

# Researchers zero in on cell malfunction causing Alzheimer's

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MIT researchers are one step closer to understanding how fragments of a normal brain protein can turn into toxic accumulations that attack and kill brain cells, causing the devastating mental deterioration characteristic of Alzheimer's disease.

Understanding the mechanism behind the buildup of a plaque of abnormal protein fragments that invades the brains of Alzheimer's victims may lead to new treatments with experimental drugs.

Researchers in two separate MIT laboratories are approaching the problem from two angles: how the protein fragments form and how they become toxic to healthy cells.

In one MIT biology laboratory, researchers are experimenting with "decoy" substances that may be able to protect the targeted brain cells from a toxic molecular attack.

And in another laboratory, biomedical engineering researchers have discovered that with environmental stimulation, the protein segments called peptides change their conformation into that of the plaque. Many investigators believe that these protein conformation changes may lead to a new understanding of the underlying mechanism of cell malfunction in a host of neurological diseases, which include scrapie, bovine spongiform encephalopathy ("mad cow" disease), Parkinson's and Alzheimer's.

In those stricken with Alzheimer's, certain types of neurons in some regions of the brain start to malfunction and die. While brain cells almost always degenerate with age, the much more rapid deterioration seen in Alzheimer's patients is driven by either genetic or environmental factors and leads to memory loss and other forms of mental deterioration.

The work of two sets of MIT researchers – one in the Department of Biology and one in the Center for Biomedical Engineering – supports a current theory on the cause of diseases like Alzheimer's. The theory is that a structural molecular transformation takes place in the toxic, extracellular protein fragments called beta-amyloid, leading to the accumulation of the characteristic and toxic senile plaques.

## A DANGEROUS BUILDUP

A peptide is a small molecule in which amino acids, the building blocks of proteins, are held together by strong chemical bonds. Proteins can often be fragmented into peptides. A beta-amyloid peptide is a fragment derived from a large normal common protein, which, in the disease, is fragmented in an abnormal fashion.

The beta-amyloid peptides found in the brains of Alzheimer's victims are clipped off a larger

normal protein called APP, which is found throughout the body. Normally, these beta-amyloid peptides are broken down to very small harmless fragments. Nobody knows why they accumulate in the disease. They become toxic with time.

Only in the brains of older people – and those genetically disposed to early-onset Alzheimer's – does APP seem to get broken up in a way that releases beta-amyloid fragments.

These fragments accumulate into abnormal fibers in the cortex to form the characteristic senile plaques, which look very distinctive under the microscope.

The goal of the research team led by Vernon M. Ingram, the John and Dorothy Wilson Professor of Biochemistry and director of the Experimental Study Group, is to come up with a way to keep the peptides from clumping together into fibers by creating "decoy" peptides that form a new, harmless fiber with the ones that are prone to clumping.

In Alzheimer's disease, these aggregates of peptides can cause some neurons to get an influx of external calcium that is too large for the cell to pump out or isolate. The beta-amyloid peptide appears to open a channel into the neuron that allows calcium to enter it, making it malfunction and die.

"Neurons of older subjects are especially prone to this attack, because they suffer from an age-related deficiency" in the cell's ability to convert nutrients to energy, which is needed to sequester unwanted calcium, Professor Ingram wrote in a July 1997 paper.

In a December 1997 paper, his team identified several decoy peptides – some of which have the promising ability to forestall a calcium overrun by the very same beta-amyloid peptide fibrils that cause problems in the brains of Alzheimer's patients. The number of potentially useful "decoy" peptides is increasing quite rapidly as the testing of new peptides proceeds.

Although the decoys have yet to be evaluated for possible side effects, the researchers say these could potentially be developed as therapeutic agents to reduce or delay the death of neurons that causes Alzheimer's.

"The search for a new therapy for this terrible disease is one of the most exciting researches I have ever undertaken," Professor Ingram said. "It promises well, but time will tell. We aim to greatly improve the quality of life in our last years.

"In addition, the science involved is fascinating – a combination of protein chemistry, electrophysiology and cell physiology. It is very interesting to see so many MIT undergraduates becoming involved in the experiments, working with the professional staff."

#### SUDDEN CHANGE OF SHAPE

One of the questions that Shuguang Zhang, principal research scientist in the Center for Biomedical Engineering, asked himself was, "Why does it take so long to get Alzheimer's?" The onset of the disease may occur years before the first symptoms appear. What was going on in brain cells during that time?

One thing that may happen is that the protein of certain brain cells actually changes conformation. The amino acids that make up proteins are complex, three-dimensional structures that can fashion themselves into spring-like coils of helices or flatter formations called beta-sheets.

Peptides that form these very stable sheet-like structures are found in the abnormal proteins that occur in the brains of those afflicted with neurological disorders such as Alzheimer's. It is the insoluble aggregation of the flat beta-sheets that is the primary component of plaque.

"The progression of the disease may be related to changes in protein secondary structure leading to the formation of insoluble beta-sheet plaques," Dr. Zhang and Professor Alexander Rich wrote in a paper in the 1997 Proceedings of the National Academy of Sciences. "It is interesting that these diseases seem to be characterized by a slow conversion of protein into an insoluble beta-sheet form."

Once the aggregated proteins accumulate in some cells and leak into other cells, these deviant cells persuade normal cells to change as well. As the number of abnormal cells increases, the whole brain begins to get clogged with them. Symptoms such as memory loss occur as the deviant cells interfere with the receptors needed for brain functions such as memory.

Drs. Zhang and Rich, the William Thompson Sedgwick Professor of Biophysics, found that a certain peptide that forms beta-sheet structures in water will – upon heating the water above 70½ Celsius – abruptly and drastically change its shape to a helix.

After cooling, the new shape took several weeks at room temperature to partially return to its previous form. Changing the acidic or basic conditions surrounding the peptides can also influence such conformation changes, Dr. Zhang said.

"If the process that causes these proteins to change shape can be slowed or reversed, diseases such as Alzheimer's, Parkinson's or Huntington's may be significantly delayed," he said.

Dr. Zhang's research is a continuation from his serendipitous discovery of a class of self-assembling peptides (MIT Tech Talk, April 28, 1993 and Feb. 9, 1994).

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