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Therapeutic Strategies for Alzheimer's Disease Targeting Tau Protein and Microtubule Axis

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a complex course, and at present, only symptom management is available. Given that microtubule disassembly and neuronal toxicity caused by Tau hyperphosphorylation and aggregation are central to the onset and progression of AD, targeting the "Tau-microtubule axis" has become one of the main directions for the development of disease-modifying therapies (DMTs). This article systematically reviews the latest progress in intervention strategies targeting the Tau-microtubule axis according to the logical framework of "Tau pathogenic mechanisms—targeting Tau expression—inhibiting Tau aggregation—stabilizing microtubule structure—modulating EB1/EB3 dynamics and restoring their downstream repair programs". First, soluble oligomers (TauO) resulting from abnormal phosphorylation of the Tau protein can cause microtubule destabilization, synaptic toxicity and pathological spread, and exhibit synergistic toxicity with Aβ. Second, mRNA-level degradation (e.g., ASO drugs such as BIIB080 and AAV-miRNA) and immunotherapies can reduce pathological Tau expression at the source or peripherally; small-molecule inhibitors (e.g., LMTX and ACI-3024) can block the formation of toxic Tau aggregates. Third, microtubule stabilizers (e.g., Epothilone D, NAP) can restore the axonal transport network, and allosteric inhibitors (e.g., EBIN) can correct pathological calcium overload in the endoplasmic reticulum by blocking the abnormal binding of EB3 to IP3R3 and activate chromatin remodeling and repair programs. Single-target strategies have the problems of low blood-brain barrier permeability and limited intracellular target access. The following developments are expected to include high-precision biomarker screening (e.g., p-tau217, Tau-PET), new delivery vehicles, and combination therapies that target multiple links in the Tau-microtubule axis.

Keywords: Alzheimer's disease, Tau-microtubule axis, Tau oligomers, EB1/EB3 activity, Disease-modifying therapy

1. Introduction

In the past five decades, as the health system has improved continuously and new technologies for diagnosing and treating diseases have been developed, the average life expectancy of people around the world has been gradually increasing. According to statistics released by the World Health Organization, by 2050, the proportion of the world's population aged 60 and over will reach 22%

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and will have increased from about 12% in 2015; countries such as Japan and South Korea have long been classified as ageing societies. Given the above, neurodegenerative diseases, especially Alzheimer's disease and other dementias (ADRD), as well as Parkinson's disease (PD), are gradually becoming serious and widespread problems in the world today, posing a serious threat to public health and placing a heavy economic burden on the entire country. Alzheimer's disease (AD) can be inherited in families or occur spontaneously. The typical clinical features of this disease are mainly cognitive deficits in memory; however, there are also some rare subtypes in which the initial signs are not memory problems but other types of cognitive disorders.

Alzheimer's disease has various neuropathological features, such as extracellular amyloid-beta (Aβ) plaques, intracellular tau-containing neurofibrillary tangles (NFTs), and neuroinflammation; these are not the only ones. However, at present, there is no cure; the existing treatments (mainly cholinesterase inhibitors and glutamatergic modulators that enhance neurotransmitter function) only alleviate symptoms and cannot stop the progression of the disease, so as the pathological process advances, the patients' conditions will continue to deteriorate. In addition to their limited clinical effectiveness, the current anti-dementia drugs also have significant restrictions on testing, application and access, and thus their cost-effectiveness has been widely questioned. Therefore, at this time, new therapeutic targets need to be explored urgently to overcome the limitations of existing drugs, which "only alleviate symptoms" [1].

The Search for therapeutic targets should be based on the pathogenesis of AD. Although the precise mechanism of AD has not been fully revealed, the most significant and widely accepted hypotheses to date, such as the cholinergic hypothesis, the β-amyloid cascade hypothesis, the tau hypothesis and the dual-cascade hypothesis, all focus on the pathological changes induced by Aβ peptides and tau protein aggregates [1]. As tau tangles are linked to neurodegeneration, a way to prevent abnormal accumulation and entanglement of tau protein should be used in the development of Alzheimer's disease drugs. This review will introduce the latest achievements at five levels: "mechanisms by which tau protein causes AD—targeting tau expression—inhibition of tau aggregation—microtubule stabilisation—restoration of EB1 and EB3 activity", and provide a comprehensive system for evaluating therapeutic strategies for researchers.

2. Mechanisms by which tau protein causes Alzheimer's disease

Tau is a heat-stable member of the microtubule-associated protein (MAP) family that binds to microtubules (MTs) and is primarily expressed in neurons. Tau is subject to many kinds of post-translational modifications, such as phosphorylation, glycosylation, ubiquitination, deamination and oxidation. Among them, phosphorylation is the most prominent type that regulates the binding of tau to microtubules. The following sections will systematically introduce the primary pathological mechanisms by which tau protein causes Alzheimer's disease (AD), such as abnormal tau phosphorylation, the formation of toxic oligomers, synergistic interaction between tau and Aβ, and intercellular propagation of tau.

The phosphorylation level of tau is regulated by the activity of some enzymes, such as MARK, Cdk5, GSK3b and GSK2A. An increase in kinase activity and a decrease in phosphatase activity result in an imbalance among these enzymes and thus excessive phosphorylation of the tau protein [2]. Hyperphosphorylation changes the shape of tau protein and prevents it from binding to microtubules. Free tau monomers bind to one another through β-sheet structures to form dimers, trimers and other larger soluble oligomers. Therefore, the self-aggregation of highly phosphorylated tau may produce soluble tau oligomers (TauO) of different sizes. At present, it is widely accepted that large tau assemblies (straight filaments, paired helical filaments (PHF), neurofibrillary tangles

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(NFT), and ghost tangles) are unlikely to be necessary or sufficient causes of tau-induced neurodysfunction and toxicity. It is smaller, more dispersed oligomers that are directly responsible for the damage in Alzheimer's disease [3]. An increasing number of studies have shown that soluble TauO is a harmful type of tau, and granular tau oligomers (gTauOs) are considered to be the most toxic form. They appear before NFTs, accumulate in synapses at a much higher rate than NFTs, and can directly cause synaptic dysfunction [2]. After the formation of soluble TauO, tau dissociates from microtubules (MTs) and thus causes a collapse in the structure of MTs. At the same time, the dissociated tau is no longer restricted to the axon and may mistakenly enter dendrites and postsynaptic regions, thus damaging synaptic integrity and impairing neural signal transmission.

Tau and AβOs also have a certain degree of synergy. Tau has been identified as a mediator of Aβ toxicity and is one of the first targets of AβO-induced neurotoxicity. Neurons from tau-knockout mice are resistant to AβOs, and reintroduction of tau restores the cells' sensitivity to Aβ. AβOs induce mislocalisation of tau to dendrites and promote tau hyperphosphorylation [2]. Tau promotes AβO-induced excitotoxicity (NMDA receptor-mediated) by recruiting Fyn kinase to the postsynaptic membrane, and the two factors mutually enhance each other in a positive-feedback vicious cycle.

In addition to the above pathophysiological responses, TauO cannot enter the nucleus and thus loses the protective effect that native tau normally provides to DNA; as a result, neuronal DNA is more easily damaged, and cell death is further promoted. Toxic TauO can also alter neuronal function and increase their excitability; thus, it may be one of the reasons for seizures in AD. Some studies have also found that TauO causes synaptic loss and neuroinflammation [3]. TauO can spread in cells, according to the above results. Tau can be secreted by neurons into the external space around cells, and then taken up by nearby neurons in a way similar to prion proteins; further, it can spread through the intact brain, thus making Alzheimer's disease a contagious disease [2].

3. Targeting tau expression and protein clearance

As tau is a primary cause of Alzheimer's disease pathology, direct-targeting therapies for this protein have gradually attracted attention and are now considered a new type of disease-modifying drugs following the introduction of anti-β-amyloid (Aβ) therapies. At present, the three main types of tau-targeted therapies are mRNA-targeted (ASO/RNAi), tau-targeting antibodies (immunotherapy), and aggregation/microtubule-targeting small molecules. Compared with the other two ways, mRNA-targeting therapy is expected to cover a broader range of tau pathology at all stages of post-translational modification and subtypes by aiming for complete elimination of pathological tau protein.

mRNA targeting of microtubule-associated protein tau (MAPT) generally reduces the *de novo* synthesis of tau protein. It is convenient to use it because it does not differentiate among various types or sub-types of tau protein; thus, all forms of tau protein can be analysed simultaneously. BIIB080 is an antisense oligonucleotide (ASO) that targets MAPT and is also the first tau-targeting ASO to enter clinical trials [4, 5]. Watson-Crick base pairing is used to bind BIIB080 with intron 9 in the MAPT pre-mRNA transcript, and then the endogenous ribonuclease h1 degrades the MAPT mRNA, thus inhibiting tau protein synthesis [6]. To assess the long-term effects, Edwards and his team conducted a Phase 1b MAD study (randomised, double-blind, placebo-controlled, 36 weeks) that was later extended by a long-term extension period of 64 to 71 weeks, and different dose groups were added to the trial design [5]. Based on the results, BIIB080 was generally well-tolerated, and the most common adverse reactions were lumbar puncture-related headaches and back pain; these were generally mild in severity. BIIB080 reduced CSF t-tau, p-tau181 and intracerebral tau PET signal in patients with mild AD, suggesting that it may inhibit tau pathology and provide support for

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disease-modifying treatment of AD. Another study is added to assess how BIIB080 affects biomarker indices and clinical outcomes in a Phase 2 experiment. Tau positron emission tomography (PET) data show that patients in the BIIB080 treatment group have reduced tau aggregation in several brain areas compared with baseline, and this is the first observation of a disease-modifying therapy reversing (or reducing) aggregated tau pathology in patients with AD. This study is an exploratory one, and the sample size (46 patients) and the number of tau PET subjects are relatively small. The Long-Term Extension (LTE) period did not have a placebo group. All the participants were White; therefore, the results may not be generalizable. MRI shows an enlarged ventricle and a reduced brain volume, but it has not been determined whether these changes are clinically significant [5]. Based on the above positive indicators, BIIB080 has entered a Phase 2 clinical trial (the CELIA study, NCT05399888) [6], and the results will provide more robust evidence of the clinical efficacy of tau-targeted ASOs.

Table 1. Major strategies and research progress targeting the Tau-microtubule axis for the treatment of Alzheimer's disease

Strategy	Drugs	Mechanism	Advantage	Limitation
mRNA-targeted	BIIB080 (ASO)	Binds MAPT pre-mRNA → RNase H1 cleavage → ↓Tau synthesis	Broad reduction of all Tau forms at source	Delivery efficiency; long-term safety unproven
Gene silencing	AAV-miRNA-MAPT	AAV delivers amiRNA for sustained MAPT mRNA silencing	Potential single-dose sustained therapy	Poor brain distribution of AAV capsids; limited whole-brain Tau reduction
Immunotherapy	Gosuranemab, Tilavonemab, etc.	Antibodies clear pathological Tau and block propagation	Highly targeted, direct clearance	Poor BBB penetration, target accessibility, brain exposure limitations
Aggregation inhibitors	Methylene Blue (MB), LMTX, ACI-3024	Prevent Tau monomer assembly into oligomers/NFTs	Directly blocks toxic aggregation	PK variability, brain occupancy, efficacy heterogeneity
Microtubule stabilizers	Epothilone D, Paclitaxel, NAP (davunetide)	Stabilize MTs, restore axonal transport	Reverses MT damage caused by Tau	Paclitaxel: low BBB penetration and neurotoxicity; peptide delivery challenges
EB1/EB3 restoration	EBIN	Binds EB3 C-terminus, blocks EB3-IP3R3 interaction, restores dynamics/homeostasis	Precise modulation, low off-target toxicity	No AD animal models or clinical validation data yet

In addition, among mRNA-targeted therapies, the gene-therapy approach developed by Hogestyn's group to deliver synthetic miRNAs that target MAPT via an adeno-associated virus (AAV) DNA delivery vector has also shown good results in preclinical studies [7]. AAV-mediated gene therapy can achieve long-term silencing of MAPT mRNA by introducing sequences encoding synthetic miRNAs into neurons and using the host cell's transport system for continuous miRNA expression; thus, it is theoretically possible to extend the effect after a single injection. However, experiments in non-human primates have shown that the existing AAV capsids have limited whole-brain distribution after intrathecal injection; only knockdown of the target has been observed at the level of individual neurons, and a reduction in tau at the overall tissue level has not been achieved.

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Therefore, the development of new AAV capsids with a wider brain distribution is required to advance this strategy to clinical trials [7].

Immunotherapies make up the largest proportion of clinical trials directly targeting the tau protein [8], and generally fall into two categories: passive immunotherapy and active immunotherapy (monoclonal antibodies and vaccines, respectively). Many tau antibodies have had their trials discontinued due to insufficient target accessibility (e.g., Gosuranemab and Tilavonemab, which are primarily extracellular) or suboptimal affinity and pharmacokinetics (e.g., RG7345 and Zagotenemab) [8]. These failures suggest that the targets are difficult to reach, the drugs have poor pharmacokinetics, and they cannot cross the blood-brain barrier to reach effective concentrations at the target sites in the brain; as a result, these drugs have failed in clinical trials and have not been able to be used clinically. Therefore, the mechanism of action of these therapies has not yet been fully elucidated in the future. At the same time, some scholars have also studied small-molecule inhibitors (such as methylene blue derivatives) that can inhibit tau aggregation, but none have shown clinical efficacy to date. mRNA-targeting strategies generally have the largest theoretical space, but problems of delivery efficiency and safety have not been solved; however, immunotherapy is developing rapidly. They are restricted to the blood-brain barrier and intracellular sites. Small-molecule inhibitors are still in the initial stages of research and have not yet shown good clinical results (see Table 1).

4. Inhibition of tau aggregation

In the course of pathology for Alzheimer's disease (AD), Tau protein is abnormally phosphorylated and misfolded at the monomer level, gradually forming toxic oligomers, pre-tangles and mature neurofibrillary tangles (NFTs), which directly cause microtubule disassembly and neuronal damage [1, 9]. Therefore, to prevent the formation of toxic oligomers and fibrillar structures of Tau protein, one of the main ways to address the "Tau-microtubule axis" and maintain microtubule stability and neuronal survival is to inhibit it [9].

Methylene Blue (MB), a classic Tau aggregation inhibitor, can effectively block Tau assembly in vitro [9]. Oral administration of methylene blue as a preventative measure in mice carrying full-length pro-aggregating human Tau (2N4R TauΔK280) has been shown in preclinical studies to significantly reduce pathological Tau misfolding and oligomerisation, thus successfully preserving spatial learning and memory performance [1]. Leuco-methylthioninium (LMTX), a reduced derivative, has also shown the effect of reduced aggregation and alleviation of Tau-induced neuroinflammation in preclinical models by enhancing blood-brain barrier permeability [1].

Methylene blue-derived compounds and natural polyphenols such as curcumin have also exhibited strong inhibition of Tau aggregation; in fact, some clinical studies have shown that they can enhance patients' memory and decrease Tau-PET signals [1]. Additionally, new small-molecule inhibitors (such as ACI-3024) have been developed in the clinic and show good blood-brain barrier penetration and targeted binding [1]. Innovations in medicinal chemistry have led to the development of many new drug candidates with excellent potency and bioavailability, and they can specifically target Tau aggregation in the human brain [1].

Although some tau aggregation inhibitors have shown promising results in preclinical studies, the following problems have been identified during the subsequent clinical trials: insufficient intracellular target occupancy, suboptimal pharmacokinetic properties, and significant interindividual differences in efficacy. A relatively low target-binding affinity may lead to different drug exposures in different people and thus increase the variability of treatment response [1]. In the future, research will likely focus on employing peripheral plasma biomarkers (such as p-tau217) and

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Tau-PET for more accurate diagnosis and early intervention, as well as combining Tau aggregation inhibitors with Aβ clearance therapies or anti-inflammatory drugs to achieve multi-target synergistic treatment [1].

5. Stabilizing microtubules

Tau protein is a normal component of microtubules that, when hyperphosphorylated and aggregated in tauopathies such as Alzheimer's disease (AD), detaches from microtubules; consequently, the microtubules lose their structural support, disrupting the movement of cellular contents by axonal transport. Therefore, directly stabilizing the structure of microtubules with small-molecule drugs or peptides to rebuild the transport network in neurons has become a type of treatment for the disease progression of Alzheimer's disease (AD) [10].

At present, the two main categories of studied microtubule stabilizers are anticancer small-molecule compounds and endogenously derived peptides. Among small-molecule compounds, paclitaxel promotes microtubule polymerization and increases the proportion of stable microtubules (such as dynein-related unstable microtubules), thereby restoring axonal transport in animal models [1]. Paclitaxel has poor blood-brain barrier permeability and peripheral neurotoxicity, so it is not ideal [10]. Epothilone D is a typical new class of small molecules that can cross the blood-brain barrier efficiently, and it has been shown to enhance axonal function, reduce pathological tau accumulation, and protect cognition in tau-mutant mice [10]. In addition, the sponge-derived compounds Peloruside A and Laulimalide bind to the non-taxol-binding sites of tubulin and can stabilize microtubules independently in the presence of Tau overexpression, thus having unique clinical application prospects [10].

In the presence of AD pathology, excessive phosphorylation of Tau often disrupts the dynamic-tracking function of the EB protein at microtubule ends and thus worsens impaired axonal transport. NAP directly inhibits the path of damage by promoting the association of EB and Tau. Among peptide-based drugs, the eight-amino acid peptide NAP (Davunetide, sequence NAPVSIPQ) is derived from the activity-dependent neuroprotective protein (ADNP) and has shown significant neuroprotective and microtubule-stabilising effects [10, 11]. NAP has an SxIP-binding motif and is associated with the end-binding protein (EB) [11]. NAP has been shown to promote the formation of EB3 homodimers and increase the binding efficiency of EB1/EB3 to Tau protein by approximately 20-fold in some studies. Under the stress of zinc toxicity, NAP re-recruits EB proteins and Tau to microtubules to prevent microtubule disassembly [11]. NAP also regulates the tyrosination cycle of tubulin in cellular and animal systems, increases the density, length and motility of EB1 comets in living cells, and significantly improves axonal transport impairment and cognitive dysfunction caused by ADNP deficiency or Tau hyperphosphorylation [10, 11].

In short, small-molecule compounds have the advantages of in vivo stability and easy administration but are prone to peripheral toxicity; peptide-based drugs are highly targeted and specific, but the efficiency of intracerebral delivery is still a problem. Therefore, combination therapy with Tau aggregation inhibitors or anti-Aβ therapies may represent the next direction for research. Microtubule stabilization strategies should focus on combination therapy, delivery optimization, and precise screening. Combination with Tau aggregation inhibitors or anti-Aβ drugs is expected to have a synergistic effect; brain-targeted delivery systems, such as nanocarriers, are necessary for the translation of peptide drugs, and screening for suitable patients using p-tau217 and Tau-PET can improve the response rate [10, 11].

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6. Restoring EB1 and EB3 activity

End-binding proteins (such as EB1 and EB3) are essential components of the microtubule plus-end tracking protein family that regulate microtubule dynamics and maintain the stability of the microtubule network [12]. Microtubule dysfunction and excessive EB3-receptor binding under pathological stress can damage the endoplasmic reticulum membrane and lead to abnormal calcium release; thus, intracellular calcium signalling is impaired, and cells undergo damage and degeneration [12]. In the course of pathology for Alzheimer's disease (AD), excessive phosphorylation of tau protein is often associated with microtubule depolymerisation and dysfunction of terminal proteins; thus, it may indirectly affect the dynamic binding of EB3, and regulation of EB3-mediated microtubule-terminal dynamics and calcium signalling is likely to have therapeutic value.

EBIN is a selective allosteric inhibitor peptide that targets this pathological interface, specifically binds to the hydrophobic pocket region at the C-terminus of EB3, and allosterically blocks its abnormal binding to endoplasmic reticulum receptors by inducing long-range conformational changes [12]. At the functional level, EBIN dose-dependently inhibits pathological calcium release and barrier damage without altering basal calcium concentrations in the endoplasmic reticulum, and is free from cytotoxicity or apoptosis; thus, it precisely regulates the physiological activity of EB3 [12]. Further studies have shown that restoration of normal function in EB3 via EBIN can prevent the downstream pathological calcium overload, promote chromatin remodelling and restore genomic accessibility, and activate key maturation and repair transcriptional programmes, including those involving MEIS2 and PAX6, to enable cells in a stress-stalled state to restart tissue regeneration and repair mechanisms [12].

This EBIN-based precise allosteric inhibition strategy avoids the non-specific cytotoxicity of the previous microtubule-stabilising agents and comprehensively restores microtubule and cellular homeostasis through a cascade of mechanisms—"inhibiting pathological calcium overload"—reestablishing chromatin accessibility—activating repair transcription networks—providing a new molecular regulatory tool and theoretical basis for targeting the Tau-microtubule axis in Alzheimer's disease (AD) [12].

7. Conclusion

The complex neuropathological features of Alzheimer's disease (AD) limit the effectiveness of single-target interventions, and microtubule disassembly and neuronal toxicity caused by Tau protein hyperphosphorylation and aggregation are the core links in the disease progression cascade. This review systematically examines the intervention strategies to address the "Tau-microtubule axis" in five dimensions, and demonstrate that, in light of the limitations of traditional "symptom-relief-only" therapy, blocking the assembly of soluble Tau oligomers (TauO), restoring microtubule structural integrity, and correcting abnormal downstream signal transduction are required. At the same time, the addition of microtubule stabilizers (such as Etoposide D and NAP) and EB3 allosteric inhibitors (such as EBIN) has further revealed and targeted the entire pathway of structural repair to "inhibit pathological calcium overload—reshape chromatin accessibility—activate repair transcription networks", providing entirely new molecular regulatory tools for protecting and restoring neuronal homeostasis.

Although therapeutic strategies that target the Tau-microtubule axis have shown good results in clinical trials, many problems still need to be solved in current research, such as low blood-brain barrier permeability, limited access to intracellular targets, risks of peripheral toxicity, and

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significant inter-patient variability in efficacy. Future clinical translation and breakthroughs will focus on the following three directions: First, optimise drug delivery systems by employing nanocarriers or new AAV capsids to enhance the exposure and targeting of the intracranial site; Second, combine peripheral plasma biomarkers (such as p-tau217) with Tau-PET imaging technology for early and accurate diagnosis and patient stratification; Third, explore multi-target combination therapy strategies that organically integrate Tau aggregation inhibition or microtubule stabilisation approaches with Aβ clearance therapies and anti-inflammatory treatments to achieve substantial breakthroughs in disease-modifying treatment for AD via multi-pathway synergistic effects.

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