Unraveling the genetic risk factors for Alzheimer's disease

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Video Abstract

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Abstract

The strongest genetic risk factor for Alzheimer's disease may impair the body's cellular recycling system, allowing the build-up of harmful byproducts in the brain. People carrying the gene variant known as APOE4 are at an increased risk for the early development of Alzheimer's and show high numbers of the brain plaques characteristic of the disease. But the underlying reason for this effect isn't clear. Now, researchers have shown that APOE4 interferes with autophagy – the body's way of recycling unneeded or harmful cellular material – providing new insights into how and why APOE4 conveys such a strong risk for Alzheimer's. The team looked at the relationship between APOE4 and a protein known as TFEB, considered a master regulator of autophagy-related genes. Prior studies have linked reduced TFEB expression to the presence of amyloid-beta plaques in the brain. Ordinarily, TFEB initiates autophagy by binding to DNA sequences known as CLEAR sites, which transcribe three important autophagy genes. This binding turns the genes "on", promoting gene expression. The researchers hypothesized that APOE4 interferes with this process. To test their hypothesis, they looked at the expression levels of the corresponding autophagy proteins – LC3B, p62, and LAMP2 – in the presence of different APOE variants. In brain specimens from Alzheimer's patients carrying APOE4, they observed lower expression of all three autophagy genes and their corresponding proteins compared to those found in patients carrying APOE3 or healthy control subjects. This prompted the team to use computer modeling to examine potential interactions between APOE4 and DNA. They found that APOE4 – but not APOE2 or APOE3 – stably binds to DNA at CLEAR sites, the same sequences used by TFEB to turn on autophagy genes. Additional experiments revealed that APOE4 actively competes with TFEB for access to CLEAR sites on DNA, hindering cells from turning on the genes they need to initiate autophagy. Consistent with this finding, lab-grown cells expressing APOE4 showed a build-up of protein aggregates – a phenotype not strongly observed in cells expressing APOE3. Overall, these discoveries show the toxic gain-of-function that comes along with the APOE4 gene variant. It seems that cells carrying this protein get bogged down with excessive unprocessed cellular waste, which helps explain the profound clinical consequences of this genetic risk factor.