Artist's impression of the destruction of a cell. Cells may be destroyed by ferroptosis, a type of programmed cell death that is dependent on iron.

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AT THE HEART OF IRON BIOLOGY

A RESEARCHER'S THREE-DECADE JOURNEY reveals iron's role in heart and liver disease and cancers

When Fudi Wang set out to understand the biology of bio-metals such as selenium, zinc, iron, manganese, and copper, he never imagined his research would culminate in a deeper understanding of how heart attacks can be fatal.

In a typical attack, a blocked artery starves the heart of oxygen. This damages heart tissue, triggering symptoms, including pain and nausea.

But the real damage happens after the blood returns to the heart. This so-called ischemia/reperfusion injury (I/R injury) is the primary cause of death following a heart attack.

A recently discovered iron-dependent form of programmed cell death plays a crucial role in this damage, according to research in mice models by Wang's team at the Zhejiang University School of Medicine, Hangzhou, and the University of South China in Hengyang.

IRON IMBALANCE AND FERROPTOSIS IS THE COMMON DENOMINATOR IN MANY DISEASES

Called ferroptosis, this programmed cell death is also a probable culprit for the heart damage sometimes caused by a widely used chemotherapy drug, according to mice studies by the same team[1].

"We knew there was a connection between the death of cardiomyocytes and several types of cardiovascular disease, but the process was a mystery," Wang says. In a review article, Wang and his colleagues argue that iron imbalance and ferroptosis is the common denominator in many types of cardiovascular disease[2].

BODY OF WORK

Wang's team has also discovered a role for ferroptosis in a hereditary iron absorption disease and liver disease[3]. Wang attributes his team's contributions to insights gained from a body of work that extends from discovering new iron metabolism genes to identifying a novel mechanism for degradation of ferroportin, the body's only way of moving iron from cells into the blood[4]. It includes collaborations with researchers at Columbia University in New York, and the University of Cambridge, UK.

More recently, the Wang team which now includes Junxia Min, a professor at the Institute of Translational Medicine at Zhejiang University, has unpacked the mechanisms that underpin ferroptosis. In the process, they have identified a slew of new drug targets for heart, liver, and kidney diseases, and cancer.

In health, ferroptosis helps eliminate cancer cells. Unlike other types of programmed cell death, ferroptosis depends on iron accumulating in a cell. That triggers the rapid generation of reactive oxygen species, which destroy cell membranes, killing the cell.

"Ferroptosis is a fundamental mechanism that is running in our body all the time," says Wang, who specializes in the impact of iron on human health (see 'Striking while iron discovery is hot' this page). That includes, it turns out, when things go wrong.

IRON OVERLOAD

In 2019, the Wang team showed that iron accumulated in the heart cells of mice following I/R injury. This iron overload triggered ferroptosis and tissue damage. Critically, when they treated the mice with drugs that inhibit ferroptosis or mop up iron, I/R injury was less severe[4].

The same set of mice studies revealed that doxorubicin, a drug used to treat common cancers such as breast and bladder cancer, increases the activity of a gene Hmox-1 in heart cells. The gene codes for an enzyme that breaks down the iron-carrying haem protein to release iron. That suggested that free iron causes doxorubicin-induced cardiac injury, says Wang. Further research from the team, suggests that the free iron probably wreaks its damage through ferroptosis.

Out-of-control ferroptosis doesn't only play havoc with heart tissue. In an earlier study, Wang, Min and their colleagues investigated a mouse stand-in for hemochromatosis, a hereditary disorder in which iron silently accumulates, damaging joints and essential organs like the heart, liver and kidneys. Often the iron overload remains undiagnosed until middle age, by which time organs are irreparably damaged, leading to pain, diabetes, heart arrhythmias and liver cirrhosis.

In the mouse stand-in for hemochromatosis, iron overload triggers liver damage through ferroptosis, Wang, Min and the team reported in 2017[5]. Their studies point to promising new targets for potential therapies.

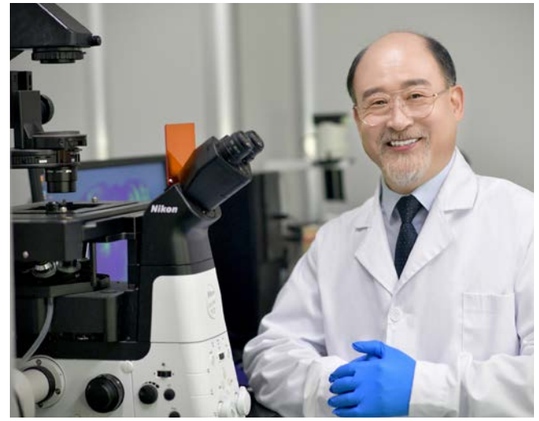
There are plenty of target leads to follow. Ferroptosis is regulated by three interconnected pathways: one involving iron accumulation, another, lipid metabolism, and the third, the antioxidant glutathione.

THREE HEROES

Harnessing the three regulatory pathways is the route to combatting dangerous ferroptosis, says Wang, comparing them to the formidable warriors in the Chinese legend 'Three heroes combating Lü Bu.' That warrior imagery made the cover of the journal *Frontiers of Medicine* in April 2023 to accompany a review article by Wang, Min and another colleague[6]. Small-molecule drugs have been designed to target ferroptosis in disease, and Wang and Min are testing these in animal and clinical studies.

"Under [Wang's] visionary leadership, we have conducted research to target iron-dependent cell death to treat disease," says Min. "Some of our research has made its way into clinical applications, such as iron-targeting drugs."

That illustrates why collaboration between basic, clinical and translational research is so critical, says Wang. "Collaboration allows us to leverage each other's strengths and accelerate basic research findings into medicines that safeguard human health." ■



▲ **Drugs that target iron-dependent cell death could help treat a range of diseases, says Fudi Wang of the University of South China in Hengyang and the Zhejiang University School of Medicine in Hangzhou, China.**

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