Molecular muscle: Small parts of a big protein play key roles in building tissues

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Wing To is a postdoctoral research associate at the Kennedy Institute of Rheumatology at Imperial College. Credit: Journal of Biological Chemistry

We all know the adage: A little bit of a good thing can go a long way. Now researchers in London are reporting that might also be true for a large protein associated with wound healing.

The team at the Kennedy Institute of Rheumatology at Imperial College reports in the Journal of Biological Chemistry that a protein generated when the body is under stress, such as in cases of physical trauma or

disease, can affect how the protective housing that surrounds each cell develops. What's more, they say, tiny pieces of that protein may one day prove useful in preventing the spread of tumors or fibrosis.

At just 174 nanometers in diameter, tenascin-C is pretty big in the world of proteins, and it looks a lot like a spider with six legs, which are about 10 times longer than its body. Thanks to those long legs, tenascin-C can do real heavy lifting when it comes to wound healing.

"Tenascin-C plays many roles in the response to tissue injury, including, first of all, initiating an immune response and, later, ensuring proper tissue rebuilding," explains Kim Midwood, who oversaw the project.

When the injury alarm is rung, tenascin-C shows up on the scene and attaches to another protein, fibronectin. Together, tenascin-C and fibronectin help to construct the housing, or extracellular matrix, that surrounds each cell.

"The extracellular matrix is the home in which the cells of your body reside: It provides shelter and nutrients and also sends signals to the cell to tell it how to behave," says Midwood. "To make a finished tissue, the matrix must be carefully built."

Tenascin-C's job is a temporary one. When your hand is cut, for example, it appears at the edges of the wound and then goes away when scar tissue develops, says postdoctoral research associate Wing To: "Tenascin-C is thought to play a major role during the rebuilding phase of tissue injury by promoting regeneration of tissue that has been damaged."

If the extracellular matrix were a construction site, tenascin-C could be seen as the scaffold upon which the weaving of fibronectin threads, or fibrils, is done. "Tenascin-C has multiple arms, and we have shown that

it has multiple binding sites for fibronectin," Midwood says. "In this way, it can bind to many fibronectin fibrils at once and help to form the whole tissue by linking the fibrils together. Then, when the repair is done, the scaffolding is taken down."

Midwood and To systematically determined where tenascin-C and fibronectin bind together. They also identified small parts of tenascin-C, known as domains, that can bind to only one fibronectin fibril apiece.

"The small domains act as caps of the scaffold. No more fibronectin fibrils can bind once these caps are in place," Midwood says. So, in essence, they found that certain pieces of tenascin-C determine when fibril building should stop once enough, but not too much, tissue is made.

The findings could be especially useful for creating therapies for conditions in which there is aberrant extracellular matrix deposition, such as in cancers, fibrotic conditions or chronic non-healing wounds, adds To.

In abnormal conditions, such as in the case of a tumor cell, "the home that's made of fibronectin helps it to survive, shelters it and provides signals that enable it to proliferate," says Midwood. "As the tumor thrives, the home keeps on growing, expanding to destroy the existing neighborhood."

Similarly, in fibrotic diseases, tissue rebuilding rages out of control – with too much fibronectin assembly – so that it takes over the whole affected organ, Midwood says.

"In the end, we found that tenascin-C has both stop and go functions cleverly concealed in the same molecule," Midwood says. "The large spiderlike protein may provide a scaffold for building, and the small

domains of the protein block excess building. Small domains may be therapeutically useful in situations where too much fibronectin drives disease."

If certain domains can stop uncontrolled matrix deposition in conditions where there is an increase in unwanted extracellular matrix, such as in fibrosis, then they could be useful tools for controlling such diseases.

Meanwhile, To says, in conditions with high levels of tenascin-C degradation by enzymes, for example in nonhealing chronic wounds, that may expose active tenascin-C domains, "if we can stop the production of these domains during disease progression with specific inhibitors, maybe we could help ameliorate the condition.

Similarly we could try and get the cells to make tenascin-C variants that are not as easily broken down by enzymes to help facilitate wound healing."

More information: Midwood and To's paper was named a "Paper of the Week" by the *Journal of Biological Chemistry*.

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