PT578
Endothelial-monocyte-activating polypeptide-2 (EMAP-2) may be a novel treatment target of Alzheimer’s disease

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Abstract
Inflammation has been raised as a candidate for unifying pathogenesis and a target of disease modifying strategy for Alzheimer’s disease (AD). A cytokine, endothelial-monocyte-activating polypeptide-2 (EMAP-2) which amplifies actions of tumor necrosis factor alpha (TNF-alpha), might be an important target, since it is involved in microglial activation and neuronal death. We hypothesize that EMAP-2 is associated with Alzheimer’s disease, and anti-EMAP-2 antibody could have therapeutic effects on cognitive impairment in amyloid beta-induced AD model animals.

We investigated the association between the EMAP-2 gene, the -9299A/G polymorphism and cognitive impairment in 641 subjects aged from 60 to 80. In addition, we compared EMAP-2 concentration in peripheral blood among people with AD (n = 30), mild cognitive impairment (n = 29), or normal cognition (n = 27). Finally, we examined the effects of anti-EMAP-2 antibody following injecting it to AD model rats on cognitive function using water maze and passive avoidance tests and on a level of cell death in the brain tissue using TUNEL assay.

We found a significant association between the -9299A/G polymorphism (GG vs AG/AA) of EMAP-2 gene and cognitive impairment. GG homozygote compared to A-allele carriers was related to lower mini-mental status examination score (p = 0.001). In addition, EMAP-2 level was significantly higher in the peripheral blood of people with AD than in that of healthy control group (p = 0.05). In the AD model rats, injection of EMAP-2 antibody improved short-term memory (p < 0.01) and fear memory (p < 0.05), and lowered the levels of neuronal cell death in the brain tissue (p < 0.05).

Our results suggested a possible involvement of EMAP-2 in AD pathogenesis, as well as the potential of humanized anti-EMAP-2 antibody as a novel option for AD treatment.

PT579
Disease-modifying therapy through enhancement of neuronal Aβ-degrading enzyme neprilysin activity for Alzheimer’s disease

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Abstract
Aggregation and deposition of amyloid-β peptide (Aβ) in the brain are triggering events of the long-term pathological cascade of Alzheimer’s disease (AD), and are closely associated with the metabolic balance between Aβ anabolic and catabolic activities. As almost all familial AD mutations cause an increase in the anabolism of a particular form of Aβ, Aβ1-42, leading to Aβ deposition and accelerating AD pathology, a chronic reduction in the catabolic activity would also promote Aβ deposition. Neprilysin is a rate-limiting peptidase involved in brain Aβ catabolism. Mounting evidence that expression levels of neprilysin are decreased in the hippocampus and cerebral cortex of AD patients from the early stages of disease development and also with aging in humans, suggests a close association of neprilysin with the etiology and pathogenesis of AD. Thus, a subtle but long-term decline in neprilysin activity appears to be at least partly responsible for the memory-related symptoms of AD, and up-regulation of neprilysin would be a promising strategy for disease-modifying therapy of AD.

We screened a compound modulating brain neprilysin activity and/or gene expression using a natural product library, and found that catechins, such as EGCg were capable of up-regulating neprilysin via gene expression. However, their bioavailabilities and blood-brain barrier permeability are not always so good, because these compounds are highly hydrophilic. So, we synthesized aliphatic catechin derivatives by introducing an alkyl chain or aliphatic moiety into EGCg to increase Log P values. Interestingly, some of the aliphatic catechin derivatives more strongly up-regulated not only neprilysin but also α-secretase, which acts to preclude Aβ production, than EGCg did. The aliphatic catechins would be promising drug candidates for therapy and prevention of AD. Currently, we are analyzing their in vivo effects on up-regulation of neprilysin.

PT580
Alteration of neuronal nitric oxide synthase dimerization contributes to the development of Alzheimer’s disease

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Abstract
Background and purpose: Although previous studies have suggested that nNOS-derived NO has neuroprotective effects on the development of AD, the underlying molecular mechanisms are not fully elucidated. Here, we investigated whether and how disruption of nNOS dimerization contributes to the development of AD.

Methods: Two-month-old hemizygous 5xFAD mice and non-transgenic control, and 6-month-old hemizygous 5xFAD mice and non-transgenic control mice were used in the experiments. A histological investigation for neuronal cell death and CD5s/p35 localization, DHE injection for measurement of ROS increase, LT-PAGE for nNOS dimerization/monomerization, and Western blot for CD5s/p35 expression were performed.

significant differences in the amyloid beta protein, Neprilysin (NEP), and SOX2 levels were not observed among the groups.

Conclusion: Our study showed that a single dose of 1X10^6 hUCB-MSCs injected intravenously into AD transgenic mice resulted in neither delivery into the brain nor generation of therapeutic benefits via paracrine activity. In order to utilize the intravenous route as an effective delivery route for AD stem cell therapy, it will be crucial to perform additional studies on how to increase the permeability of the BBB and how to decrease the entrapment of cells in organs such as the lung and liver.
Results: No differences in synaptic marker or expression of synaptic markers were found in the cortex of 5xFAD mice at 6 months of age compared with control littermates. nNOS dimerization was disrupted in the 5xFAD cortex, accompanied by an increase in ROS production. Furthermore, the levels of p25, a CDK5 activator, increased significantly and it colocalized with nNOS in the 5xFAD cortex.

Conclusion: Taken together, our results demonstrate that nNOS dimers are disrupted in the 5xFAD cortex with CDK5 activation, may be involved in the disruption of nNOS dimerization and the development of AD.

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Keywords: Alzheimer’s disease, neuronal nitric oxide synthase, dimerization, cyclin-dependent kinase 5, p25

PT581

Multiple accumulation of neurodegenerative disease-related proteins in familial granulin mutation brains

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Abstract

Granulin (GRN) mutations were identified in patients with familial frontotemporal lobar degeneration (FTLD) with ubiquitin pathology in 2006 studies. GRN transcript haloinously is sufﬁciently has been proposed as a disease mechanism that leads to the loss of functional progranulin (PGRN) protein. GRN mutations were first found in tau-negative FTLD patients, however, recent ﬁndings indicate that these mutations are associated with other neurodegenerative disorders with tau pathology, including Alzheimer’s disease and corticobasal degeneration. Moreover, PGRN reduction in tau transgenic mice is associated with increasing tau phosphorylation and accumulation.

To investigate the inﬂuence of a decline in PGRN protein on other forms of neurodegenerative-related protein accumulation, four human GRN mutation cases (age at death; 54, 55, 56 and 78 years old) were investigated by histochemical and biochemical analyses.

The results showed neuronal and glial tau accumulation in all cases analyzed. Massive neuronal tau staining revealed pretangle forms and glial tau in both astrocytes and oligodendrocytes. Furthermore, phosphorylated α-synuclein-positive structures were also found in oligodendrocytes and the neuropil. Immunoblot analysis of fresh frozen brain tissues revealed that tau protein was present in the sarcosyl-insoluble fraction, which was composed of three- and four-repeat tau isoforms, resembling Alzheimer’s disease.

Our data suggest that PGRN reduction might be the cause of neuronoglial multiple proteinopathies, including TDP-43 proteinopathy, taulopathy and α-synucleinopathy, due to the accelerating accumulation of abnormal proteins.

PT582

Myristic Acid Hitchhiking on Sigma-1 Receptor to Fend Off Neurodegeneration

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Abstract

Neurodegenerative diseases are linked to tauopathy as a result of cyclin dependent kinase 5 (cdk5) binding to its p25 activator instead of its p35 activator and becoming over-activated. The overactive complex stimulates the hyperphosphorylation of tau proteins, leading to neurofibrillary tangles (NFTs) and stunning axon growth and development. It is known that the sigma-1 receptor (Sig-1R), an endoplasmic reticulum chaperone, is involved in axon growth by promoting neurite sprouting through nerve growth factor (NGF) and tropomyosin receptor kinase B (TrkB). It has also been previously demonstrated that a Sig-1R deficiency impairs the process of neurogenesis by causing a down-regulation of N-methyl-D-aspartate receptors (NMDArs). The study sought to understand the relationship between Sig-1R and tauopathy. It was discovered that the Sig-1R helps maintain proper tau phosphorylation and axon development by facilitating p35 myristoylation and promoting p35 turnover. Neurons that had the Sig-1R knocked down exhibited shortened axons and higher levels of phosphorylated tau proteins compared to control neurons. Here we discuss these recent findings on the role of Sig-1R in tauopathy and highlight the newly presented physiological consequences of the Sig-1R-lipid interaction, helping to understand the close relationship between lipids and neurodegeneration.