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Fixing Genetic Risk of Alzheimer's disease

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Abstract (Summary)

Alzheimer's is a disease of the brain, in which nerve cells die and their connections with other nerve cells are lost. People who have Alzheimer's disease have set of symptoms that can include memory loss and difficulties with thinking, problem-solving or language disturbance many scientists believe accumulation of the protein amyloid in the brain that leads to nerve cell death is the main cause. However, it appears that many risk factors also play a role in the disease like increase age, high cholesterol levels, high blood pressure and genetics like APOE4 mutation now in a new study published in Nature Medicine, researchers revealed how apoE4 confers its risk for Alzheimer's disease in human brain cells. They were able to erase the damage caused by apoE4 by changing it, with a small molecule, into a harmless apoE3-like version. They tested on human cells because mouse models failed in clinical trials they can't mimic the human disease by creating neurons from skin cells donated by AD patients and confirmed that apoE4 does, indeed, cause damage in human cells finally, the researchers looked for ways to repair the abnormalities caused by apoE4. In earlier work, they developed a class of compounds that can change the structure of the harmful apoE4 protein so it resembles the innocuous apoE3 protein, referred to as apoE4 "structure correctors However still the scientist are working to improve the compounds so they can be tested in human patients in the future.

Introduction

Alzheimer's disease is the most widespread disease of a large class of disorders which clinically are known as "dementias", they are diseases characterized by a progressive deterioration of thinking ability and of memory. Alzheimer's is a disease of the brain, in which nerve cells die and their connections with other nerve cells are lost.[1]

People who have Alzheimer's disease have set of symptoms that can include memory loss and difficulties with thinking, problem-solving or language disturbance the cause of the disease is stated to be unknown although, many scientists believe accumulation of the protein amyloid in the brain that leads to nerve cell death is the main cause. However, it appears that many risk factors also play a role in the disease like increase age, high cholesterol levels, high blood pressure and genetics less than 5% of people develop the disease in the fourth or fifth decade of life (40s or 50s). At least half of these early onset patients have inherited gene mutations associated with their Alzheimer's disease like apoE4. Moreover, the children of a patient with early onset Alzheimer's disease who has one of these gene mutations has a 50% risk of developing Alzheimer's disease. The aim of this report to see a potential solution for the primary genetic risk factor (APOE4) for Alzheimer's disease.[2]

Discussion:

A person is twice as likely to develop Alzheimer's if they have just one copy of the gene apoE4. When someone has two copies, the risk increases by 12-fold, the increased risk of AD associated with one or two alleles is also found in African-Americans and Caribbean Hispanics, however approximately 42% of persons with AD do not have an APOE e4 allele. Thus, APOE genotyping is not specific for AD. The absence of an APOE e4 allele does not rule out the diagnosis of AD Scientists have been unclear about why apoE4 is so much more damaging to brain cells than other versions of the protein. But now in a new study published in Nature Medicine, researchers revealed how apoE4 confers its risk for Alzheimer's disease in human brain cells. What's more, they were able to erase the damage caused by apoE4 by changing it, with a small molecule, into a harmless apoE3-like version.[3]

Model choice:

Usually Most Alzheimer's research and drug development are done in mouse models of the disease. However, a succession of clinical trial failures has spurred scientists to turn to other models. Because mouse models failed in clinical trials they can't mimic the human disease Instead, scientist decided to use human cells to model the disease and test new drugs. Thanks to induced pluripotent stem cell technology, they were able to examine, for the first time, the effect of apoE4 on human brain cells. To do so, the researchers created neurons from skin cells donated by Alzheimer's patients with two copies of the apoE4 gene, as well as from healthy individuals who had two copies of the apoE3 gene. The researchers confirmed that, in human neurons, the misshapen apoE4 protein cannot function properly and is broken down into disease-causing fragments in the cells. This process results in a number of problems commonly found in Alzheimer's disease, including the accumulation of the protein tau and of amyloid peptides. Notably, the presence of apoE4 does not change the production of amyloid beta in mouse neurons. But in human cells, scientists noticed apoE4 has a very clear effect on increasing amyloid beta production, which highlights the species difference in the way apoE4 controls amyloid beta metabolism. Increased amyloid beta production is not seen in mouse neurons and could potentially explain some of the discrepancies between mice and humans regarding drug efficacy.[3, 4]

Fixing a Toxic Protein:

Once confirmed that apoE4 does, indeed, cause damage in human cells. related to Alzheimer's disease, scientists had a key question remaining: how does the presence of apoE4 lead to cell damage? Is the presence of apoE4 resulting in a loss of normal apoE3 function, or does the addition of apoE4 cause the toxic effects?

The answer was simple if the damage is caused due to the loss of a protein's function, you would want to increase protein levels to supplement those functions. But if the accumulation of a protein leads to a toxic function, you want to lower production of the protein to block its detrimental effect the researchers examined brain cells that did not produce either form of the apoE protein, and the neurons looked and functioned just like cells with apoE3. However, if the researchers added apoE4, the cells became riddled with pathologies related to Alzheimer's disease. This discovery indicates that the presence of apoE4—and not the absence of apoE3—promotes the disease. Finally, the researchers looked for ways to repair the abnormalities caused by apoE4. In earlier work, they developed a class of compounds that can change the structure of the harmful apoE4 protein so it resembles the innocuous apoE3 protein, referred to as apoE4 "structure correctors". Treating human apoE4 neurons with a structure corrector eliminated the signs of Alzheimer's disease, restored normal function to the cells, and improved cell survival. However still the scientist are working to improve the compounds so they can be tested in human patients in the future.[4]

Conclusion:

in conclusion Alzheimer is a disease characterized by a progressive deterioration of thinking ability and of memory one of its causes is genetic susceptibility as in mutation of APOE4 gene, scientist now found a way to erase this risk factors by converting the APOE4 to an harmless APOE3 and soon they will be tested in humans.

References:

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