Alzheimer's research pinpoints antibodies that may prevent disease

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Antibodies to a wide range of substances that can aggregate to form plaques, such as those found in Alzheimer's patients, have been identified in the blood and cerebrospinal fluid of healthy people. Levels of these antibodies decline with age and, in Alzheimer's patients, with increasing progression of the disease.

These findings by Stanford University School of Medicine researchers and outside collaborators, described in a paper to be published online July 6 in the journal Proceedings of the National Academy of Sciences, raise the possibility that many of us are carrying antibodies in our blood that could be playing a role in staving off or slowing the progression of Alzheimer's disease. This seems to be true even when we are young and healthy and would presumably have had little or no exposure to the substances that build up in the brain to cause this disorder.

Alzheimer's disease is characterized by the build-up of amyloid plaques in the brain. These are large aggregations of a protein breakdown product, or peptide, called A-beta. Many experiments have shown that immunization with A-beta can reduce the formation of amyloid plaques. Clinical trials now underway are exploring whether this can safely produce cognitive benefits in Alzheimer's patients, while other trials are treating patients directly with antibodies to A-beta.

But A-beta is a slippery character. A number of different modified, mutated, or metabolized forms of this peptide may also be involved in the disease. Furthermore, it is believed that more than the plaques

themselves (which are also found in the brains of people with no Alzheimer's symptoms), it is smaller aggregations of a few A-beta molecules, called oligomers, which are most toxic to neurons.

"Other studies have found antibodies against A-beta, but nobody has ever done a large-scale analysis using hundreds of different samples and almost a hundred different peptides to look for what's already in people's bodies," said the paper's first author, Markus Britschgi, PhD, an instructor working as a researcher in the laboratory of Tony Wyss-Coray, PhD. Wyss-Coray, associate professor of neurology and neurological sciences, is the paper's senior author.

Britschgi, Wyss-Coray, and their colleagues used a microarray technology in which a large number of different peptides are affixed to pixels on a microchip, which signals binding of those peptides by antibodies. This technology was developed in a neighboring lab by another co-author of the paper, William Robinson, MD, assistant professor of rheumatology, and other Stanford scientists.

The investigators customized microarrays containing close to 100 different peptides apiece, including A-beta and several of its metabolized, modified, and mutant forms. The peptides were displayed in various degrees of aggregation, ranging from single molecules to small assemblages, or oligomers, to denser aggregates called fibrils. Also included on the chip were certain peptides whose constituent amino-acid sequences are unrelated to A-beta's but that are capable of aggregating to form other, rare plaque-associated dementias.

The researchers incubated these chips with blood samples from more than 250 individuals, who were between 21 and 89 years old, some with Alzheimer's disease and others without it. They observed antibodies targeting many forms and aggregation-states of A-beta in both healthy and diseased subjects' blood, with antibodies to oligomers showing the

most immunoreactivity. They then showed that overall levels of these antibodies decline with age and, in those with Alzheimer's, with advancing stages of the disease.

"This was the first study to show an age-related decline in the levels of these antibodies," said Britschgi.

A follow-on experiment showed that the same antibodies, whether isolated from plasma of either Alzheimer's patients or healthy controls, were able to protect freshly cultured mouse neurons in a dish from destruction by A-beta, which is typically highly toxic to these neurons.

Furthermore, the researchers studied samples from vervet monkeys, who, like humans, develop A-beta-derived brain plaques as they age. Earlier experiments performed at another institution have shown that immunizing older monkeys with A-beta substantially cleared their plaques. In this new study, the Stanford team obtained blood samples extracted from those monkeys before and after immunization, and compared levels and diversity of relevant antibodies in pre- and post-inoculation samples. They observed several such antibodies in the pre-immunized samples, as well as significant post-immunization increases in levels of several different antibodies.

Interestingly, in both monkeys and healthy human subjects the investigators' microarrays also detected antibodies to a couple of mutated peptides associated with rare dementias which have brain plaques bearing a striking resemblance to those of Alzheimer's with a notable exception. Oddly, these dementia-related peptides' amino-acid sequences are nothing like that of A-beta's, yet antibodies against them occur even in the blood of healthy study subjects who have never been diagnosed with any of those rare dementias.

Wyss-Coray and Britschgi think this may mean that at least some of the

antibodies they've isolated target not plaque-generating peptides' amino-acid sequences, but rather some common shape these molecules assume in the early, oligomeric stages of their aggregation, when they are most toxic.

The methods the researchers used, for which Stanford has filed provisional patent applications, could lead to improved monitoring of clinical trials of immunotherapeutic treatments for Alzheimer's disease, Wyss-Coray said. "With our microarray, you could easily look for antibodies to hundreds of different peptides. It would be possible to see whether certain types of antibodies correlate better with cognitive benefits than others do."

Another possibility, said Wyss-Coray, is to try immunizing Alzheimer's patients with peptides that, unlike A-beta, have amino-acid sequences unlike any of those occurring naturally in the human body — but that, by virtue of their three-dimensional similarity to A-beta as they begin to aggregate, generate antibodies to A-beta oligomers as well. This would reduce the possibility of an autoimmune reaction to such a vaccine, which resulted in the halting of an otherwise promising clinical trial several years ago, he said.

Source: Stanford University Medical Center (news : web)