Mini Review

Complement C3 and Alzheimer’s Disease

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Abstract

Complement system, a major constituent of innate immunity, is closely associated with the development of Alzheimer’s disease for the increasing mRNA expression of C1q, C2, C3 and etc in the temporal cortex and hippocampus. Recently studies indicate complement protein 3 activated by oligomeric β-amyloid and motivated synaptic pruning pathway after combining with complement receptor CR3 located in gliacyte, and then mediate synapse loss during Alzheimer’s disease early stages. And more, C3 was testified as an astroglial target of NFκB and activated NFκB/C3 wreckage synaptic density and dendritic morphology through C3aR and intraneuronal calcium respectively when exposed to β-amyloid. What’s more, C3 could influence amyloid pathology via both APOE-dependent and APOE-independent mechanisms. Significantly, C3 is also a strong dependency on the presence of C/EBPδ and the increasing of β-amyloid plaque burden is associated with C/EBPδ deficiency, which is similar to the increasingly total Abeta and fibrillar amyloid plaque burden in APP;C3(-/-) mice. In this paper, we review the major findings and current knowledge on the mechanism of C3 activation and its special effects on the development of Alzheimer’s disease.

ABBREVIATIONS

AD: Alzheimer’s Disease; Aβ β-amyloid; CSF: Cerebrospinal Fluid; APP: Amyloid Protein Precursor; TNF-α: Tumor Necrosis Factor-alpha; COX-2: Prostaglandins; TGFβ: Transforming Growth Factor- Beta; C3R: C3 Receptor; NF-κB: Nuclear Factor kappa B; BACE1: Beta-site Amyloid Precursor Protein Cleaving Enzyme-1; MIC: Mild Cognitive Impairment; JNK: Jun N-terminal Kinase; AP1: Activator-Protein 1; STATs: Signal Transducers and Activation of Transcription

INTRODUCTION

Though neuron inflammation hypothesis is still considered to be a downstream effect of Amyloid cascade hypothesis [1], it arouse much more enthusiasm to explore its role in the pathogenesis of AD especially Aspirin can ameliorate inflammatory process and improve cognition [2-4]. Immune system is a pivotal mediator during the process of inflammation. Increasing evidence show that complement pathway play a important role during the development of AD, not only both in postmortem AD tissue and APP transgenic mouse had been observed high expression of complement protein and activation of complement signaling [5-6] but also in CSF had detected many abnormal complement proteins like C3,C4 and etc [7]. Senile plaque and neurofibrillary tangles are the major characteristic pathology and they are induced by Aβ and p-tau, respectively. Emerging studies show activated C3 is associated with Aβ, NF-κB and is also related to p-tau. Therefore, the following substance will review around these orientations.

Oligomeric Aβ: A Key Mediator of C3 Activation

Amyloidogenic pathway is essential progress for the development of AD and many insoluble fragments of APP like Aβ40, Aβ42 are constitute of senile plaque [8]. But some researches suggest that soluble Aβ oligomers play a important role during the pathogenesis of AD [9], and the Aβ oligomers induced AD-like pathology through inducing ROS production, lipid peroxidation, activating acetylcholinesterase and inhibiting antioxidant enzyme activity in cognition regions [10], and more important is that synaptic dysfunction is associated with soluble Aβ oligomers during the early stages of AD [11].

Complement 3 is the central component of the complement system, which can be cleaved into C3a and C3b [12], and these activation fragments were found early stage of AD in plaques [13]. And more C3 mediates early synapse loss in APP/PS1 mice by complement cascade [14]. However, the detailed mechanism between Aβ and complement cascade is still unknown. A new...
Central component system is an important direction to research AD. For the complements, are they regulated by other factors such as Aβ purging pathways? Reckoned are needed to answer. And more, questions like what boosts the form of Aβ, what and how the development of amyloid cascade hypothesis. Meanwhile, the studies between complements and Aβ promote the cascade hypothesis, which has explained the progress of many lesion pathogenesis, it is still unclear. However, partially the amyloid diseases, though many works have done to explore its pathways that activated microglia [15], and NF-κB can promote it secrete some "neuro-protective" mediators such as IL-10, TNF-α, COX-2, IL-6, IL-1β etc; for another thing, it secretes some "pro-inflammatory" mediators like IL-6. Microglia can be activated in different ways and play different roles, for one thing, it can secrete many pro-inflammatory cytokines and reactive species [15]. Activated microglia in Alzheimer’s disease may contribute to ascertaining the pathogenesis of AD. In microglia, microglial C3aR and C3 were an activating C1q/C3R pathway. Together, oligomeric Aβ not only play a pivotal role in the pathogenesis of AD but also a key mediator to activate C3.

### Neuroinflammation and C3

Neuroinflammation, one of important pathological changes in AD, which is associated with activated microglia which secrete a series of pro-inflammatory cytokines and reactive species [15]. Microglia can be activated in different ways and play different roles, for one thing, it can secrete many pro-inflammatory mediators like TNF-α, COX-2, IL-6, IL-1β etc; for another thing, it secretes some "neuro-protective" mediators such as IL-10, TGFβ, Arginase. NF-κB pathway is one of the pro-inflammatory pathways that activated microglia [15], and NF-κB can promote BACE1 expression and the phagocytosis and clearance of Aβ, that mediated by microglia [16,17]. C3a has been testified to regulate synaptic refinement and neuronal survival [18] and lower C3 in MIC CSF was associated with cognitive decline [19]. Emerging study indicates that C3 disrupted dendritic morphology and network function through neuronal C3aR and C3 was an astroglial target of NFκB [20]. Significantly, JNK, AP1 and STATs are also pro-inflammatory pathways [15] and to research theirs relation between C3 and these pathways in nerve cells especially in microglia may contribute to ascertain the pathogenesis of AD.

### CONCLUSION

Alzheimer’s disease is an age related neurodegenerative diseases, though many works have done to explore its pathogenesis, it is still unclear. However, partially the amyloid cascade hypothesis has explained the progress of many lesion and the studies between complements and Aβ promote the development of amyloid cascade hypothesis. Meanwhile, the questions like what boosts the form of Aβ, what and how the Aβ purging pathways were needed to answer. And more, for the complements, are they regulated by other factors such as oxidative stress or external environment? Together, C3 even complement system is an important direction to research AD.

### REFERENCES


Cite this article