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Development of A Novel Sporadic Mouse Model of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder. Mouse models have been indispensable to offer insights into the crucial pathophysiology of AD. However, the majority of mouse models are developed by overexpression of familial AD genetic mutations such as APP and PS1/2, which account for only a small percentage of AD cases. In this manuscript, we summarized the development of a novel late-onset sporadic AD model, namely Thy1-ApoE4/C/EBPβ double transgenic mouse, carrying no genetic mutations but displaying key AD pathologies in an age-dependent manner. This mouse model is developed based on the C/EBPβ / AEP pathway that plays a crucial role in driving AD development.

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia with an insidious onset, long course and progressively exacerbating pathological changes [1, 2]. The typical symptoms of AD include cognitive impairment, memory loss and behavioral dysfunction, while the hallmarks of AD pathology are featured by brain atrophy, the deposition of extracellular β-amyloid (Aβ) plaques and the formation of intracellular neurofibrillary tangles (NFT) in the brain (Figure 1). The amyloid senile plaques are deposited by crippled clearance and abnormal processing of amyloid precursor protein (APP) by several secretases leading to excessive accumulation of Aβ [3, 4], and NFT is formed by highly phosphorylated and/or truncated microtubule-associated tau proteins [5, 6].

AD is generally divided into familial and sporadic AD. The familial AD (also known as early onset AD) constitutes a small portion in AD cases (less than 1%), which is caused by autosomal dominant mutations of human APP, presenilin 1 and 2 (PSEN 1/2). By contrast, most of AD cases (> 99%) are sporadic AD (also known as late onset AD) with an unknown etiology involving various factors such as age, genetics, life style and environmental influence [7]. Despite of abundant research, the exact mechanism how these factors interact

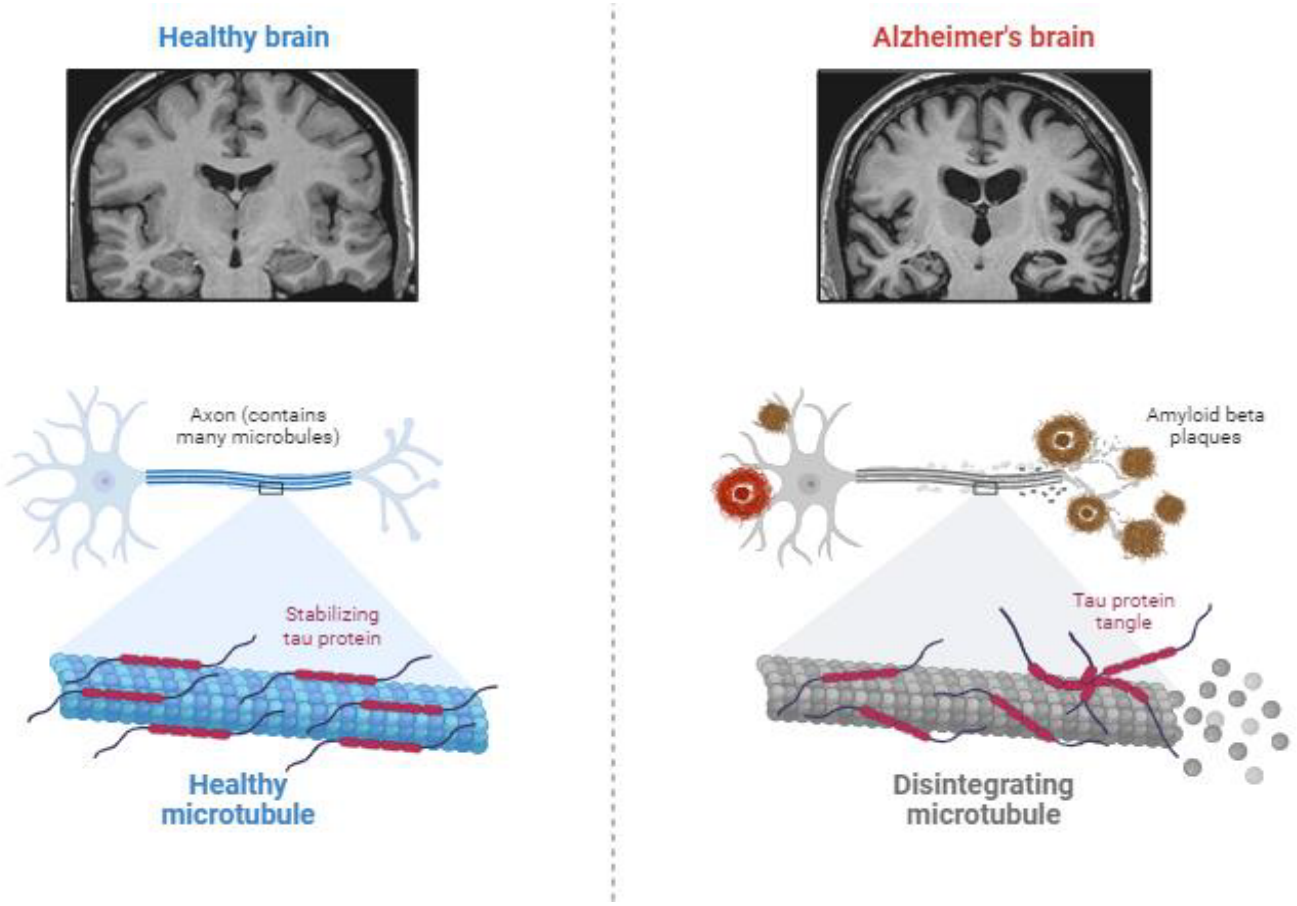

Figure 1: Pathology of Alzheimer's disease.

and contribute to neurodegeneration as well as cognitive impairment remains incompletely understood [8].

2. Development of AD mouse model

For decades of AD research, animal models serve as an essential tool to understand the regulatory mechanisms underlying AD pathogenesis and to test therapeutic approaches in preclinical studies [9]. The most commonly used experimental AD animal models are rodents based and great efforts have been paid to generate transgenic mouse models by overexpressing genetic mutations implicated in familial AD [10, 11]. These mouse models essentially display certain key histopathology of AD patients, yet none of them capture all aspects of AD pathological, biochemical and behavioral features [12, 13]. Furthermore, most of the genetic mutation-based familial AD mouse models represent an extreme condition that would never occur in human AD patients. Therefore, appropriate models that mimic late onset AD are urgently needed to bridge the gap between the basic research and clinical translation.

2.1 Familial AD mouse models

Since the first **transgenic mouse model** was developed in 1995 [14], hundreds of AD mice were genetically engineered and extensively described [10-12, 15-17]. In general, most of the AD mice are developed by transgenic tool of APP mutation, either alone or combination with familial AD mutations such as PSEN1, PSEN2 and/or microtubule-associated protein tau (MAPT), although there is no tau mutation in AD.

For instance, the APP/PS1 mouse model was generated through the co-expression of the APP^{Swe} mutant and ΔE9 mutant of PSEN1 [18]. The 5 × FAD strain, a widely used AD model, combines the APP^{Swe} mutation with the Florida (I716V) and London (V717I) mutations of APP, along with the M146L and L286V mutations of PSEN1 [19]. These two models replicate AD pathological hallmarks such as Aβ plaques, neuronal degeneration and progressive cognitive deficits, but not tau pathology. Therefore, the 3 × Tg strain, which accommodates three mutations, i.e., APP with APP^{Swe} mutation, tau with P301L mutation and PS1 with M146V

mutation, was developed [20]. As expected, this experimental model presents both β-amyloid deposits and tau pathology in a tempo-spatial manner.

2.2 C/EBPβ / AEP pathway plays a key role in driving AD development

Recently, the C/EBPβ / asparagine endopeptidase (AEP) pathway has been identified as a core regulatory mechanism triggering the occurrence and development of AD [21]. C/EBPβ, an important transcription factor, regulates various cellular and biological functions; while AEP (also called legumain) is a lysosomal asparagine endopeptidase that can be auto-catalytically activated by sequential removal of N- and C-terminal peptides at different pH values [22]. The expression of both C/EBPβ and AEP is age-dependently increased in the brain, tightly correlated to AD development [23]. On one hand, C/EBPβ promotes the expression of genes essential for AD pathologies, including APP, MAPT and β-secretase (BACE1) [24, 25]. On the other hand, it also plays an essential role in mediating transcription of AEP, which acts as a novel δ-secretase that simultaneously cleaves APP, Tau, and BACE1, generating fragments like APP N585, APP C586, Tau N368 and BACE1 N294 (Figure 2). These truncated proteins further accelerate Aβ accumulation and Tau aggregation [26, 27]. Conversely, deletion of AEP or C/EBPβ from AD mouse models substantially diminishes AD pathologies, restoring the cognitive functions [26-28].

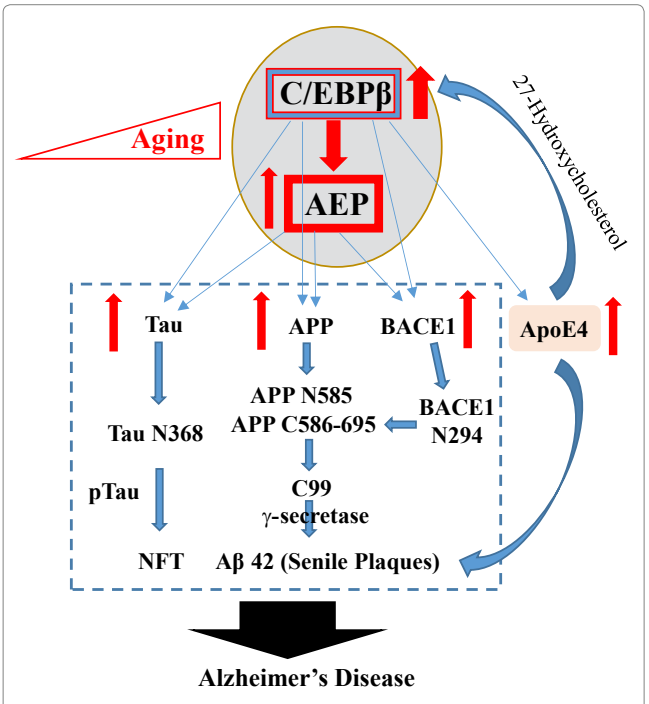

Figure 2: The role of C/EBPβ / AEP pathway in the development of Alzheimer's disease

2.3 Thy1-ApoE4/C/EBPβ transgenic mouse as a novel sporadic AD model

Our recent work developed a new mouse line with neuronal specific expression of human apolipoprotein E4 (ApoE4) and C/EBPβ genes, which acts as a sporadic AD model without any AD mutated genes [29, 30]. ApoE4 is a major genetic risk determinant for AD and drives its pathogenesis via Aβ-dependent and -independent pathways [31]. Under physiological conditions, ApoE is mainly expressed and secreted by astrocytes, mounting evidence shows that ApoE4 is also expressed in neurons under stresses or pathological condition [32, 33]. In comparison to ApoE3, C/EBPβ selectively promotes ApoE4 expression in neurons of AD patients, leading to Aβ clearance impairment and increased aggregation [34]. Interestingly, ApoE4 alleles strongly increased C/EBPβ activation in AD patient brains with escalating Braak stages, and this effect was more prominent than ApoE3 alleles [35]. Remarkably, ApoE4 also synergistically activates CEBPβ/AEP pathway through feedback with 27-hydroxycholesterol, exacerbating AD pathologies [35]. Therefore, mouse with neuronal specific expression of human ApoE4 and C/EBPβ driven by the mouse Thy1 promoter (Thy1-ApoE4/C/EBPβ) was developed and was proven to act as a sporadic model via extensive examination [29, 30].

There are 3 amino acids difference between mouse Aβ42 and human counterpart. Mounting evidence shows that human Aβ42 is much more prone to aggregate than mouse Aβ42 *in vitro* [36, 37]. The homology between mouse and human Tau proteins is around 89% [38]. Mouse Aβ has been questioned to aggregate into pathological fibrils, though extensive previous studies support that mouse Aβ and mouse Tau undeniably aggregate into amyloid deposits [39-41], mimicking the pathological features in human AD patient brains. To interrogate whether mouse senile plaques and NFT in Thy1-ApoE4/C/EBPβ transgenic mice indeed mimic human counterparts in 3xTg mice, these two models were compared model side-by-side. Notably, the sporadic AD mice display gradual Aβ aggregation and NFT formation in the brain validated by Aβ PET and Tau PET, similar to 3xTg mice. By using mouse endogenous machinery, this ApoE4/C/EBPβ double transgenic strain gradually develops Aβ and tau pathologies in a spatio-temporal manner without expression of any FAD mutation genes. Moreover, mouse Aβ and Tau aggregates extracted from this model display neurotoxicity and can propagate in the brains of AD mouse [29].

#11 A, a brain permeable AEP specific inhibitor with great oral bioavailability, blocks AEP cleavage of APP and

Tau dose-dependently. It has been previously shown that AEP inhibitor #11A reveals promising therapeutic efficacy in 3xTg mice [42]. To test whether #11 A is also a disease-modifying clinical candidate for pharmacologically treating sporadic AD, this sporadic AD mouse model was treated with #11 A, which strongly inhibits AEP and prevents mouse APP and Tau fragmentation by AEP, leading to reduction of mouse Aβ42 (mAβ42), mAβ40 and mouse p-Tau181 levels in Thy1-ApoE4/C/EBPβ transgenic mice in a dose-dependent manner. Chronic oral administration of #11 A decreases mAβ aggregation as validated by Aβ PET assay, Tau pathology, neurodegeneration and brain volume reduction, leading to alleviation of cognitive impairment [43]. Hence, this sporadic AD model of ApoE4/C/EBPβ transgenic mice demonstrate comparable AD pathological features to the well-established 3xTg familial AD mice in the absence of any human mutations, underscoring that C/EBPβ/AEP signaling is the single key mechanism driving AD pathogenesis. The stress or lesion-induced neuronal ApoE4 acts as a core trigger that activates the crucial pathway initiating the entire AD pathological cascade in a tempo-spatial manner.

3. Conclusion

Mouse models significantly contributed to our understanding of AD pathophysiology, offering valuable insights into disease mechanisms and potential therapeutic targets. Identification of C/EBPβ/AEP as a single key mechanism driving AD pathologies allows us to establish the sporadic AD mouse model that fully simulates the tempo-spatial features of AD patients. However, challenges in translating findings to the clinics underscore the need a multifaceted approach that integrates advanced preclinical models, robust biomarkers, and a comprehensive understanding of human disease heterogeneity. Therefore, aligning preclinical study methods with clinical research practices and addressing these challenges and leveraging emerging technologies will be pivotal in driving the next wave of breakthroughs in AD research, ultimately leading to effective treatments for this devastating disease.

4. Author's Contribution

All the authors contributed equally. They browse the final version and approved it for publication.

5. Acknowledgments

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6. Declaration of Interests

The authors declare no competing interests.

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