New insights into cause of diabetes emerge from U-M research

April 30 2008

University of Michigan researchers have new clues to what goes awry at the cellular level in type 2 diabetes.

Their results, published in this week's issue of the *Journal of the American Chemical Society (JACS)*, challenge conventional views of how the disease is initiated and may lead to development of drugs to treat aging-related diseases, as well as diabetes.

One of the most striking hallmarks of type 2 diabetes is the presence of clumped protein fibers called amyloids in the insulin-producing cells of the pancreas. Previous research has suggested that amyloid formation somehow damages the membranes surrounding those cells, killing the cells and precipitating diabetes.

But associate professor of chemistry and biophysics Ayyalusamy Ramamoorthy and co-workers show in the new study that membrane damage can occur independently of amyloid formation and that the protein involved, known as Islet Amyloid Polypeptide Protein (IAPP), has separate regions responsible for amyloid formation and membrane disruption.

"It was already known that amyloid fibers themselves are not especially harmful to cells, but it was thought that the process of amyloid formation might generate toxic intermediates that caused membrane damage. This issue has been the subject of active debate," Ramamoorthy said.

By breaking off one end of the protein and testing the resulting fragment's properties, the U-M group learned that the fragment can disrupt membranes and cause cell death as effectively as the full-length protein, without forming amyloids.

Then, comparing the human form of the IAPP with the rat version, which does not cause cell death, the researchers found that a difference of a single amino acid (protein building block) accounts for the toxicity. In conjunction with chemistry and pharmacology professor Robert T. Kennedy, Ramamoorthy is now studying the protein in living cells and obtaining the same results as with the model cell membranes used in the recent JACS paper.

Although IAPP is believed to contribute to the development of type 2 diabetes, drugs to suppress the role of IAPP in diabetes have not yet been developed, mainly because the molecular mechanism by which IAPP becomes toxic has been a mystery. In addition, the presence of toxic and non-toxic forms of the same protein in human body considerably complicates the discovery of what makes the protein toxic.

"Interestingly, this is exactly the same problem that has been limiting research progress in discovering drugs to treat other devastating aging-related amyloid diseases like Alzheimer's, Parkinson's, Huntington's and mad cow disease," Ramamoorthy said. "Our key finding of a version of the protein that exists in only one stable toxic form considerably simplifies the search for compounds to prevent these diseases."

Next, the researchers plan to use atomic-level molecular imaging solid-state NMR techniques to make nanoscopic movies to further elucidate the causes of type 2 diabetes. In addition, they plan to explore how changes in cell membrane molecules with age contribute to the development of aging-related diseases.

Source: University of Michigan