New look identifies crucial clumping of diabetes-causing proteins

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(Medical Xpress)—People get type 2 diabetes. So do cats. But rats don't, and neither do dogs. Subtle differences in the shape of proteins protect some and endanger others.

"All mammals make this same protein called amylin, and it only differs a little bit from species to species," says Martin Zanni, a UW–Madison chemistry professor. "The mammals that get type 2 diabetes, their amylin proteins aggregate in the pancreas into plaque that kills the cells around them. As a result, you can't make insulin."

Without insulin, hungry cells can't tap sugar in the bloodstream for energy, and high blood sugar levels cause type 2 diabetes and its complications—stroke, nerve damage and kidney disease among them.

Animal species that don't get type 2 diabetes find a way to keep plaque from forming in their pancreas and disrupting insulin production. Describing how their amylin proteins differ may provide a target for new treatments for diabetes and other plaque-involved disease such as Alzheimer's and Parkinson's.

A study published today by Zanni and collaborators in the *Proceedings of the National Academy of Sciences* paints that target on small clumps of mis-folding proteins in the middle of the plaque formation process.

"For about 30 years, we thought this problem was solved, because a lot of experiments pointed to the middle part of amylin molecules as the

cause," Zanni says.

Named for its amino acid structure, the FGAIL regions of amylin proteins were believed to lock together—"like boards in a wood floor," Zanni says—into rigid sheets. The sheets, called beta-sheets, break apart, forming the dangerous plaque.

But experiments published in 2007 showed that the FGAIL section of amylin is floppy and loose, like a loop of rope.

"This result made no sense compared to the 30 years of prior studies," Zanni says. "Why should the small differences in the amylin protein of various mammals play such a deciding role if those differences are located in a flexible, floppy and forgiving region of the protein?"

Zanni and collaborators showed that the floppy FGAIL region can contribute to the formation of plaque, but first, the amylin proteins must clump together in an arrangement in which the FGAIL region is indeed a rigid beta-sheet.

"That 30-year-old hypothesis is partly correct: the FGAIL region does indeed form the beta-sheets, but only for a little while until those sheets are broken to make the flexible loop," Zanni says.

The intermediate clumping step is where animal species resistant to type 2 diabetes are making their move.

"Our results indicate that the proteins in rats, dogs and other animals do not stop the plaques themselves, but instead target this upstream step," Zanni says, "preventing the intermediate from forming and thereby the plaques as well."

Using a technique called two-dimensional infrared spectroscopy

developed in Zanni's lab, the new study—which included collaborators at the University of California, Irvine, University of Chicago, Argonne National Lab and State University of New York at Stony Brook—provides the first picture containing specific details of what the intermediate clumps look like.

"Good drugs work by fitting into nooks and crannies," says Zanni, whose work is funded by the National Institutes of Health. "Thus, it is much easier to design a drug when the shape of the toxic protein is known, which is what our data is beginning to provide."

More information: Mechanism of IAPP amyloid fibril formation involves an intermediate with a transient β-sheet, www.pnas.org/cgi/doi/10.1073/pnas.1314481110

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