How cell structure can lead to health issues

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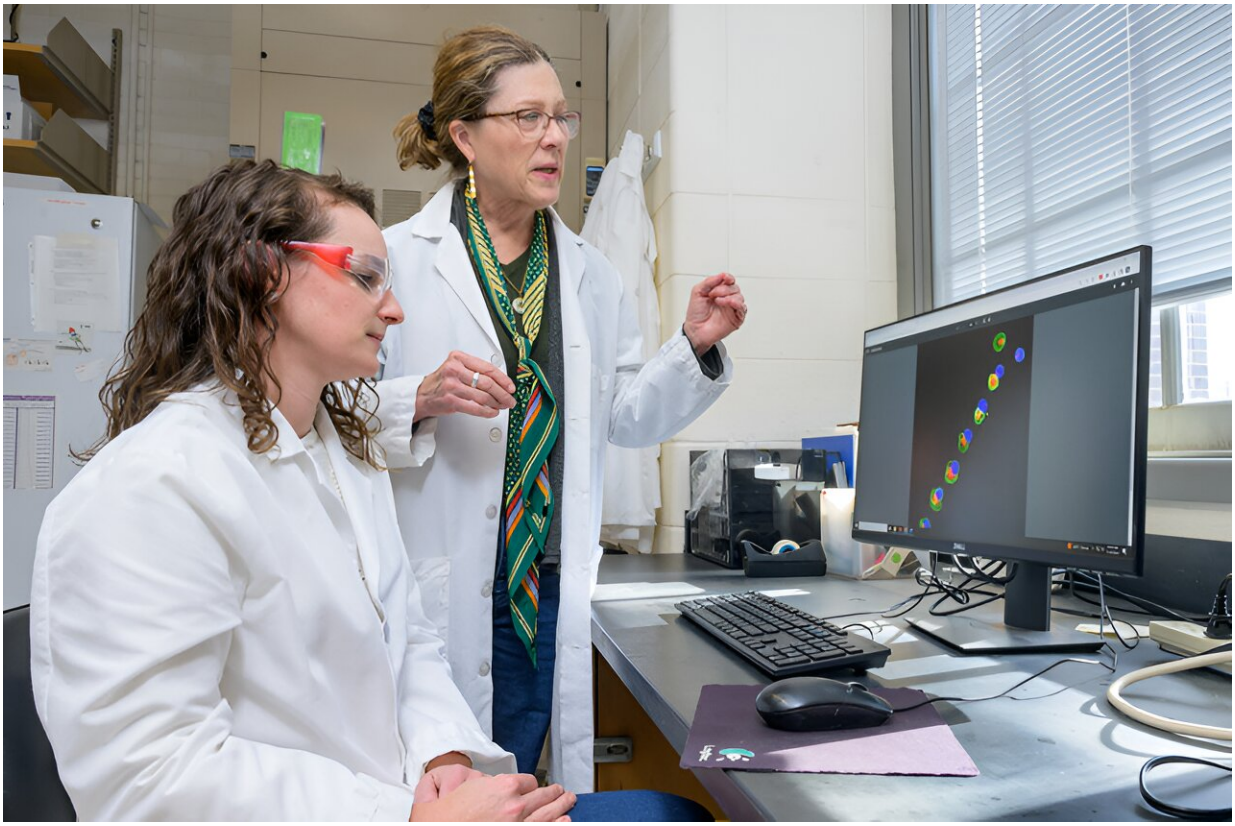

Velia Fowler (standing), chair of the Department of Biological Sciences and pioneering researcher in the architecture of cells, examines F-actin and other proteins in the structure of red blood cells with lab manager Megan Coffin. Fowler has shown that dysregulation of F-actin can contribute to a wide range of health issues, including blood disorders, cataracts and osteoarthritis. Credit: University of Delaware

Human bodies make 2 million red blood cells per second. They each live for 120 days and spend that time zooming completely around the body every 20 seconds, carrying oxygen from the lungs to other tissues and bringing back carbon dioxide that is exhaled.

Velia M. Fowler, professor and chair of the Department of Biological Sciences at the University of Delaware, can tell you almost everything about the architecture of those cells.

The disk-shaped cells have two dimples, one on each side, and are perfectly symmetric when at rest. In the blood stream, they flexibly deform and fold to squeeze through narrow capillaries smaller than they are, returning to their original biconcave shape when they emerge.

"I always liked the red cell shape because it's just so beautiful," Fowler said. "I always wanted to figure out how it worked."

Fowler's lab at UD studies cell architecture and how each cell's interior structural scaffolding creates its unique shape, mechanical strength and physiological functions. This scaffolding is made of a protein called actin, which assembles into filaments (F-actin) that resemble a helical strand of beads. Unlike the structural scaffoldings in buildings, the F-actin in cells is dynamic, with actin subunits, "beads," coming on and off the filament ends every second.

F-actin is a key regulator of cellular architecture and how appropriate cellular forms support cellular functions, according to Fowler. Dysregulation of F-actin can lead to changes in cell shapes and biomechanics, which can contribute to a range of diseases including blood disorders, immunodeficiencies, muscle myopathies, cataracts, presbyopia, osteoporosis, osteoarthritis and tendinosis.

The lab studies how the dynamic F-actin scaffolding creates particular

cell shapes and how this contributes to normal cell function or dysfunction. The research is focused on red blood cells, the cells in the ocular lens and cells in the musculoskeletal system.

"We're trying to understand the locations of F-actin structures [inside the cells], their dynamic organizations, shapes and the gradients of concentration, and how they contribute to cell functions. I just love that interplay," Fowler said.

Fowler and her team are examining two different aspects of F-actin in red blood cells: how the red blood cell precursors rearrange their F-actin to get rid of their nucleus, enabling the mature cells to circulate many times through the tiny capillaries; and how F-actin assembles into a thin network at the membrane (skin) of the cell and interacts with a motor protein called myosin to control cell shape and flexibility.

The work with the ocular lens studies how F-actin structures in lens cells contribute to lens transparency and focusing for vision. The research in bone, cartilage and tendon cells examines how F-actin structures are maintained to prevent problems in the musculoskeletal system. The latter work is done with the Delaware Center for Musculoskeletal Research Center.

The broad impact of F-actin in cells was one of the reasons biomedical engineering doctoral student Heather Malino joined Fowler's lab. She was attracted to the foundational aspect of the research, rather than specializing in practical solutions to health problems like prosthetics.

"Learning about the fundamental biological phenomenon that happens can be really rewarding because you're looking at the cellular and molecular processes," she said. "You find out something about the lens, but cells are cells. So things that we learned about the lens, can also be more overarching to different processes in the body."

Building on the past

The work builds on groundbreaking discoveries related to the F-actin network that Fowler has made throughout her 40-year career. As a post-doctoral fellow Fowler was the first to discover myosin in red blood cells. Without myosin motors pulling on F-actin networks to create tension, the red blood cell precursors would not be able to generate enough force to expel their nucleus, and the mature cells would not be able to withstand the repetitive cycles of deformation, folding and unfolding required during their lifespan.

She also discovered a previously unknown protein called tropomodulin. Tropomodulin stops the ends of the F-actin from growing or shrinking, stabilizing them at a certain length. When the filaments are the same length, the networks they create when binding to other proteins in various types of cells are stronger and more stable. If the filaments are different lengths, the networks are irregular and mechanically weaker, and cell shapes are abnormal.

Fowler showed that tropomodulin's function is critical for development of the heart and blood cells, and for proper function of many cells and tissues, including eye lens, neurons in the brain, epithelial cells lining the gut, endothelial cells lining blood vessels, as well as platelets, red blood cells. It is required for efficient muscle contraction in both skeletal and cardiac muscles.

"I started with a molecule that had a function in one tissue, and I thought the function had to happen in these other tissues," she said. "I connected the dots."

Recently, Fowler was part of a team that discovered that a mutation in the tropomodulin proteins which prevents the protein from functioning properly causes a severe inherited cardiomyopathy in children. This is

the first time the protein's function has been directly linked to heart disease in humans. The research was published in the journal *Communications Biology*.

Fowler was recently recognized as a 2023 Lifetime Fellow of the American Society of Cell Biologists (ASCB), partly for her work on tropomodulin. She is one of 19 scientists from around the world to receive the honor this year. The society includes the top researchers in the field and counts several Nobel Prize winners as members.

"Dr. Fowler has advanced our understanding of fundamental questions in cell biology," Jia Song, associate professor of biological sciences, said in her letter nominating Fowler for the award. "Her groundbreaking work, published in more than 140 research articles, has significantly advanced our understanding of actin cytoskeletal function in architecture and behavior of diverse cells."

More information: Catalina Vasilescu et al, Recessive TMOD1 mutation causes childhood cardiomyopathy, *Communications Biology* (2024). DOI: 10.1038/s42003-023-05670-9

Provided by University of Delaware