Exposing collagen's double life

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MIT associate professor Collin Stultz, a cardiologist and biomedical engineer, studies the structure of collagen. Photo: Patrick Gillooly

(PhysOrg.com) -- Collagen, a type of connective tissue that makes up about 30 percent of the human body, plays many roles. The structural protein is an important component of muscle, skin, bones and cartilage, and forms scar tissue when injuries heal.

However, it's one of collagen's lesser-known functions that piqued the interest of MIT associate professor Collin Stultz, a cardiologist and biomedical engineer, several years ago. When cholesterol builds up in the arteries, giving rise to plaques, collagen forms a protective layer that envelops the plaques. If collagen fails to hold the plaques together, they burst, spilling out cholesterol, other fatty molecules, and blood-clotting

agents — usually with disastrous consequences.

“Catastrophic heart attacks — the kind where you’re walking down the street, or watching TV, and then keel over and die — are most often associated with a rupture of the collagen layer,” says Stultz, the W.M. Keck Associate Professor of Biomedical Engineering.

Understanding how collagen breaks down could help scientists develop new treatments for atherosclerosis and other diseases that involve collagen, such as arthritis. Over the past eight years, Stultz has published a series of papers that have helped transform the prevailing theories on collagen, which has traditionally been thought of as a rigid, rope-like molecule.

In his most recent paper, published online in the journal *Biochemistry* last month, Stultz and his colleagues showed that, depending on the temperature, collagen can switch between its usual rigid structure and a much floppier, more flexible shape — a finding that collagen researcher Barbara Brodsky of Robert Wood Johnson Medical School described as “intriguing.”

“The concept of multiple conformations is a big contribution to our thinking,” says Brodsky, who was not involved in the study.

A better fit

For the past couple of decades, scientists have been trying to figure out the relationship between collagen and the enzymes, known as collagenases, that break it down in the body. Because collagen is a critical component of so many structural elements, such as bone and skin, its degradation is very carefully controlled.

Structural studies that require crystallizing the protein (a common

technique also used to reveal the double helix structure of DNA) showed that collagen is a tightly wound triple helix. However, that structure puzzled scientists because it offers no access for collagenase enzymes to bind to and break down the protein. “If you just look at the structures, you would say collagen should never be broken up by these enzymes,” says Stultz.

Stultz suspected that the low temperatures (10 degrees Celsius) required to crystallize collagen in those studies might be masking some aspect of the protein’s true structure. He did computer modeling that suggested higher temperatures, such as room or body temperature, allow some sections of the collagen molecule to unwind, becoming floppy. That structure also opens up a site that fits collagenase perfectly, allowing it to break down the protein.

“We think of collagen as being a very rigid molecule, while in practice there may be regions of collagen that are very floppy and loose,” says Stultz.

To test this idea experimentally, Stultz and paper co-authors Ramon Salsas-Escat, a graduate student, and Paul Nerenberg, a recent PhD recipient, exposed room-temperature collagen to a mutated form of collagenase that only recognizes unfolded collagen. Previous studies had shown no degradation under these conditions, but Stultz and his colleagues waited longer (up to six days), and found that some of the collagen was broken down.

They also found that the percentage of floppy collagen molecules at any given time depends on the temperature. At room temperature, about one in 1,000 are floppy, and the number should be higher at body temperature.

Over the past couple of decades, researchers have tried to develop drugs

that inhibit collagenase enzymes, to prevent arterial plaques from rupturing, but no such drugs have been approved. Stultz's new findings raise the possibility of targeting the collagen itself, rather than the enzyme. That is, they could try to make collagen more rigid, so it won't be susceptible to collagenase degradation.

Stultz is now screening computer databases for small molecules that could stabilize collagen in its tightly wound state, which could also help preserve collagen in arthritic joints. Such drugs may also have an impact on cancer metastasis, because tumor cells must break down collagen in the basement membrane (which lines the surfaces of organs and blood vessels) before they can spread through the body.

More information: Paper: pubs.acs.org/doi/full/10.1021/bi9021473

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