Alzheimer's disease pathogenesis

The Alzheimer's disease pathogenesis is complex and not fully understood, but it is believed to involve several factors, including genetics, inflammation, oxidative stress, and abnormal protein accumulation.

One of the hallmarks of AD is the accumulation of beta-amyloid (Aβ) plaques in the brain. Aβ is a protein fragment that is produced when a larger protein called amyloid precursor protein (APP) is broken down. In AD, Aβ accumulates and forms plaques between nerve cells, leading to inflammation and damage to brain cells.

Whether Aβ itself is a key toxic agent in AD pathogenesis and the precise mechanism of Aβ-elicited neurotoxicity are still debated. Emerging evidence demonstrates that the Aβ channel/pore hypothesis could explain Aβ toxicity because Aβ oligomers are able to disrupt membranes and cause edge-conductivity pores that may disrupt cell Ca2+ homeostasis and drive neurotoxicity in AD. However, all available data to support this hypothesis have been collected from “in vitro” experiments using high concentrations of exogenous Aβ. It is still unknown whether Aβ channels can be formed by endogenous Aβ in AD animal models. Here, we report an unexpected finding of the spontaneous Ca2+ oscillations in aged 3xTg AD mice but not in age-matched wild-type mice. These spontaneous Ca2+ oscillations are sensitive to extracellular Ca2+, ZnCl2, and the Aβ channel blocker Anle138b, suggesting that these spontaneous Ca2+ oscillations in aged 3xTg AD mice are mediated by endogenous Aβ-formed channels [1)].

Another hallmark of Alzheimer's disease is the formation of neurofibrillary tangles, which are made up of abnormal tau proteins. Tau proteins normally help to stabilize the structure of neurons, but in AD, they become abnormally modified and clump together, leading to the breakdown of the neuronal structure and function.

In addition to Aβ plaques and neurofibrillary tangles, inflammation and oxidative stress are also thought to play a role in the pathogenesis of AD. Chronic inflammation in the brain can damage neurons and contribute to the accumulation of Aβ plaques. Oxidative stress, which occurs when there is an imbalance between free radicals and antioxidant defenses, can also damage neurons and contribute to the development of AD.

Genetic factors are also important in the development of AD. Mutations in genes such as the amyloid precursor protein (APP) gene and the presenilin 1 and 2 genes have been associated with early-onset familial forms of AD. Other genes, such as the apolipoprotein E (APOE) gene, have been linked to an increased risk of developing late-onset AD.

Overall, the pathogenesis of AD is complex and involves multiple factors. While there is still much to learn about this devastating disease, understanding the underlying mechanisms may lead to the development of new treatments and preventive strategies.

Inhibition of MEF2C exacerbates the toxic effect of Aβ and , damages synaptic plasticity, reduces the

ability of learning and memory of APP/PS1 mice, and increases the level of OS via the Nrf2-ARE signal pathway [2].

AD is a neurodegenerative disease, and its pathogenesis has been attributed to extracellular aggregates of amyloid β (Aβ) plaques and intracellular neurofibrillary tangles made of hyperphosphorylated τ-protein in cortical and limbic areas of the human brain. It is characterized by memory loss and progressive neurocognitive dysfunction. The anomalous processing of APP by β-secretases and γ-secretases leads to production of Aβ40 and Aβ42 monomers, which further oligomerize and aggregate into senile plaques. The disease also intensifies through infectious agents like HIV. Additionally, during disease pathogenesis, the presence of high concentrations of Aβ peptides in central nervous system initiates microglial infiltration. Upon coming into vicinity of Aβ, microglia get activated, endocytose Aβ, and contribute toward their clearance via TREM2 surface receptors, simultaneously triggering innate immunoresponse against the aggregation. In addition to a detailed report on causative factors leading to AD, the present review also discusses the current state of the art in AD therapeutics and diagnostics, including labeling and imaging techniques employed as contrast agents for better visualization and sensing of the plaques. The review also points to an urgent need for nanotechnology as an efficient therapeutic strategy to increase the bioavailability of drugs in the central nervous system [3].

The hippocampus and entorhinal cortex (EC), the earliest affected areas, are considered relative to early memory loss in Alzheimer's disease (AD). The hippocampus is composed of heterogeneous subfields that are affected in a different order and varying degrees during Alzheimer's disease pathogenesis. Gao et al. conducted a comprehensive proteomics analysis of the hippocampal subfields and EC region in human postmortem specimens obtained from the Chinese human brain bank. Bioinformatics analysis identified region-consistent differentially expressed proteins (DEPs) which associated with astrocytes, and region-specific DEPs which associated with oligodendrocytes and the myelin sheath. Further analysis illuminated that the region-consistent DEPs functioned as connection of region-specific DEPs. Moreover, in region-consistent DEPs, the expression level of S100A10, a marker of protective astrocytes, was increased in both aging and AD patients. Immunohistochemical analysis confirmed an increase in the number of S100A10-positive astrocytes in all hippocampal subfields and the EC region of AD patients. Dual immunofluorescence results further showed that S100A10-positive astrocytes contained apoptotic neuron debris in AD patients, suggesting that S100A10-positive astrocytes may protect brain through phagocytosis of neuronal apoptosis. In region-specific DEPs, the proteome showed a specific reduction of oligodendrocytes and myelin markers in CA1, CA3, and EC regions of AD patients. Immunohistochemical analysis confirmed the loss of myelin in EC region. Above all, these results highlight the role of the glial cells in AD and provide new insights into the pathogenesis of AD and potential therapeutic strategies [4].

It has been suggested by multiple previous studies that a bunch of AD key influencing factors might be attributed to genes encoding human leukocyte antigen (HLA), whose variety is an essential part of human adaptive immunity. A wide range of activities involved in immune responses may be determined by HLA genes, including inflammation mediated by the immune response, T-cell transendothelial migration, infection, brain development and plasticity in AD pathogenesis, and so on. The goal of a article of Wang et al. was to review the recent epidemiological findings of HLA (mainly

HLA class I and II) associated with AD and investigate to what extent the genetic variations of HLA were clinically significant as pathogenic factors for AD. Depending on the degree of contribution of HLA in AD pathogenesis, targeted research towards HLA may propel AD therapeutic strategies into a new era of development [5].

Mutations in the Presenilin 1 (PSEN1) gene are the most common cause of autosomal dominant familial Alzheimer's disease [6].

Several pathway analyses of genome-wide association studies reported the involvement of metabolic and immune pathways in Alzheimer's disease (AD). Until now, the exact mechanisms of these pathways in AD are still unclear.

Chen et al., conducted a pathway analysis of a whole genome AD case-control expression dataset (n=41, 25 AD cases and 16 controls) from the human temporal cortex tissue. Using the differently expressed AD genes, they identified significant KEGG pathways related to metabolism and immune processes. Using the up- and down- regulated AD gene list, they further found up-regulated AD gene were significantly enriched in immune and metabolic pathways. They further compare the immune and metabolic KEGG pathways from the expression dataset with those from previous GWAS datasets, and found that most of these pathways are shared in both GWAS and expression datasets [7].

Dysregulation of the PI3K/Akt/mTOR signaling cascade has been associated with the pathology of neurodegeneration, specifically Alzheimer's disease (AD). Both in vivo models and post-mortem brain samples of individuals with AD have commonly shown hyperactivation of the pathway.

In the study of Hodges et al., examined how neuron subset-specific deletion of Pten (NS-Pten) in mice, which presents with hyperactive mammalian target of rapamycin (mTOR) activity, affects the hippocampal protein levels of key neuropathological hallmarks of AD. They found NS-Pten knockout (KO) mice to have elevated levels of amyloid-β, α-synuclein, neurofilament-L, and pGSK3α in the hippocampal synaptosome compared with NS-Pten wild type mice. In contrast, there was a decreased expression of amyloid precursor protein, tau, GSK3α, and GSK3β in NS-Pten KO hippocampi. Overall, there were significant alterations in levels of proteins associated with AD pathology in NS-Pten KO mice. This study provides novel insight into how altered mTOR signaling is linked to AD pathology, without the use of an in-vivo AD model that already displays neuropathological hallmarks of the disease [8].

Pathologies and dementias of the nervous system such as Alzheimer disease can result when tau proteins become defective and no longer stabilize microtubules properly.

Microtubule-associated protein tau is the major component of paired helical filaments (PHFs) associated with the neuropathology of Alzheimer's disease (AD). Tau in the normal brain binds and stabilizes microtubules. Tau isolated from PHFs is hyperphosphorylated, which prevents it from binding to microtubules. Tau phosphorylation has been suggested to be involved in the development

of NFT pathology in the AD brain. Recently, we showed that 14-3-3ζ is bound to tau in the PHFs and when incubated in vitro with 14-3-3ζ, tau formed amorphous aggregates, single-stranded straight filaments, double stranded ribbon-like filaments and PHF-like filaments that displayed close resemblance with corresponding ultrastructures of AD brain. Surprisingly however, phosphorylated and non-phosphorylated tau aggregated in a similar manner, indicating that tau phosphorylation does not affect in vitro tau aggregation (Qureshi et al (2013) Biochemistry 52, 6445-6455). In this study, we have examined the role of tau phosphorylation in tau aggregation in cellular level. We have found that in human M17 neuroblastoma cells, tau phosphorylation by GSK3β or PKA does not cause tau aggregation, but promotes 14-3-3ζ-induced tau aggregation by destabilizing microtubules. Microtubule disrupting drugs also promoted 14-3-3ζ-induced tau aggregation without changing tau phosphorylation in M17 cell. In vitro, when incubated with 14-3-3ζ and microtubules, nonphosphorylated tau bound to microtubules and did not aggregate. Phosphorylated tau on the other hand did not bind to microtubules and aggregated. Our data indicate that microtubule-bound tau is resistant to 14-3-3ζ-induced tau aggregation and suggest that tau phosphorylation promotes tau aggregation in the brain by detaching tau from microtubules and thus making it accessible to 14-3-3ζ [9].

1)

Li S, Ji X, Gao M, Huang B, Peng S, Wu J. Endogenous Amyloid-formed Ca2+-permeable Channels in Aged 3xTg AD Mice. Function (Oxf). 2023 May 26;4(4):zqad025. doi: 10.1093/function/zqad025. PMID: 37342418; PMCID: PMC10278988.

2)

Ren J, Zhang S, Wang X, Deng Y, Zhao Y, Xiao Y, Liu J, Chu L, Qi X. MEF2C ameliorates learning, memory, and molecular pathological changes in Alzheimer's disease and. Acta Biochim Biophys Sin (Shanghai). 2022 Jan 25;54(1):1-14. doi: 10.3724/abbs.2021012. PMID: 35130621.

3)

Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine. 2019 Jul 19;14:5541-5554. doi: 10.2147/IJN.S200490. PMID: 31410002; PMCID: PMC6650620.

4)

Gao Y, Liu J, Wang J, Liu Y, Zeng LH, Ge W, Ma C. Proteomic analysis of human hippocampal subfields provides new insights into the pathogenesis of Alzheimer's disease and the role of glial cells. Brain Pathol. 2022 Jan 11:e13047. doi: 10.1111/bpa.13047. Epub ahead of print. PMID: 35016256.

5)

Wang ZX, Wan Q, Xing A. HLA in Alzheimer's Disease: Genetic Association and Possible Pathogenic Roles [published online ahead of print, 2020 Sep 7]. Neuromolecular Med. 2020;10.1007/s12017-020-08612-4. doi:10.1007/s12017-020-08612-4

6)

O'Connor A, Abel E, Fraser MR, Ryan NS, Jiménez DA, Koriath C, Chávez-Gutiérrez L, Ansorge O, Mummery CJ, Lashley T, Rossor MN, Polke JM, Mead S, Fox NC. A novel presenilin 1 duplication mutation (Ile168dup) causing Alzheimer's disease associated with myoclonus, seizures and pyramidal features. Neurobiol Aging. 2021 Feb 5:S0197-4580(21)00046-4. doi: 10.1016/j.neurobiolaging.2021.01.032. Epub ahead of print. PMID: 33648786.

7)

Chen J, Xie C, Zhao Y, Li Z, Xu P, Yao L. Gene expression analysis reveals the dysregulation of immune and metabolic pathways in Alzheimer's disease. Oncotarget. 2016 Oct 6. doi: 10.18632/oncotarget.12505. PubMed PMID: 27732949.

8)

Hodges SL, Reynolds CD, Smith GD, Jefferson TS, Nolan SO, Lugo JN. Molecular interplay between hyperactive mammalian target of rapamycin signaling and Alzheimer's disease neuropathology in the NS-Pten knockout mouse model. Neuroreport. 2018 Jun 29. doi: 10.1097/WNR.0000000000001081. [Epub ahead of print] PubMed PMID: 29965873.

9)

Li T, Paudel HK. 14-3-3ζ Mediates Tau Aggregation in Human Neuroblastoma M17 Cells. PLoS One. 2016 Aug 22;11(8):e0160635. doi: 10.1371/journal.pone.0160635. eCollection 2016. PubMed PMID: 27548710.