New findings pull back curtain on relationship between iron and Alzheimer's disease

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Massachusetts General Hospital researchers say they have determined how iron contributes to the production of brain-destroying plaques found in Alzheimer's patients.

The team, whose study results appear in this week's Journal of Biological Chemistry, report that there is a very close link between elevated levels of iron in the brain and the enhanced production of the amyloid precursor protein, which in Alzheimer's disease breaks down into a peptide that makes up the destructive plaques.

Dr. Jack T. Rogers, the head of the hospital's neurochemistry lab who oversaw the team's work, said the findings "lay the foundation for the development of new therapies that will slow or stop the negative effects of iron buildup" in patients with the progressive neurodegenerative disease, symptoms of which include memory loss, impaired judgment, disorientation and personality changes.

While it had been known that an abundance of iron in brain cells somehow results in an abundance of amyloid precursor protein, or APP, and its destructive peptide offspring, Rogers' team set out to open up new avenues for therapies by determining what goes on at the molecular level. In 2002, they identified the molecular location where APP and iron interact, a discovery that laid the groundwork for the work being reported now.

Today it is clear that, under healthy conditions, iron and APP keep each other in check: If there's too much iron in a brain cell, more APP is made, and then APP and a partner molecule escort excess iron out. And, as the team reported last month in a related paper in the journal Cell, if there's too little iron, fewer APP molecules are made available to help escort iron out. As a result, iron accumulates, and the process begins again in a feedback loop.

Rogers said the team's work detailed in the two recent papers "seals the loop" in what has been understood about APP and iron and paves the way for the development of drugs that will beef up the ability of APP and its partner to eject iron and restore the iron balance when needed.

The researchers also identified, in the JBC paper, another important player in the system of checks and balances used to regulate iron in brain cells. Known as IRP1, which stands for iron-regulating protein 1, the special molecule attaches to the messenger RNA that holds the recipe for making APP. When there's less iron in the brain cell, IRP1 is more likely to hook up with the RNA, which prevents the production of APP. When there's abundant iron present, IRP1 doesn't hook up with the RNA, and APP production becomes excessive.

The new information solidified the team's hunch that the particular region where IRP1 binds to the messenger RNA is a potential drug target.

"With other research teams, we are investigating novel therapies that remove excessive iron, and we're looking at the precise spot on the messenger RNA where IRP1 binds to screen for drugs that specifically prevent APP production," said Dr. Catherine Cahill, one of the lead authors.

More information: The team's research was funded by the National

Institutes of Health, the Alzheimer's Association and the Institute for the Study of Aging. The resulting "Paper of the Week" will appear in the *JBC's* Oct. 8 issue.