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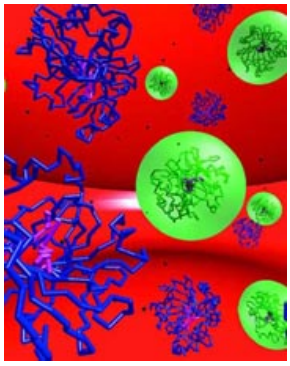

Understanding Complications of Diabetes on the Smallest Scale May Point to New Treatments

ARLINGTON, Va., April 14, 2004 -- Biomedical engineers are beginning to understand some of the basic mechanisms underlying many of the complications of diabetes. The research may lead to new treatment strategies.

By combining atomic level imaging with computer modeling, researchers at the University of Michigan are building a comprehensive picture of how too much sugar in the bloodstream wreaks havoc upon collagen, a basic building block of many structures in the human body.

Collagen destruction underlies a wide range of diabetic complications ranging from kidney damage to the erosion of nerves serving the legs and feet to blood vessel disease.

All of these complications seem to stem from a common underlying reaction of proteins and lipids with the sugar molecules that should have been ferried out of the bloodstream. These excess sugars glue themselves to proteins, forming advanced glycation end products (AGEs). There may be dozens of AGEs, but only the few have been identified.

An immediate goal in this line of research is to identify AGEs and determine their role in specific disease complications. Whitaker investigator Ann Marie Sastry, Ph.D., of the University of Michigan is leading a group that is investigating AGEs using advanced imaging and computer modeling techniques.

A prime target of AGEs is collagen, one of the most abundant and vital structural proteins in the human body. Comprising more than 25 percent of the body's total protein mass, collagen is an extremely sticky and long-lasting molecule that is highly susceptible to AGE binding. This causes collagen molecules to become irretrievably entangled in a process called cross-linking, which stiffens tissues that are supposed to be flexible or elastic, wreaking havoc on blood vessels, retinas, kidneys and nerves.

"And therein likes the problem," says Sastry, an associate professor of mechanical and biomedical engineering. "There are dozens of possible culprit AGEs and multiple pathways for their synthesis, both enzymatic and nonenzymatic, but only a small fraction of these molecules can be imaged using traditional approaches.

"Meanwhile, the damage is cumulative in the most important structural proteins. So as engineers and computational mechanicians, we take a pragmatic, mathematical approach: We're trying to develop ways to disable the gun, instead of tracking each and every bullet."

Sastry's group is using atomic force microscopy on proteins to allow rapid imaging of individual threads of collagen, clearly revealing their molecular alterations when thickened by AGE binding. Her team has also developed computer simulation techniques to characterize the effects of AGE-related damage to collagen in diabetes. Her work demonstrates that in the disease, fine threads of collagen become enlarged and more plentiful, and they form cross-links. Together these changes rob collagen of its flexibility.

Working with Eva Feldman, M.D., Ph.D., professor of neurology at the University of Michigan, Sastry has found that collagen cross-linking has a different effect on the mechanical properties of different tissues, such as nerve and skin.

"And now we can predict how structural properties of collagens change with glycation and how these changes at the molecular level translate into alterations at the tissue level," Sastry says. "This knowledge gives us some new targets to try to interrupt the cycle of

damage."

In related research, Sastry and Christian Lastoskie, Ph.D., associate professor of civil and environmental and biomedical engineering at Michigan, are studying the receptor for advanced glycation end products (RAGE). These receptors act as docking sites for AGEs at the cellular level. The attachment of AGEs on these receptors sets off a cascade of signals inside the cell, resulting in a number of specific effects. These include increasing the production of growth factors, triggering the cell death cycle, and stimulating growth in the matrix between cells.

One possible target for breaking the cycle of tissue destruction in diabetes would be to prevent AGEs from binding to cells altogether. But this can only be achieved by knowing more about RAGE: the number of sites, how they function, and how their biochemistry is altered when they interlock with AGEs.

Toward that end, Sastry's lab is contributing data and simulations that Lastoskie's group is using to determine how many RAGEs are present in nerve and other cells and where they are located on the cell surface. Lastoskie is also at work to determine the crystal structure of RAGE, which would give both groups potential targets for successfully interrupting the docking of AGEs.

Sastry received a Whitaker Foundation Biomedical Engineering Research Grant in 1998 for modeling peripheral nerve damage in diabetic neuropathy.

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