Proteins linked to longevity also linked to Alzheimer's

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Biology professor Leonard Guarente. Photo: Donna Coveney

Over the past 20 years, scientists have learned that proteins called sirtuins play a vital role in longevity and stress response in organisms as diverse as humans, yeast and mice. A new paper from MIT biologists now reveals a surprising additional role for sirtuins: They appear to suppress the production of amyloid beta proteins, which form plaques in the brains of Alzheimer's patients.

The finding, reported in the July 23 issue of *Cell*, suggests that targeting sirtuins could offer a promising new approach to treating Alzheimer's, says Professor Leonard Guarente, leader of the research team.

Guarente and his colleagues showed that boosting the activity of a sirtuin called SIRT1 stifled the production of amyloid beta proteins and

enhanced brain function in mice engineered to express Alzheimer's symptoms. This marks the first time sirtuins have been linked to those proteins.

Several drug companies are now developing and testing compounds that enhance sirtuin activity. Guarente, who consults for one of those companies, Sirtris (a unit of GlaxoSmithKline), believes that sirtuin activators may eventually prove useful against Alzheimer's, which affects up to one-third of people who reach age 80.

Protein clumping

Though amyloid plaques are a defining feature of Alzheimer's disease, many researchers now believe that the symptoms are caused by smaller clumps of two or three amyloid beta (A-beta) fragments, not the larger plaques.

A-beta peptides form when proteins called amyloid precursor proteins (APPs) are broken into smaller pieces. However, APPs can also be cleaved at other sites, producing harmless protein fragments. APP's normal function is unknown, but it has been established that people with a gene mutation that stimulates overproduction of APP are more likely to develop Alzheimer's at an early age (before age 65).

Another mutation that stimulates early-onset Alzheimer's (which accounts for 5 to 10 percent of cases) occurs in the gene for the enzyme that cleaves APP into A-beta peptides. Although those genes for early-onset Alzheimer's have been identified, "with late-onset Alzheimer's, we still don't know why some people get it and other people don't," says Guarente.

Guarente, who first discovered the life-extending ability of sirtuins 20 years ago, started studying their role in Alzheimer's after some recent

studies showed that the gene that produces sirtuins, SIRT1, appears to protect mice from the effects of Alzheimer's disease. When those studies came out, "I thought that the mice with extra SIRT1 probably had just as much A-beta, but that SIRT1 was protecting them against it," Guarente recalls. "It turns out that they were actually making less A-beta peptide."

In the Cell paper, Guarente and his colleagues showed that SIRT1 activates the production of an enzyme (alpha-secretase) that carves APPs into harmless fragments, preventing the formation of Alzheimer's-associated amyloid peptides. Mice engineered to produce excess sirtuins had reduced peptide levels, while mice with SIRT1 knocked out showed elevated peptide levels.

Furthermore, learning and memory deficits in the Alzheimer's mice were improved when SIRT1 was overproduced and worsened when the gene was deleted. The researchers also found that SIRT1 activates the so-called notch-signaling pathway via the elevated levels of alpha-secretase, which protects neurons and helps maintain brain function.

A new target for Alzheimer's

The research, funded by the American Parkinson Disease Association, National Institutes of Health and the Paul F. Glenn Foundation, demonstrates that drugs that activate SIRT1 in the brain may be a promising approach to treating Alzheimer's, says Guarente. Any such drug would have to be able to cross the blood-brain barrier, which prevents large molecules from diffusing into the brain.

Sirtris, a company co-founded by Guarente and then bought by GlaxoSmithKline, is now testing SIRT1 activators in a clinical trial for diabetes. Guarente believes that related drugs could have an impact on a range of neurodegenerative diseases, as well as diabetes and other

diseases of aging.

However, any potential drug for Alzheimer's would likely take several years to reach clinical trials, because of the need to find a drug that crosses the blood-brain barrier, says Guarente.

Rudolph Tanzi, professor of neurology at Harvard Medical School, says the new findings also suggest another approach: targeting one specific aspect of SIRT1's activity. Tanzi's lab recently found that mutations in the gene that produces alpha-secretase (ADAM10) are associated with late-onset Alzheimer's disease.

"If this is how SIRT1 protects against Alzheimer's -- by turning on ADAM10 -- you could try finding a drug that specifically addresses that mechanism," instead of globally activating SIRT1, says Tanzi.

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