Perspectives on the Tertiary Prevention Strategy for Alzheimer's Disease

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Abstract: Amyloid-beta (Aβ) plays a pivotal role in Alzheimer's disease (AD) pathogenesis, and is the most promising disease-modifying target for AD. A succession of failures in Aβ-targeting clinical trials, however, has prompted questions on whether Aβ is the true cause of AD and a valid therapeutic target. Therefore, current therapeutic targets and intervention strategies must be reconsidered. In addition to Aβ, multiple pathological events such as tau hyperphosphorylation, oxidative stress and neuroinflammation are involved in the disease pathogenesis and cause cross-talk between these pathological pathways, which synergistically drive disease progression. Increasing evidence also reveals that the pathogenesis varies at different stages of the disease. Therefore, targeting Aβ alone at all stages of the disease would not be sufficient to halt or reverse disease progression. In the light of the pathophysiologic similarities between the development of ischemic stroke and AD, we can formulate management strategies for AD from the successful practice of ischemic stroke management, namely the tertiary prevention strategy. These new perspectives of tertiary prevention target both Aβ and different pathological pathways of AD pathogenesis at different stages of the disease, and may represent a promising avenue for the effective prevention and treatment of AD.

Keywords: Alzheimer's disease, beta-amyloid, tau hyperphosphorylation, stroke, therapeutic strategy.

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia and is characterized by a progressive loss of memory and cognition [1]. Nearly 44 million people worldwide were living with dementia [2]. AD not only causes great stress and suffering to patients and caregivers but also adds a substantial economic burden to society. However, the available drugs only alleviate the symptoms of AD, and no therapies currently prevent or effectively treat the disease. The exact etiology of the disease remains unclear. The widely accepted amyloid cascade hypothesis has made Aβ the primary therapeutic target. Despite tremendous investments in developing new drugs, nearly all Aβ-targeting clinical trials for symptomatic AD have failed in succession. Thus, there is an urgent need to re-think the current therapeutic target and intervention strategies for treating this devastating disease.

Brain Aβ begins to accumulate more than ten years prior to the onset of symptoms, and the neurodegeneration triggered by Aβ is serious and irreversible at the dementia stage [3]. AD has proven to be a complicated disease with multiple aspects in its pathogenesis, such as Aβ toxicity, tau hyperphosphorylation, oxidative stress and neuroinflammation [4]. Notably, the pathogenesis varies during different stages of

the disease. Thus, a simple anti-Aβ intervention may be less likely to succeed in AD patients because this intervention targets only one of the multiple and complex pathways that interact in determining synaptic dysfunction and neuronal loss. Both AD and stroke are chronic and complicated diseases, and stage-dependent treatment has been met with considerable success in stroke. Thus, targeting multiple pathways at different disease stages may represent a promising intervention strategy in AD management.

At present, most multi-factorial and complex diseases are managed by tertiary prevention strategy, which includes the primary, secondary and tertiary prevention. Primary disease prevention aims to prevent disease or injury of before it occurs either through eliminating disease-modifiable risk factors or increasing resistance to disease, including immunization against diseases, and maintaining a healthy diet and lifestyle. Secondary disease prevention aims to detect and address an existing disease or injury prior to the appearance of symptoms, including screening tests to detect disease in its earliest stages and treating the disease or injury to prevent further progression. Tertiary disease prevention aims to improve the patient's quality of life by softening the negative impacts of an ongoing symptomatic disease. This approach includes rehabilitation and treatment methods that halt disease progression. In line with this, we proposed the tertiary prevention strategy for AD (Fig. **1**). Avoiding systemic diseases, sleep disorders and environmental risk factors, maintaining healthy diet and exercise, and preventing the production of Aβ at the preclinical stage should represent the primary methods for AD prevention. Current therapeutics fo-

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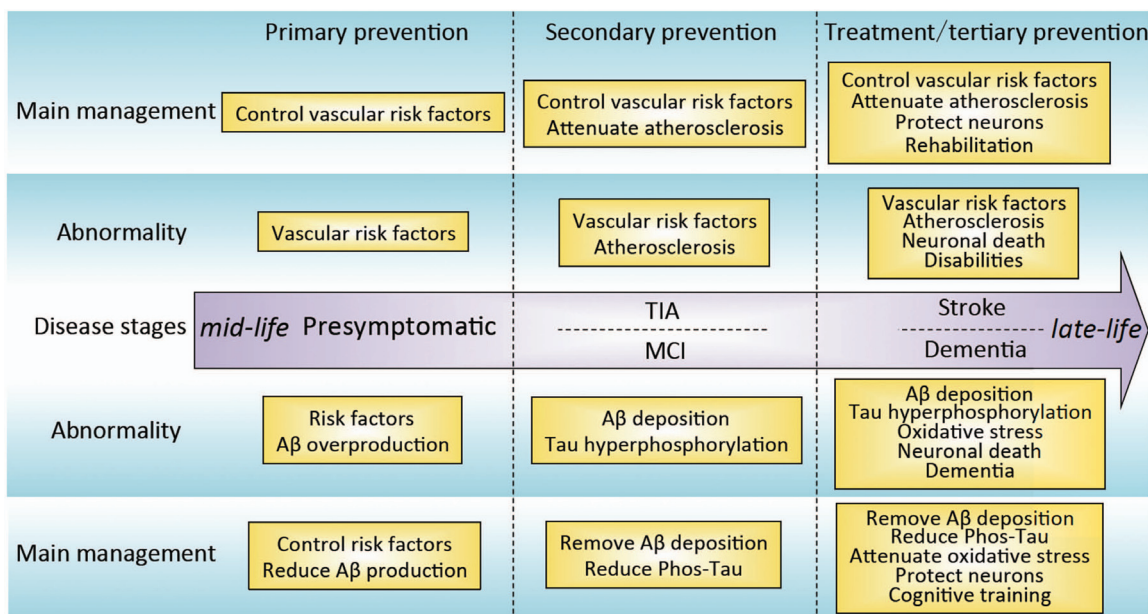#Xian-Le Bu and Shu-Sheng Jiao contribute equally to this work.

Fig. (1). Pathophysiological abnormalities and management of stroke and AD. The development of AD is similar to that of stroke. Both diseases start at mid-life and affect the elderly and can be divided into presymptomatic, TIA/MCI and stroke/AD dementia stages. Aβ and various risk factors for AD are analogous to the vascular risk factors for stroke; they, like vascular risk factors, represent the etiology of the disease. Both diseases have different pathophysiological abnormalities and, correspondingly, different therapeutic targets at different stages of the diseases. Abbreviations: Aβ, amyloid-β; TIA, transient ischemic attack; MCI, mild cognitive impairment; phos-Tau, phosphorylated Tau

cuses on the removal of Aβ plaques, the protection of synaptic function and neurons, and the attenuation of tau hyperphosphorylation at the MCI stage, called secondary prevention. For symptomatic AD patients, not only Aβ but also other pathological pathways, such as tau hyperphosphorylation, neuroinflammation, oxidative stress and synaptic injury, should be targeted (tertiary prevention or treatment).

CURRENT Aβ-TARGETING CLINICAL TRIALS FOR AD

There are currently no disease-modifying therapies for AD, although acetylcholinesterase inhibitors and the NMDA receptor antagonist memantine are clinically applicable pharmacological treatment options. The preclinical stage, MCI stage and dementia stage have been established to represent the course of AD [5]. However, these clinically available agents have been developed for AD patients with dementia, and no drugs are currently indicated for patients who are in the MCI stage or even the preclinical stage. More importantly, all available drugs only alleviate the symptoms of AD patients for a short period of time and do not halt or reverse the relentless process of AD progression. The limited efficacy of these drugs means that they are not in full accordance with prevention and treatment principles throughout the entire course of the disease.

The current understanding of AD pathogenesis is primarily based on the Aβ cascade hypothesis [6]. At present, disease-modifying therapeutic strategies for AD primarily focus on reducing Aβ production, inhibiting Aβ deposition and facilitating Aβ clearance. However, all of these efforts thus far have failed at the clinical trial stage.

Reducing Aβ Production

The inhibition of Aβ production using β- or γ-secretase inhibitors has proven unsuccessful in clinical trials. Tarenflurbil, semagacestat and avagacestat are γ-secretase inhibitors, but all were abandoned after failed phase 2 or 3 trials [7-9]. Although cerebrospinal fluid (CSF) and plasma levels of Aβ were reduced, these agents failed to improve cognitive status in patients with mild-to-moderate AD. Furthermore, AD patients administered semagacestat showed a further decline in cognition and a higher risk of skin cancers and infections [8]. The BACE-1 inhibitor LY2886721 reduced CSF Aβ40 and Aβ42 by 75% in a phase 1 study, but it also failed in a phase 2 trial due to liver toxicity [10]. To reduce the toxicity observed in clinical trials, safer secretase inhibitors or modulators that do not alter the physiological functions of the secretases are being sought. However, this represents a substantial challenge.

Facilitating Aβ Clearance

Over the last decade, Aβ immunotherapy has been the most attractive and promising Aβ clearing strategy for AD; however, human trials have produced disappointing results. The first active Aβ vaccine AN1792 lowered brain Aβ plaques, but did not provide benefits in synaptic integrity or cognitive performance [11]. Bapineuzumab is a monoclonal antibody that targets N-terminal Aβ and recognises both soluble and aggregated Aβ species. Although it decreased the level of cortical fibrillary Aβ [12, 13], treatment with bapineuzumab did not improve clinical outcomes in a phase 3 trial [14, 15]. Solanezumab, a monoclonal antibody that targets the central domain of Aβ and only recognises soluble

Aβ, captured both peripheral and central soluble forms of Aβ but also failed to show clinical efficacy in patients with moderate AD [16]. Crenezumab is a monoclonal antibody that binds all forms of Aβ, including monomers, oligomers and fibrils. In phase 2 clinical trials, crenezumab failed to meet its goals in patients with mild to moderate AD. The phase 2 trial of another antibody, Ponezumab, which targets the C terminal of Aβ, was also discontinued due to lack of efficacy on the primary endpoints of change in the brains or CSF Aβ burden in mild to moderate AD patients. Because there are natural anti-Aβ antibodies in the blood, immuno-globulin (IVIg) is expected to shift Aβ from the central nervous system (CNS) to peripheral blood and subsequently to lower brain Aβ levels. However, IVIg failed to improve the deterioration of cognition in patients with mild to moderate AD [17].

Inhibiting Aβ Deposition

Aβ aggregation is a critical event in AD pathogenesis [18]. Numerous compounds that inhibit Aβ oligomerization and block Aβ toxicity have been tested in AD patients. PBT2 is an anti-aggregation agent that affects the copper and zinc-mediated toxic oligomerization of Aβ. AD patients administered PBT2 had a dose-dependent reduction in CSF Aβ levels but failed to demonstrate clinical benefit [19]. Another anti-aggregation agent, scyllo-inositol, was also of no benefit to cognition in a phase 2 trial [20].

Thus, once symptoms are present, interventions that target Aβ alone show few or no benefits in cognition. Despite the adverse effects of these therapies, which compromise the therapeutic effects [21, 22], the failures of these human trials are primarily attributed to the intervention time, which is too late to reverse the disease. Furthermore, targeting Aβ alone may not be sufficient to halt or reverse disease progression when the disease becomes full blown. Although the current therapeutic focus is shifting from treatment at middle or late stages toward prevention at early stages of the disease, there is also an acute need to develop treatments for patients at late stages of the disease. Many critical questions regarding the etiology and pathogenesis of AD remain to be answered. A better understanding of the pathogenesis of the disease is required to design appropriate therapeutic strategies for AD.

THE COMPARISON BETWEEN STROKE AND AD

Both ischemic stroke and AD are prominent age-related diseases in the elderly. The pathology of these two disorders is quite different. However, they share some common pathogenesis such as those mediated by inflammation, oxidative stress, immune exhaustion and cerebrovascular changes [23]. Stroke was demonstrated to convey an increased risk of AD [24], and in turn AD increases the risk of stroke [25]. Vascular risk factors can cause endothelium dysfunction accelerating the progression of AD [26-28]. Numerous studies indicate that decreased endothelial nitric oxide in stroke may contribute to AD-related pathology and cognitive decline [29-33].

There are several pathophysiologic similarities between the development of ischemic stroke and AD. The comparison between stroke and AD may help us better understand the cause of AD. Both diseases start in mid-life and affect the elderly. In this comparison, vascular risk factors for stroke such as hypertension are analogous to Aβ and various risk factors for AD; each represents possible etiologies of their respective diseases. Atherosclerosis is analogous to tau hyperphosphorylation and represents vascular or neuronal injuries, respectively. The symptoms of transient ischemic attack (TIA) would be analogous to mild cognitive impairment (MCI); both indicate functional impairment prior to stroke or dementia. Finally, stroke would be an analogue to AD dementia and represents the final stages of the respective diseases. This comparison makes it easier to understand the roles of Aβ and tau in the etiology of AD.

IS Aβ THE REAL CAUSE AND VALID THERAPEUTIC TARGET OF AD?

In addition to the succession of failures of Aβ-targeting therapies in phase 2 and 3 clinical trials, autopsy studies demonstrate that neurofibrillary tangles (NFTs) - but not Aβ deposition - correlate well with cognitive status in AD patients [34]. Whether Aβ is the true cause of AD and a valid therapeutic target is under scrutiny. Skeptics propose that Aβ is the downstream result of AD [35] and that the therapeutic target should move from Aβ to tau [36]. A comprehensive understanding of the roles of Aβ and tau in the etiology of AD is a necessary prerequisite in developing effective intervention strategies.

As discussed above, there are several pathophysiologic similarities between the development of ischemic stroke and AD. In stroke, atherosclerosis of the brain arteries (but not the etiology-related vascular risk factors) is closely correlated with the disease severity; in this scenario, phosphorylated tau but not Aβ is closely associated with AD severity. Thus, we cannot deny a causative role for Aβ in AD pathogenesis.

Where tau is to be placed in the amyloid cascade is controversial. Autopsy studies indicate that tau pathology precedes Aβ pathology [37]. Numerous studies demonstrate a high incidence of atherosclerosis-related histological changes, regarded as age-related change, in the intima of the peripheral arteries of children, adolescents and even neonates [38]. However, ischemic stroke predominantly occurs in old age with characteristic atherosclerosis, which is caused by various vascular risk factors and progresses with aging. The different causes and outcomes of atherosclerosis in youth and in the elderly may help in understanding the course of tau phosphorylation in AD progression. Just as early age-related atherosclerosis differs from atherosclerosis in the elderly (which is caused by various risk factors and most likely leads to stroke), the detectable changes in CSF phosphorylated tau prior to Aβ accumulation in preclinical stages are also different from the drastically hyperphosphorylated tau at later stages that correlates well with the severity of neurodegeneration. The earlier tau pathology (prior to Aβ pathology) may represent age-related neuronal degeneration, whereas later changes in tau phosphorylation most likely result from Aβ as well as AD-related pathogenic pathways. Thus, Aβ should be located upstream of tau in AD pathogenesis.

Brain Aβ deposition is estimated to begin two decades prior to signs of cognitive impairment [39]. Pathological,

biologic, genetic, and animal modelling studies provide strong scientific underpinning for the Aβ etiology hypothesis [6]. The compelling finding that a rare mutation in the APP gene decreases Aβ production and protects against late-onset AD also confirms the causative role of Aβ in AD pathogenesis [40]. Aβ trigger, Aβ threshold and Aβ driver scenarios provide a more thorough understanding of the temporal relationship by which Aβ mediates neuronal death and initiates and facilitates the progressive neurodegenerative changes of AD via several mechanisms, whereas tau pathology is a pivotal pathway [41]. Excessive brain Aβ generation and accumulation, especially Aβ oligomerization, lead to tau hyperphosphorylation, neuroinflammation, and oxidative stress and finally result in synaptic degeneration, neuronal loss and subsequent cognitive decline [6, 42]. Therefore, Aβ is a valid therapeutic target and should have a prominent role in AD therapy.

TARGETING MULTIPLE PATHOLOGICAL CASCADES FOR AD MANAGEMENT

Less than 5% of AD patients are of the early onset form associated with certain mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) [43]. Most AD patients suffer from the sporadic form with onset over age 65 years old. Their etiology and pathogenesis is complex. Individuals with pathological aging usually have relatively large amounts of Aβ in the brain, and limited neurofibrillary tau pathologies and cognitive impairments are found [44-46]. Thus, Aβ explains part of the clinic-anatomical heterogeneity in AD [47], and Aβ accumulation may be necessary but not sufficient to induce the associated neurodegenerative changes and cognitive impairment. Consequently, we must increase our understanding of downstream pathological events at later stages of the disease.

Tau Phosphorylation

Tau phosphorylation is a clinical feature of several neurodegenerative diseases [48]. Tau is about three or four fold more hyperphosphorylated in AD brain [49]. Tau hyperphosphorylation seems to initiate and promote tau aggregation into NFTs [50, 51]. Additionally, tau aggregates can spread from one neuron to a neighbouring one [52, 53], and NFT staging increases over time [54]. Abnormally hyperphosphorylated tau contributes to neuronal dysfunction and behaviour impairment in P301L tau transgenic mice [55]. Numerous studies reveal that the hyperphosphorylated tau could sequester normal microtubule-associated proteins, disrupt microtubule dynamics, block intracellular trafficking of the neurons, promotes cell cycle re-entry, inhibit proteinase, facilitate tau aggregation, and induce apoptotic escape, all of which synergistically lead to the neurodegeneration in AD (reviewed in [56, 57]). Evidence also showed that Aβ can trigger tau hyperphosphorylation and Aβ toxicity is tau-dependent in the dendritic compartment of neurons [58, 59]. Tau seems to act downstream of Aβ to drive neuronal death [58, 60]. In APP/PS1 mice, tau inactivation not only improved neuronal death and cognitive decline but also decreased Aβ load [61], implying that downstream tau may increase Aβ toxicity via a feedback loop. Methylene blue, a tau aggregation inhibitor, could suppress abnormal tau accumulation in mice [62] and prevent disease progression in a phase 2 clinical trial on AD patients [63]. Therefore, Aβ and tau may interact with each other, thereby accelerating synaptic and neuronal dysfunction. Thus, Aβ serves as the disease initiator in the preclinical stage, whereas tau-related pathological changes contribute more to the neurodegeneration at later stages.

Inflammation

Increased levels of serum inflammatory cytokines are observed in AD patients [64, 65]. Longitudinal studies show that both acute and chronic inflammation are involved in disease progression [66, 67]. Animal studies also demonstrate that systemic inflammation leads to AD-like pathology [68]. Infections caused by various pathogens have been proven to increase the risk of cognitive impairment [69], and inflammation may partially account for the association between infections and cognitive decline [70]. The major routes by which peripheral inflammation communicates with CNS have been clearly elucidated [71]. 'Inflammaging' refers to aging that is accompanied by a low-grade chronic up-regulation of certain inflammatory responses that may exacerbate AD progression [72]. Inflammation was demonstrated to cause blood-brain barrier (BBB) dysfunction [73], which may inhibit Aβ clearance from the brain. Additionally, the exposure of microglia to systemic inflammatory factors may lead to the excessive activation of microglia and subsequently drive neuronal degeneration (reviewed in [74]). Neuroinflammation also involves tau-related neurodegeneration and promotes the development of senile plaques and NFTs (reviewed in [75]). A recent notable finding shows that microglia-associated neuroinflammation induced by Aβ deposition leads to epigenetic suppression of neuroligin 1 expression and subsequent synaptic dysfunction [76]. Inflammasome is an intracellular multiprotein complex, and it involves in IL-1β and IL-18 secretion and pyroptotic cell death [77, 78]. Recently, accumulating evidence demonstrates that microglia-specific activation of the inflammasomes, such as nucleotide binding and oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, contributes to AD pathogenesis [78, 79]. A compelling study shows that NLRP3 deficiency switches microglial cell from M1 to the M2 phenotype and thereby increases Aβ clearance [80]. These studies indicate that inflammation plays an important role in AD progression. The modulation of inflammasome complex activation could be a promising strategy for AD therapy.

Oxidative Stress

Numerous studies have shown that excessive oxidative stress is present in the brains of AD patients [81]. A postmortem study found that oxidative stress was more localized in synapses and was significantly correlated with cognitive status [82]. Mitochondrial dysfunction and transition metals are known to be involved in disease etiology. Mitochondrial dysfunction due to soluble Aβ in mitochondria and the interaction of transition metal (copper, zinc and iron) with Aβ could lead to the overproduction of reactive oxygen species (ROS) [83-87]. Oxidative stress could promote Aβ production, increase Aβ oligomerization, mediate Aβ-induced cytotoxicity, facilitate tau phosphorylation, and lead to synaptic

loss (reviewed in [88]). Antioxidants, e.g., vitamin E, could slow progression in mild to moderate AD patients [89]. Oxygen radical scavenger Edaravone can significantly attenuate AD-type pathologies and cognitive deficits [90]. Therefore, the interactions between oxidative stress and Aβ, tau, mitochondria, and transition metal facilitate ROS overproduction and subsequently cause synaptic dysfunctions, forming a cross-talk that promotes AD progression.

Cerebrovascular Changes

An autopsy study showed that cerebrovascular lesions are more frequent in AD patients than in normal controls [91]. Moreover, the incidence and severity of cerebrovascular lesions are strongly correlated with Braak stages [92]. Thus, there may be an association between cerebrovascular lesions and AD. Vascular risk factors such as diabetes mellitus and cerebrovascular diseases promote conversion from mild cognitive impairment (MCI) to AD [93, 94]. Both diabetes mellitus and stroke have similar endothelial dysfunction promoting AD occurrence and development [26, 95, 96]. *In vitro* and *in vivo* studies prove that pathological cerebrovascular changes affect cerebral ischemia, Aβ production and Aβ clearance in the AD brain (reviewed in [97]). Thus, cerebrovascular changes should be important target in the prevention and treatment of AD.

In the light of this, AD is likely to have multiple pathogenic pathways downstream of Aβ accumulation. These pathways, including tau hyperphosphorylation, neuroinflammation, oxidative stress and cerebrovascular changes, may promote each other and form cross-talk during disease progression. All serve as important contributors and synergistically produce the clinical syndromes at later AD stages. Thus, these non-amyloid pathogenic pathways should also be targeted for successful AD treatment.

PATHOGENESIS ACCORDING TO AD STAGE

AD has been divided into three continuous stages, including the preclinical stage, MCI stage and dementia stage [5]. The trajectory of the pathogenesis is very important for defining the therapeutic targets at different disease stages and thus successful AD management. AD biomarkers (CSF assays and neuroimaging) help in identifying the pathophysiological processes underlying AD development [3]. Additionally, there may be a temporal order to these markers [98]. A better understanding of when these biomarkers change is critical for understanding which targets are appropriate for halting or reversing the neurodegenerative process.

In the Presymptomatic Phase

When individuals are in the presymptomatic phase with normal cognition, biomarkers of brain Aβ are the first to become abnormal. These biomarkers include reductions in CSF Aβ42 and increases in positron emission tomography (PET) amyloid imaging. CSF Aβ was estimated to be reduced 10 to 20 years prior to the clinical symptoms of dementia; Aβ deposition could be detected 15 years prior [99]. These abnormalities of Aβ biomarkers are the earliest detectable signs in presymptomatic AD [3, 100]. The development of Aβ biomarkers also enables an early presymptomatic diagnosis and differentiation from other types of neurodegenerative disorders, which provides a critical opportunity for anti-Aβ drugs to prevent AD onset in presymptomatic individuals who are at the highest imminent risk of progressing to symptomatic AD [101].

At MCI Stages

The biomarkers of increased CSF tau, fluorodeoxyglucose (FDG) PET and structural magnetic resonance imaging (MRI) become positive only when synaptic injuries and neurodegeneration sharply increase during AD. CSF total tau and hippocampal volume become abnormal less frequently than CSF Aβ42 [102]. Hypometabolism and hippocampal atrophy are later events that present after Aβ deposition; they present significantly sooner in patients with MCI and AD than in individuals with normal cognition [103]. Using various imaging modalities, hippocampus and entorhinal cortex volumes [104] and FDG-PET-assessed glucose uptake [105] were proven to be the best biomarker candidates for predicting conversion to AD. Similar to the total CSF and phosphorylated tau, FDG PET and structural MRI are biomarkers that are used to measure downstream neurodegeneration (reviewed in [3]), and tau hyperphosphorylation together with Aβ contributes to the synaptic injuries and neuronal degeneration at MCI stages.

During Dementia Stages

Several other biomarkers appear in patients with clinical cognitive impairment. Amyloid PET has been shown to change little over time, whereas FDG PET hypometabolism expands significantly in AD patients with dementia [106]. Molecular PET imaging with specific radioligands targeting biological processes such as microglial activation and reactive astrocytes could help us visualize the progression and the severity of neuroinflammation in AD [107]. These methods show that tau hyperphosphorylation and non-amyloid pathologies substantially accelerate disease progression during the stages that present with dementia.

Temporal ordering of biomarker abnormalities tracks the pathophysiological changes versus time, implying that AD pathogenesis varies according to the stages of the disease [108]. The excessive accumulation of Aβ and age-related early synaptic injuries initiates pathophysiological changes in the preclinical stage. The cross-talk between Aβ and tau leads to synaptic injuries and neurodegenerative changes after an Aβ trigger event at the mild cognitive impairment stage. During the stages that present with dementia, clinical cognitive deficits are the consequences of progressive neurodegeneration caused by a sequence of events, including Aβ toxicity, tau phosphorylation, inflammation, oxidative stress and other pathological events.

The current understanding of the AD pathogenesis is limited. Further efforts should elucidate the trajectory of AD pathogenesis and establish practical diagnostic criteria for clinical use, which is key in developing effective strategies for AD prevention and treatment.

PERSPECTIVE ON TERTIARY PREVENTION STRATEGY FOR AD

Because of the similarities between AD and stroke, we can apply successful stroke management strategies for AD management.

The Successful Management of Ischemic Stroke

The major strategy for stroke management, named the tertiary prevention strategy, has proven to be successful. Improving the modifiable risk factors, such as diet, lifestyle (e.g., physical activity and smoking), hypertension, diabetes and hypercholesterolemia, represent the primary factors in stroke prevention [109]. Secondary prevention by controlling risk factors plus targeting atherosclerosis at the TIA stage is also an effective measure to prevent stroke occurrence [110]. When primary prevention and secondary prevention have failed, treatment or tertiary prevention becomes the most useful approach to fight the disease. Composite therapeutics targeting vascular risk factors, atherosclerosis, neuronal protection, and rehabilitation represent treatment or tertiary prevention option following stroke [111]. The accurate understanding of the pathogenesis of ischemic stroke and a strategy targeting different pathological pathways at different stages of the disease (the tertiary prevention strategy) greatly reduces the incidence and outcomes of this disease.

A Tertiary Prevention Strategy for AD

As discussed above, the course of ischemic stroke can be divided into the pre-symptom stage, the TIA stage and the stroke stage by the appearance of vascular risk factors, atherosclerosis and stroke. Similarly, AD dementia is divided into the preclinical stage, the MCI stage and the dementia stage by the revised diagnostic criteria, which shifted from the diagnosis of a single syndrome to the staging of a complex disease and clinical manifestations. Although the current criteria for AD staging are primarily used in research, biomarker development could assist in detecting presymptomatic AD pathology and in conducting prevention trials in early AD stages.

Because several etiopathogenic mechanisms are involved in AD and the pathogenesis varies at different stages of the disease, the current single target of Aβ at any stage of the disease may be far from sufficient to halt or reverse disease progression. Different targets should be targeted at different stages of AD in a manner similar to that in the tertiary prevention strategy for ischemic stroke. Current drug studies rely on molecular approaches wedded to the Aβ cascade hypothesis; however, adjusting the modifiable risk factors, such as those associated with diet, smoking, sleep and exercise, are likely to play significant roles in preventing AD [112-116]. According to the "Latent Early-Life Association Regulation" (LEARn) model, environmental agents (e.g., drugs, diet, and toxicological exposure) perturb AD-associated gene regulation at very early stage, leading to delayed Aβ overproduction [117-120]. Furthermore, chronic hypoxia [121-123] and systemic diseases [70, 124-128] may also be risk factors and contribute to AD pathogenesis. Therefore, success in the primary prevention of stroke via controlling vascular risk factors at the presymptomatic stage implies that controlling modifiable factors (e.g., diet, smoking, sleep, exercise, hypoxia, systemic diseases and environmental factors), preventing the production of Aβ, protecting synaptic function and inhibiting tau hyperphosphorylation at the preclinical stage should represent the primary prevention of AD.

However, these strategies may show limited efficacy in MCI and symptomatic AD patients; similarly, targeting vas-

cular risk factors alone is an ineffective approach to treatment for TIA and stroke. Atherosclerosis and TIA could be analogous to tau hyperphosphorylation and MCI, respectively; thus, therapeutics should focus on the removal of Aβ plaques, the protection of synaptic function and neurons, and the attenuation of tau hyperphosphorylation at the MCI stage, called secondary prevention. Because these comprehensive therapeutics targeting the root cause and all secondary lesions are the treatments or tertiary prevention for stroke, we should give priority not only to Aβ but also to other pathological pathways, such as tau hyperphosphorylation, neuroinflammation, oxidative stress, synaptic injury and neuronal protection, in the treatment or tertiary prevention of symptomatic AD. Besides the pharmacological treatment, the non-pharmacological treatment such as acupuncture [129], transcranial magnetic stimulation [130-132] and deep brain stimulation [133, 134] might be also beneficial. (Fig. **1**).

Several primary and secondary prevention trials for AD are underway. Two studies note that relative reductions in the prevalence of several modifiable risk factors (e.g., physical inactivity, smoking, midlife hypertension, midlife obesity, diabetes, and depression) significantly reduce the incidence of AD, which implies great potential for AD prevention [135, 136]. The Alzheimer's Prevention Initiative (API) trial enrolled 300 cognitively normal individuals over the age of 30 from families carrying the PSEN1 mutation to test the preventative effects of the anti-Aβ monoclonal antibody crenezumab in AD [137]. The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) is another preventive trial that seeks to enroll 400 cognitively normal younger individuals with dominantly inherited AD and aims to test two monoclonal antibodies (gantenerumab and solanezumab) targeting different forms of Aβ [138]. The Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, proposed as a secondary prevention trial, focuses on clinically normal individuals aged 65 to 85 years with amyloid accumulation on screening PET scans and those with subtle cognitive symptoms [139]. The therapeutic agent for this trial is the monoclonal antibody solanezumab. Whether solanezumab can slow the rate of cognitive decline remains unknown. Most current and past clinical trials for AD treatment that target at Aβ or other targets alone represent tertiary prevention, and all have failed up to now. Comprehensive therapies targeting Aβ as well as non-amyloid pathological pathways should be developed for future tertiary preventative trials.

The tertiary prevention strategy holds promise for AD management; however, the creation of such a strategy for AD faces numerous hurdles, including a complete understanding of the disease pathogenesis, the establishment of highly sensitive and specific methods to detect AD patients at the early stage of the disease, the identification of biomarkers that are pathogenesis-specific and can reflect the severity and stage of the disease, the validation of the pathogeneses downstream to Aβ as therapeutic targets, and the development of effective drugs or interventions. Related efforts are urgently needed to fight the disease.

CONCLUSION

AD is a slowly evolving disorder in which Aβ acts as a trigger of several pathophysiological processes and cognitive

dysfunctions. In addition to Aβ, multiple events involved in this progressive neurodegenerative disorder and their pathogenesis vary according to the stage of the disease. AD is a heterogeneous, multi-factorial, and age-related disease and is perhaps better represented by terms such as "systemic disease" or "Alzheimer's syndrome" [124, 140]. The current intervention strategy that targets Aβ alone in AD treatment is far from sufficient to halt or reverse disease progression. To achieve success in AD management, an accurate understanding of the pathogenesis and identification of modifiable risk factors of the disease are necessary. The tertiary prevention strategy should represent a promising avenue in AD management.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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