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Preventing diabetes damage: Zinc's effects on a kinky, two-faced cohort

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In type 2 diabetes, a protein called amylin forms dense clumps that shut down insulin-producing cells, wreaking havoc on the control of blood sugar. But zinc has a knack for preventing amylin from misbehaving.

Recent research at the University of Michigan offers new details about how zinc performs this "security guard" function. The findings appear in the July 8 issue of the *Journal of Molecular Biology*.

Amylin is something of a two-faced character. In healthy people who have normal levels of zinc in the insulin-producing islet cells of the pancreas, amylin actually pitches in to help with blood sugar regulation, says Ayyalusamy Ramamoorthy, a U-M professor of chemistry and of biophysics in the College of Literature, Science, and the Arts. In fact, an analog of amylin called Symlin is used in conjunction with insulin to manage blood sugar levels in diabetics.

This good behavior on amylin's part comes about because zinc acts like a security guard at a rock concert, whose job is keeping fans from turning troublesome and destructive. In molecular terms, zinc prevents amylin---also known as Islet Amyloid Polypeptide (IAPP)---from forming harmful clumps similar to those found in Alzheimer's, Parkinson's, Huntington's and various other degenerative diseases.

But in a zinc-starved cellular environment of someone with type 2 diabetes, amylin has no watchful guard to rein it in. It's free to clump together with other amylin molecules in the molecular equivalent of a

gang.

The clumping ultimately leads to the formation of ribbon-like structures called fibrils, and because fibril formation has been linked to a number of human diseases, it was long assumed that fibrils themselves were toxic. But accumulating evidence now suggests that the actual culprits may be shorter snippets that assemble in the process of forming full-length fibrils. For this reason, it's important to understand the whole aggregation process, not just the structure of the final fibril.

Ramamoorthy and colleagues are trying to better understand exactly how zinc interacts with amylin, in hopes of finding ways of treating or preventing type 2 diabetes and other diseases associated with aging. In earlier work, they showed that when zinc binds to amylin, at a point near the middle of the amylin molecule, the amylin molecule kinks, which interferes with the formation of toxic clumps. In the current work, they show that the binding of zinc in the middle makes one end of the amylin molecule, called the N-terminus, become more orderly.

"This is significant, because the N-terminus is very important in clump formation and amylin toxicity," Ramamoorthy said.

In addition, the researchers found that before amylin can begin forming fibrils, zinc must be rousted from its nesting place. This eviction is costly in energetic terms, and the sheer expense of it discourages fibril formation. And because a single zinc molecule can bind to several amylin molecules, it ties up the amylin in assemblages that, unlike certain other aggregations, are not intermediates in the pathway that leads to fibril formation.

However zinc, like amylin, has a dual nature. At conditions similar to those outside islet cells, where even a tiny amount of amylin aggregates in the blink of an eye, zinc inhibits fibril formation. But in conditions

resembling the inside of the cell, the inhibitory effect begins to wane and other factors, like insulin, take on zinc's security guard duties. Ramamoorthy's group found that this happens because amylin has not one, but two binding sites for zinc. Zinc prefers to bind at the first site---the one in the middle of the amylin molecule, where its binding discourages fibril formation. But when there's too much zinc around, all the binding sites in the middle positions are occupied and zinc must attach to amylin at the second site, which counteracts the effect of the first site. This may explain why decreased levels of insulin---the backup security guard---inside islet cells of diabetics result in islet cell death.

The experiments described in the Journal of Molecular Biology paper were all done in an artificial environment, not a living organism where zinc levels constantly fluctuate. In future experiments, Ramamoorthy hopes to more closely approximate natural conditions in order to better understand how amylin interacts with islet cells and what triggers its toxicity toward the cells. The results of these studies will facilitate the development of metal-based therapies for type 2 diabetes, similar to the promising metal-based drugs developed for Alzheimer's and other neurodegenerative diseases, Ramamoorthy said.

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