

Polymeric Nanotherapeutics for Alzheimer's Disease: Summary and Outlook

Alzheimer's disease (AD), one of the most prevalent progressive neurodegenerative disorders, is characterized by neurological dysfunction and is closely linked to learning and memory impairment. Despite tremendous effort being involved, several anti-AD drugs come into clinical trials difficult to succeed due to the complex AD pathogenesis and the blood-brain barrier (BBB). Given the complexity, many hypotheses have been put out to explain the etiology of AD, including the A β cascade hypothesis, tau hypothesis, cholinergic hypothesis, neuroinflammation hypothesis, and others. The primary pathological characteristics of AD are precipitated plaques composed of β -amyloid (A β) and neuronal fiber tangles (NFTs) made of aberrant tau protein. Extensive researches have concluded that the imbalance of A β homeostasis can produce various toxic amyloid aggregates and finally lead to serious neuron damage and cognitive impairment. Furthermore, the dysregulation of tau protein homeostasis can cause toxic NFTs, leading to microtubule dysfunction and synapse loss, which is associated positively with the development of AD. Increased ROS production as a result of pathological protein processes sets off a chain reaction of oxidative stress. Increased microglial activity, cellular stress, and inflammatory cytokine expression all contribute to an increase in neuronal inflammation, which is hypothesized to encourage cell death and additional protein/peptide aggregation. As previously mentioned, misfolded protein aggregation, oxidative stress, inflammation, and cell death are the basic pathways that have an impact on AD.

Despite decades of clinical trials employing standard treatments, extremely effective therapy for AD has remained elusive. Numerous drugs against AD, including small compounds, peptides, proteins and antibodies, were investigated to find an effective treatment for AD. However, important drawbacks, such as low solubility, poor stability in physiological circumstances and difficulty in multi-target combination therapies, restrict the continued utilization of these medicines. Additionally, the low BBB permeability makes these drugs ineffective for the treatment of AD. In order to solve the current dilemma of AD treatment, it is particularly important to develop multifunctional therapeutic agents with ideal physical and chemical properties. Because of their excellent biocompatibility, steady physiochemical properties, and synthesis and modification flexibility, functional polymer materials have huge promise to address the hurdles in existing

therapeutic bio-reagents applications for AD.

In the last decades, a wide spectrum of functional polymer nanomaterials has been investigated, as potential means for polymeric nanotherapeutics of AD. There are several ways to deliver drugs by functional polymer nanomaterials to control the A β homeostasis, such as curcumin-modified liposome and brain-targeting polymeric nanomicelle loaded with 3D6-Fab antibody fragments.^[1] Unlike the intercellular location of A β , tau is found in the cytoplasm of neurons in the brain, making it difficult for anti-tau therapies to preferentially target neurons' cytoplasm after crossing the BBB. The fusion peptide TPL and responsive polymeric micelles can increase the transport efficiency of neuroprotective peptide and rapamycin through the BBB and into the cytoplasm of neurons.^[2] In addition, polymeric nanostructures can control A β aggregation by electrostatic interaction, hydrophobic interaction, and other mechanisms in addition to serving as medication carriers that target amyloid. For example, multifunctional polymeric nanoparticles modified with A β -targeting peptide and autophagy-inducing peptide and self-assembled nanochaperones based on mixed-shell polymeric micelles can recognize and bind A β onto the surface, prevent A β aggregation and promote its clearance.^[3–5] In addition, nanochaperone can also be designed to interact with abnormal tau, inhibited tau aggregation, block tau spreading and mitigate tau-mediated cytotoxicity.^[6,7] Furthermore, compared to conventional chemical or biological therapies, functional polymer nanoparticles are more effective at treating oxidative stress, mitochondrial damage, inflammation, and cell death. Since AD is a complex disease with multi-factors and many pathological states, polymeric nanomaterials with multiple functions are increasingly promising for AD treatment. PEGylated dendrigraft poly-L-lysines can co-delivery therapeutic gene and peptide drug across the BBB, which can not only reduce the A β plaque deposition but also inhibit the phosphorylated-tau-related fibril formation.^[8]

With an in-depth review of the available contents and therapeutic evidence, we have recognized that although various polymer nanomaterials have been developed as nanotherapeutics for AD, they still face several challenges for improving therapeutic efficacy in clinic applications:

(1) Given the complicated and ambiguous mechanisms underlying AD, disease-modifying therapies should focus

on a variety of pathogenic variables and related targets, including protein homeostasis imbalance, microglial cell disorder, neuroinflammation, ROS, metal ion homeostasis imbalance, etc. As single-target therapies continue to break down, it is necessary to develop new multifunctional polymer nanomaterials with different therapeutic possibilities by modifying and optimizing their properties to target multiple processes of AD. Meanwhile, future attention can be focused on the combination of therapeutic polymer nanomaterials and drugs with different targets to achieve synergistic treatment of AD. In addition, functional polymer nanomaterials are expected to be designed to interact with the biological microenvironment, thereby realizing multi-target AD treatment by regulating different biological processes, such as activation of autophagy or immune.

(2) The BBB regulates the passage of substances between the central nervous system (CNS) and peripheral blood circulation to maintain a constant environment within the CNS. It is arguably the most tightly controlled interface *in vivo*, and frequently prevents the entry of more than 98% of small-molecule medications and nearly all macromolecule pharmaceuticals. Although the integrity of BBB would be compromised as AD progresses, it still substantially hinders drug entry into the brain and lowers treatment efficacy. Functional polymer nanoparticles have gained popularity as a potential solution for delivering medications across BBB to treat AD. They can be designed to penetrate the BBB by passive diffusion, carrier-mediated endocytosis, adsorption-mediated endocytosis, or receptor-mediated endocytosis. Under various pathogenic conditions, lipophilic and partly hydrophilic polymers can diffuse into cells in a passive transport mechanism. Polymer nanomaterials with cations on their surfaces can achieve adsorption-mediated transcytosis through electrostatic interaction with the surface microanionic part of brain endothelial cell lumen. Meanwhile, modification with specific ligands, including peptides, folic acid, polysaccharides, or antibodies can endow polymer nanoparticles with great BBB permeable ability by enhancing BBB deficiencies. Although the application of nanomaterials in the field of AD therapy has shown great potential, the development of polymer nanocarriers is still in the pre-clinical development phase. Due to the poor efficiency and the unclear mechanism of BBB permeability, widespread support is still needed for research aiming at improving the BBB penetration efficacy of functional polymer nanoparticles.

(3) Biosafety is also an important concern in developing polymer nanomaterials for AD treatment. Considering that AD is a typically neurological disease in the brain, the requirements of toxicity for the nanomaterials are stricter than the diseases of other tissues. Thus, the biocompatibility and biodegradability of existing polymer nanomaterials must be evaluated in depth to ensure the safety application in brain. At the same time, innovative polymer nano-

materials suitable for brain applications should be developed. Furthermore, the targeting specificity of functional polymer nanomaterials must be improved in the future to promote accumulation in AD lesions while reducing side effects in normal tissues.

(4) Although numerous *in vitro* studies have documented the potential efficacy of functional polymer nanomaterials, *in vivo* research is still limited. To study the most effective functional polymer nanomaterials-based AD treatment, the behavior of polymer nanoparticles *in vivo* needs to be determined. A suitable animal model is key to understanding the effect of polymer nanomaterials *in vivo*. However, the AD animal model, even the 5×FAD transgenic mouse model, is out of sync with the development of human AD disease and has inconsistent pathological manifestations. Attempts should be made to develop other animal models that are physiologically, genetically and morphologically closer to humans, which is necessary for the study of functional polymer nanomaterials *in vivo* appliances.

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