone!

Dive deeper into the science

READ THESE STUDIES

- Dixon et al. Ferroptosis: An iron-dependent form of nonapoptotic cell death.
- Mortensen et al. Polyunsaturated fatty acids drive lipid peroxidation during ferroptosis.
- Miao et al. Iron metabolism and ferroptosis in type 2 diabetes mellitus and complications: mechanisms and therapeutic opportunities.
- Fang et al. The molecular and metabolic landscape of iron and ferroptosis in cardiovascular disease.
- Chen et al. The multifaceted role of ferroptosis in liver disease.
- Sachinidis et al. Dysmetabolic iron overload in metabolic syndrome.
- Deugnier et al. Dysmetabolic iron overload syndrome (DIOS).
- Venn-Watson et al. Hemochromatosis and fatty liver disease: building evidence of insulin resistance in bottlenose dolphins.
- Otogawa et al. Erythrophagocytosis by liver Kupffer cells promotes oxidative stress, inflammation and fibrosis in rabbit model: Implications for the pathogenesis of human NASH.
- Venn-Watson et al. C15:0 strengthens red blood cells, stops liver iron deposition, lowers ROS and repairs mitochondrial function.
- Wei et al. C15:0 lowers lipid peroxidation in the liver (see Supplementary Materials).
- Nerd out on all the C15:0 science at DiscoverC15.com.