

One collagen shipment, ready for delivery

An ER membrane protein helps load collagen into vesicles.

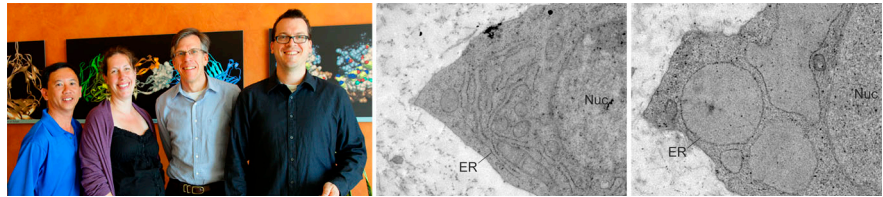
A factory needs a good distribution pipeline for its products, and so does a cell that manufactures collagen. Wilson et al. (1) describe a protein that helps pack several varieties of collagen into vesicles so they can be shipped from the cell.

Collagen was one of the first proteins identified, but researchers are still trying to elucidate the mechanics of its secretion. After their synthesis in the ER, individual collagen molecules interweave to form a trimer (2) and then travel to the Golgi apparatus for further modification. One mystery is how a stiff collagen trimer that is more than 300 nm long could cram into the standard COPII-coated vesicles—which are only about 60 nm to 80 nm in diameter—that ferry cargo from the ER to the Golgi (3). Researchers surmise that cells deploy capacious vesicles that can accommodate collagen trimers, but they haven't spotted these carriers in vivo.

A further mystery is what shepherds collagen into transport vesicles. A previous study (4) suggested that the protein Mia3 performs the job for collagen VII, one of the more than 20 varieties of the extracellular matrix protein. However, the work suggested that Mia3 doesn't load another version of the protein, collagen I.

To find out more about Mia3's function, Wilson et al. deleted the gene from mice. The animals died at birth, and their stunted skeleton and fragile skin pointed to faulty collagen secretion. Wilson et al. discovered that cartilage formation in the animals' bones was tardy and that chondrocytes, cells specialized to synthesize cartilage, were slow to mature. As a result of these and other defects, the skeleton failed to mineralize.

The consequences of losing Mia3 went beyond the skeleton. Collagen built up in cells throughout the animals' bodies, the researchers found. Electron microscopy vividly portrayed the secretory stagnation. The ER in chondrocytes was bloated, presumably jam-packed with collagen.



FOCAL POINT
(Left to right) Khanhky Phamluong, Deanna Wilson, Andrew Peterson, Mark Solloway, and colleagues (not shown) took a closer look at how the protein Mia3 helps export collagen from cells. Compared with the endoplasmic reticulum in a cell from a normal mouse (center), the ER in a cell from a mouse lacking Mia3 is bloated (right). The researchers think that without Mia3's assistance collagen piles up inside the ER.

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Cells from the Mia3 knockout mice failed to export not only collagen VII but at least five other collagen varieties—including collagen I—that span several classes of the protein. The collagen buildup also spurred cells to activate the unfolded protein response, a stress reaction that kicks in when misfolded proteins accumulate in the ER.

“Mia3 is clearly a facilitator of collagen processing in the ER,” says senior author Mark Solloway. The protein is in the right place and has the right structure to help bundle collagen into vesicles for shipment to the Golgi. Mia3 spans the ER membrane, and one end of the protein hooks onto collagen, whereas the other end attaches to the COPII coat of a cargo-ready vesicle. The work suggests that Mia3 is not a specialist and loads multiple collagen varieties.

Several questions about Mia3 remain unanswered. The researchers found that secretion of two large extracellular matrix (ECM) proteins, aggrecan and fibronectin, was normal in the knockout mice. Whether Mia3 helps the ER ship other large proteins is uncertain. “The next hurdle will be to define the full repertoire of targets,” says Solloway. Another lingering question is whether the protein works alone.

Cells from the knockout mice managed to extrude some collagen, suggesting that there may be additional collagen export mechanisms.

The health impact of changes in Mia3 levels also remains unclear. Although studies have found that cells in several cancer types turn down Mia3 production, the protein's function in tumors—and whether that role involves collagen secretion—is murky. In addition, recent studies linked several polymorphisms in the Mia3

gene to an increased risk of heart attack. Collagen forms much of the cap of an atherosclerotic plaque. By reducing collagen secretion, these Mia3 variants might weaken the cap, causing it to fracture and trigger a heart attack.

Alternatively, collagen-rich tissues, including the blood vessels, may be prone to cellular stress if secretion is impaired.

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