Profile of Nancy C. Andrews

Jennifer Viegas, *Science Writer*

Nancy Andrews says, "I like having big questions to attack." Over the last two decades, she has studied mammalian iron homeostasis and human iron diseases, for which her team has identified many associated genetic mutations. Her laboratory created more than 30 mouse models of iron-related diseases and pathways, including a model that elucidates the role of iron in neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's diseases. Elected to the National Academy of Sciences in 2015, Andrews is the first woman to be appointed dean of the Duke University School of Medicine. She is also vice chancellor for academic affairs at Duke, where she holds the Nanaline H. Duke Professor of Pediatrics chair and is a professor of pharmacology and cancer biology.

Portrait of Nancy Andrews. Image courtesy of Duke University School of Medicine.

First Doctor and Scientist in Her Family

Andrews grew up in Syracuse, New York. Her father was a lawyer dedicated to working for the underserved. Her mother was a social worker. Andrews says, "There weren't any doctors or scientists in my family. My parents made me feel like I could do anything I wanted to do, even though options for women were more limited when I was young." From an early age she enjoyed math and using logic and information to solve puzzles and support arguments. Science came easily to her, and she was invited to work in a laboratory at Syracuse University while she was still in high school.

Andrews chose Yale University for her undergraduate studies. There she met Joan Steitz, a professor of molecular biophysics and biochemistry who became a mentor. While she was earning her bachelor's degree in molecular biophysics and biochemistry, Andrews worked in Steitz's laboratory. She entered Harvard Medical School in 1980 and, in her second year of medical school, went to the Massachusetts Institute of Technology (MIT) to work toward her PhD. She spent more than three years in the laboratory of David Baltimore, her dissertation advisor. For much of that time, Baltimore's laboratory was located on the fifth floor of the MIT Cancer Center, where Andrews worked alongside Nobel laureates, such as Phillip Sharp and Andrew Fire.

After MIT, Andrews returned to Harvard Medical School, where she earned her MD degree in 1987. After pediatrics residency and clinical fellowship training, she spent almost three years working with Stuart Orkin. Andrews says, "He was a great role model as a pediatric hematologist and basic scientist whose work was always impeccable, impactful, and of the highest quality." Mentor David Nathan, chairman of pediatrics at Children's Hospital Boston, had encouraged Andrews to work in pediatrics, which she did for many years, leading to several positions, including endowed chairs at Harvard Medical School.

Genes and Hormones in Iron Diseases

While at Harvard, Andrews developed a specialty in using both mouse and human genetics to study iron transport. She says, "I chose iron to work on because very little was known about how iron was handled in mammals. Also, iron diseases are common, and iron biology gave me a way to connect my clinical work with my lab work." In 1997, she and her colleagues identified the gene mutated in microcytic mutant mice; the gene mutant *Nramp2* is now called divalent metal transporter 1 or *Slc11a2* (1). The mutation causes a defect in intestinal iron transport. The following year, Andrews and her colleagues determined by genetic mapping that the same mutation is carried by anemic Belgrade rats, which are rodent models studied for their failure to assimilate iron in red blood cell precursors (2).

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 3428 in issue 13 of volume 113.

In 1999, Andrews and her team disrupted the gene encoding the primary transferrin receptor, which is a cell surface molecule that assists in iron uptake (3). The researchers showed that embryos lacking the transferrin receptor Tfr1 could develop through midgestation, but that they were severely anemic. Andrews says, "We concluded that the transferrin receptor is essential for erythropoiesis (production of red blood cells) but not for formation of many other structures and tissues."

As a hematologist, Andrews cared for patients with the rare metabolic disorder glycogen storage disease type 1a (GSD1a), which can cause benign liver tumors and anemia. While trying to understand why the tumors, called adenomas, might be associated with or cause anemia, Andrews and her team discovered that adenomas produce high levels of mRNA for hepcidin, a key iron regulatory hormone (4). The finding both explained anemia in the GSD1a patients and suggested that inappropriately high expression of hepcidin might account for most, or all, features associated with the anemia of chronic diseases in general. Andrews says, "At that time the pathophysiology of the anemia of chronic disease had not been worked out. All that was known was that it was very common in the setting of infection, inflammation, cancer or organ failure. Our hypothesis—that increased hepcidin caused anemia of chronic disease—has subsequently been confirmed by us and others." A later study showed that Tfr1 normally acts to sequester a protein, HFE, which can signal to promote hepcidin expression (5).

Andrews credits Joseph Martin, who served as dean of the Harvard Faculty of Medicine from 1997 to 2007, as a mentor. She says, "I learned much about how to be a dean from watching and interacting with Joe, and it served me well when I became dean of the School of Medicine at Duke." Andrews accepted that position in 2007, along with her professorships at Duke. The previous year she was elected to the Institute of Medicine (now the National Academy of Medicine) and as a fellow of the American Association for the Advancement of Science. In 2007, she was also elected fellow of the American Academy of Arts and Sciences. Three years later she received the Vanderbilt Prize in Biomedical Science.

Andrews moved her research laboratory to Duke in early 2008. Both at Duke and in her prior work she had seen patients with congenital iron deficiency anemia with autosomal recessive inheritance. After studying the genes of these individuals, she and her colleagues identified *Tmprss6* as the gene in which mutations causing the anemia occur (6). They named the clinical disorder IRIDA for iron-refractory iron deficiency anemia. Her team later determined that *Tmprss6* acts upstream on the same pathway as genes for the blood protein hemojuvelin (7), which plays an essential role in the regulation of hepcidin expression.

Iron Deficiency in Neurodegenerative Diseases

It has been known for almost a century that excess iron accumulates in specific parts of the brains of individuals with neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Huntington's diseases, but whether the iron was a cause or result of neurodegeneration was unclear. Some investigators have proposed that excess iron in neurons could kill nerve cells and cause disease. Andrews says, "I've spent more than 20 years studying how cells and tissues handle iron, and some of the prevailing hypotheses about neurodegeneration didn't make sense to me."

For her Inaugural Article, she and her team used mutant mice to examine how changes in iron status affect dopaminergic neurons, which are affected in Parkinson's disease (8). The results were surprising and suggested that neuronal iron deficiency, rather than neuronal iron overload, might contribute to neurodegeneration. Andrews says, "It's possible to have too much iron in the vicinity of the affected neurons, yet still have iron deficiency in the neurons themselves, and that's what we think might be happening in Parkinson's disease. It's even possible to have too much iron in the neurons, but have it not be available for vital neuronal functions."

Training and Career Development of Physician-Scientists

Andrews has long been recognized not only for her contributions to the field of iron metabolism but also for her mentoring of junior scientists. She has received many related awards, including the 2011 Mentor Award for Basic Science from the American Society of Hematology. Her enthusiasm for science has had a positive impact on her home life, too. Her husband is a professor of pharmacology and cancer biology at Duke, where he is also a professor of pediatrics. Their two children are interested in science and following in the footsteps of their mother by pursuing careers in medicine.

Andrews recently closed her laboratory at Duke. She cites several reasons, including a desire to make more time for work with organizations outside Duke to promote science and scientific careers. In addition, Andrews says, "It was hard for me to justify continuing to seek grant funding when young people were struggling to get started. And it has become much harder to get funding for the kind of adventurous science I enjoy most. I may re-open a lab later, after I've finished in administration or, perhaps more likely, I would love to help a younger person get going with their science, maybe working at the bench and certainly helping to mentor, contribute ideas, share my experience. That's just a fantasy for now, but I hope someday I'll be back in the lab."

1 Fleming MD, et al. (1997) Microcytic anaemia mice have a mutation in Nramp2, a candidate iron transporter gene. *Nat Genet* 16(4): 383–386.

2 Fleming MD, et al. (1998) Nramp2 is mutated in the anemic Belgrade (b) rat: Evidence of a role for Nramp2 in endosomal iron transport. *Proc Natl Acad Sci USA* 95(3):1148–1153.

3 Levy JE, Jin O, Fujiwara Y, Kuo F, Andrews NC (1999) Transferrin receptor is necessary for development of erythrocytes and the nervous system. *Nat Genet* 21(4):396–399.

4 Weinstein DA, et al. (2002) Inappropriate expression of hepcidin is associated with iron refractory anemia: Implications for the anemia of chronic disease. *Blood* 100(10):3776–3781.
5 Schmidt PJ, Toran PT, Giannetti AM, Bjorkman PJ, Andrews NC (2008) The transferrin receptor modulates Hfe-dependent regulation of hepcidin expression. *Cell Metab* 7(3):205–214.
6 Finberg KE, et al. (2008) Mutations in TMPRSS6 cause iron-refractory iron deficiency anemia (IRIDA). *Nat Genet* 40(5):569–571.
7 Finberg KE, Whittlesey RL, Fleming MD, Andrews NC (2010) Down-regulation of Bmp/Smad signaling by Tmprss6 is required for maintenance of systemic iron homeostasis. *Blood* 115(18):3817–3826.
8 Matak P, et al. (2016) Disrupted iron homeostasis causes dopaminergic neurodegeneration in mice. *Proc Natl Acad Sci USA* 113(13): 3428–3435.