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GENETICS

Ironing Out an Old Problem

Genetics of Iron Mechanisms Revives Long-Dormant Field



Nancy Andrews studies the molecular biology of iron deficiency and overload disorders, such as hemochromatosis.

Led by Nancy Andrews, associate investigator of the Howard Hughes Medical Institute at Children's Hospital and HMS associate professor of pediatrics, the study is the latest in a recent flurry aimed toward a molecular understanding of how iron travels through the body.

"Things have moved so fast in the last three years," Andrews says. "I think within five years we will have a complete picture."

The long-term goal of the research is to improve diagnosis and treatment for disorders of iron metabolism. These include iron deficiencies, a group of conditions that affect up to one billion people worldwide, and iron overload diseases, such as hemochromatosis, the most common genetic disorder among whites. Hemochromatosis affects up to one in 200 Caucasian Americans, causing diabetes, impotence, arrhythmia, and liver failure if untreated--and doctors often fail to diagnose it. Moreover, researchers are realizing that iron loading is more common among African Americans than previously thought.

Prevailing thought among scientists holds that iron--an essential ingredient for making blood and generating energy--reaches all cells in the body through a molecular revolving door called the transferrin cycle. In the April *Nature Genetics*, Harvard researchers are refuting this broad dogma and defining more precisely a narrower role the transferrin cycle plays.

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Iron Revival

Iron metabolism was intensely studied in the 1950s and '60s, when the physiology of this essential but potentially toxic metal was a research focus at hematology departments nationwide, Andrews says. The work slowed down because techniques to find key genes in vivo were unavailable.

The field picked up again in 1996 when researchers discovered *Hfe*, the gene causing hemochromatosis, and in 1997 when two groups at Harvard, including Andrews's lab, discovered that another gene, *Nramp2*, is responsible for transporting dietary iron into the cells lining the small intestine (see *Focus* August 15, 1997).

Andrews began her research on iron by analyzing a legacy of the old work: strains of mice dating back to the 1920s and '30s that had defects so carefully described by hematologists that Andrews could tell they likely had mutations in iron transport genes. This work led her group to identify the intestinal iron transporter.

At the same time, it raised doubts about the current dogma regarding the transferrin cycle, whose discovery constitutes the major advance in the field during the 1980s. A central aspect of iron metabolism, the transferrin cycle begins with the transferrin receptor, a protein found on the surface of many cell types, particularly immature red blood cells. It binds iron attached to its carrier protein, transferrin, and causes receptor-studded vesicles to be pinched off inside the cell (see diagram). Iron then leaves these vesicles through the transporter *Nramp2* and enters mitochondria, which use it to make heme for hemoglobin and generate energy.

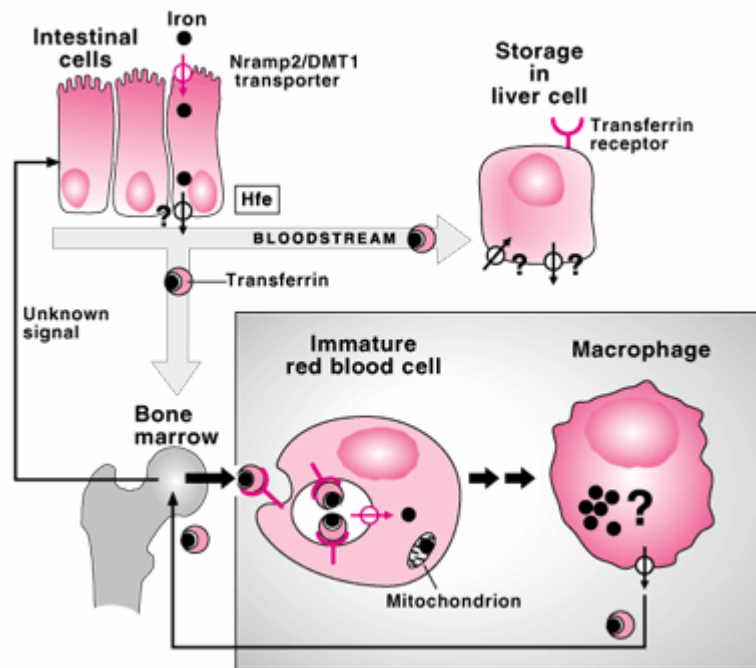


Image by Steven Moskowitz, Advanced Medical Graphics

Hoping to better understand disorders of iron metabolism, Nancy Andrews and her colleagues have created several strains of mutated mice that allow them to trace iron's path through the body. Dietary iron enters intestinal cells through the Nramp2 transporter, recently renamed DMT1. Having left the cells through a still-unknown exporter (black), iron pairs up with transferrin in the bloodstream. Some iron enters liver cells for storage, while most of it enters immature red blood cells in the bone marrow through the transferrin cycle (see story). Mitochondria then insert iron into heme, which is later turned into hemoglobin. The bone marrow somehow signals the intestine to adjust the amount of iron absorbed from food. Of the body's total iron content—about 4 grams—only 2 milligrams is absorbed from food every day, the remaining 3.998 grams are all reused iron that is recycled through the macrophages in ways not yet understood at a molecular level.

Reconsidering Iron Delivery

In the current study, Andrews and colleagues at Brigham and Women's Hospital tested whether this cycle was the major mechanism to get iron into all cells of the body, by creating mutant mice lacking the transferrin receptor.

The results confirmed their hunch that the transferrin cycle instead served the more specialized role of concentrating iron mostly in red blood cells, which need especially large amounts of the metal. Not surprisingly, embryos lacking both copies of the gene died in utero of severe anemia. Up to mid-gestation, they survived by importing iron through some other mechanism, but as they grew larger, that alternative could no longer support the demands of blood formation, Andrews says. Most other organs looked normal.

Curiously, the only exception to this was the nervous system. The scientists detected a wave of cell death in the brains of the mutant embryos at a developmental stage when no brain cells normally die. This could mean that developing neurons need so much energy that only the transferrin cycle can pump in enough iron, Andrews says. Iron is known to be important in the brain: it accumulates in neurodegenerative diseases, and iron deficiency during early years of life leads to cognitive defects.

The mice lacking only one copy of the gene had abnormally small red blood cells that contained less hemoglobin than normal—again suggesting that the transferrin cycle operates at maximal capacity during normal erythropoiesis and that half the normal number of transferrin receptors are insufficient to do the job.

Since these mice exhibit a form of anemia, the transferrin receptor gene might be mutated in some anemic people, says Andrews, who, as a pediatric hematologist, sees

patients with rare forms of this disease.

Moreover, the mutant mice showed a symptom that provides a clue to another pressing question in the field, namely, which proteins control how much dietary iron the intestine absorbs, Andrews adds. The mutant mice have low levels of total body iron, and this probably relates to the fact that the bone marrow has long been known to send a signal to the intestine, where it somehow increases the level of iron taken up from food. Andrews suspects that part of this mysterious signal may be a fragment of the transferrin receptor that is clipped off the cell surface. Without the transferrin receptor, the intestine in the mutant mice may never "know" about the lack of iron in the body's cells.

But the transferrin receptor alone does not increase intestinal iron absorption, Andrews says. Along with the transferrin receptor knockout, her team mutated in mice the human hemochromatosis gene *Hfe*. The HFE protein and the transferrin receptor protein are known to bind tightly to one another, and Andrews hopes that by crossing these different mouse strains, she will be able to sort out how that interaction determines iron uptake.

A Model for Hemochromatosis

In research soon to be published, the scientists have introduced the human hemochromatosis mutation into the mouse *Hfe* gene to compare its effect to that of completely disabling the protein. The mice carrying the human mutation showed a mild iron overload phenotype that resembles the situation in humans with the disease, taking up about three times the normal amount of dietary iron. Interestingly, the human mutation--which probably arose in a seventh century Celt and has spread wherever Celtic people have migrated--may have survived because its phenotype of increased iron uptake would have been an advantage in times when iron-rich food was scarce and life expectancy was low. In Ireland, one in 64 people has the disease.

If the current treatment for hemochromatosis--bloodletting--strikes you as worthy of the Iron Age, you are not alone. Though the method is cheap and effective, patients hate having a needle stuck in their arms every month, Andrews says. Ultimately, knowing the molecular biology underlying this and other iron diseases should lead to more modern treatments.

--*Gabrielle Strobel*

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