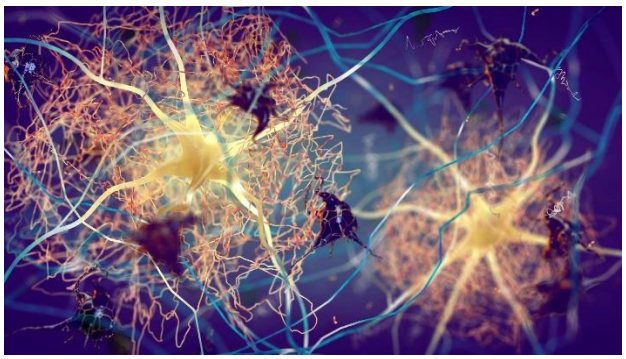
In Alzheimer's Disease Oligodendrocytes Identified as Key Amyloid β Producers

Researchers used mouse models to demonstrate that neurons were not the only source of abnormal amyloid β proteins contributing to the pathology of Alzheimer's disease. They found that oligodendrocytes play a significant role in the abnormal neuronal hyperactivity in Alzheimer's disease and are a major source of amyloid β protein.



Study

In the present study, the researchers explored four open-access single-nucleus ribonucleic acid (RNA) datasets to investigate the expression of genes involved in amyloid β production, such as the genes that code for beta-secretase, amyloid precursor protein, and various components of gamma-secretase such as presenilin 1 and 2, and nicastrin.

Open-access proteomics databases were also used to confirm that the RNA expression levels observed in the single nucleus RNA datasets also translated to similar levels of protein expression. Immunohistochemical analyses using specific antibodies were used to confirm the presence of beta-secretase and amyloid precursor proteins in oligodendrocytes in mice.

Post-mortem tissue from patients who had sporadic Alzheimer's disease, as well as from healthy controls, were used for in-situ hybridization and RNA scoping to determine whether Alzheimer's disease altered the amyloid β-producing capacity of oligodendrocytes. For this, they examined the expression of the genes BACE1 and APP, which code for beta-secretase component 1 and amyloid precursor protein, respectively, and the MBP gene, which codes for myelin basic protein and is expressed only in oligodendrocytes.

The study also included a densitometric analysis of BACE1 and APP expression in neurons and oligodendrocytes to examine the amount and variability of these two genes' expression in each type of cell.

Furthermore, the researchers aimed to confirm that oligodendrocytes did indeed produce amyloid β protein and did not just express the components for amyloid β production. They obtained oligodendrocytes from human induced pluripotent stem cells from patients with familial Alzheimer's disease as well as from healthy controls and tested these cell lines for amyloid β production.

The study also compared the amyloid β production between oligodendrocytes and neurons by producing cortical neurons from the same pluripotent stem cells used to derive oligodendrocytes and examining the production of amyloid β in both cell lines.

The researchers also conducted knockout experiments in mice to investigate whether the amyloid β produced by oligodendrocytes could form amyloid β plaques in vivo. The amyloid β plaque loads in the motor, retrosplenial, and visual cortices of the mice were assessed when the mice reached the age of four months.

Findings

The study found that not only do oligodendrocytes produce greater amounts of amyloid β than neurons, but also contribute significantly to the abnormal neuronal hyperactivity observed in Alzheimer's disease. Furthermore, selective suppression of amyloid β production in the oligodendrocytes was found to improve Alzheimer's disease pathology.

In the in vivo observations in the mouse models, suppression of amyloid β production in oligodendrocytes was also found to restore neuronal function. The oligodendrocytes were also observed to produce a higher proportion of soluble aggregates than neurons, with a non-linear relationship between the amyloid β monomer and aggregate concentrations.

The researchers believe that restoring neuronal function after suppressing oligodendrocyte amyloid β production is surprising given that the reduction of amyloid β plaques is only modest. In comparison, suppressing amyloid β production in neurons results in an almost total elimination of amyloid β plaques. These findings support those from previous studies that indicated that neuronal amyloid β is responsible for plaque formation in Alzheimer's disease.

Conclusion

Overall, the findings showed that oligodendrocytes produce higher levels of amyloid β than neurons, contributing to the abnormal neuronal hyperactivity that is part of Alzheimer's disease pathology. Although neuronal amyloid β plays a more prominent role in plaque formation, suppressing amyloid β production in oligodendrocytes restored neuronal function in mice and improved Alzheimer's disease pathology.

Source:

https://www.news-medical.net/news/20240724/Oligodendrocytes-identified-as-key-amyloid-ceb2-producers-in-Alzheimers-disease.aspx