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The Trash Compactor

Plaques, Bad Cholesterol Get Partial Rehab in Alzheimer's

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Science Editor

New studies out this week rehabilitate two proteins of ill repute, at least as far as their roles in Alzheimer's disease are concerned.

One shows that the low-density lipoprotein (LDL) receptor – currently famous for its role in heart disease – may be protective in Alzheimer's disease, while the other study, which investigated the role of insulin-related growth factor or IGF-1 signaling in the disease, adds to a growing body of evidence that plaques are protective rather than detrimental.

Insulin-related growth factor regulates aging-related pathways up and down the evolutionary tree. But there have been conflicting reports about its role in Alzheimer's disease.

In their studies, which appear in the Dec. 11, 2009, issue of *Cell*, the authors used mice that had two genetic alterations to shed some more light on the role of IGF-1 in Alzheimer's.

First, the animals had human transgenes that made them susceptible to developing Alzheimer's disease. Additionally, they have only one copy of the IGF gene, and so, only roughly half of the normal amount of IGF signaling.

Transgenic animals with one copy of the IGF gene performed better in memory and other behavioral tasks than those with both copies of their IGF gene intact, suggesting that reduced IGF signaling could partially protect against a genetic predisposition to Alzheimer's.

Animals with one IGF copy also had fewer of several biomarkers of Alzheimer's disease, including neural inflammation.

But on what was once seen as the mother of all Alzheimer's biomarkers, the situation was the opposite: The animals with reduced IGF signaling had the same number of plaques as their unprotected counterparts, senior author Andrew Dillin, who is at the Salk Institute, told *BioWorld Today*. But the amyloid plaques in the mice with reduced IGF signaling were more compact, which apparently made the A-beta less toxic.

The mice also had much less soluble A-beta oligomers, a precursor to plaques that is now thought to be more toxic

than the plaques themselves.

Soluble intermediates "are not as easy to see as the plaques," Dillin explained. But his team used several techniques to demonstrate that animals with reduced IGF signaling had lower levels of soluble A-beta, suggesting that reducing IGF signaling somehow improves the process of getting the soluble intermediates to aggregate into the less toxic plaques.

Beyond the possibility of manipulating IGF – or its downstream targets – therapeutically, Dillin said that the data show that manipulating pathways that extend lifespan will lead to more than just a prolonged period of infirmity tacked onto a regular lifespan. "The ability to extend youthfulness will not only extend lifespan but will also increase. . . healthspan," he said.

Dillin is co-founder of Cambridge, Mass.-based Proteostasis Therapeutics, a company whose goal it is to target key "protein homeostasis" pathways to fight multiple genetic and degenerative disorders.

Proteostasis Chairman Chris Mirabelli, who is also a managing director at Proteostasis investor Healthcare Ventures, said that the work illustrates the emerging concept that there are a variety of genetic diseases and age-onset diseases where there is an impairment of the cell's ability to maintain protein homeostasis. Where a more classical philosophy of drug discovery is to "think of one protein as a bad actor" and develop diseases targeting that protein, Proteostasis' approach is to "upregulate the cell's innate ability to correct the problem" – for example, by hurrying A-beta along from toxic soluble oligomer to the less harmful plaques.

Another paper, this one in the Dec. 10, 2009, issue of *Neuron*, uses transgenic mice to show that the LDL cholesterol receptor also may be worth testing as an anti-Alzheimer's target.

The LDL receptor is well-known for its role in cardiovascular disease. But it is also present in the brain, where it binds apolipoprotein E or apoE; variants in the apoE gene are the strongest risk factors for developing Alzheimer's disease.

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In their paper, the authors created transgenic animals that overexpress LDL receptors in the brain and were prone to developing Alzheimer's disease. Such animals had levels of ApoE that were decreased from 50 percent to 90 percent. The authors also saw less soluble Aβeta, fewer plaques, and less indication of neuroinflammation in animals that were overexpressing the LDL receptor.

"Our study clearly demonstrates the beneficial effects of LDLR overexpression in the brain on pathogenic A-beta

aggregation and subsequent neuroinflammatory responses," senior author David Holtzman, who is on the faculty at the Washington University School of Medicine, said in a press release.

"Given the results from these studies, the therapeutic potential of previously identified compounds, and potential new agents, which regulate LDLR in peripheral tissues merit additional testing in animal models of A-beta amyloidosis," he added. ■