Review Paper:

Biomimetic nanoparticles for Alzheimer's disease targeting Tau tangles

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Abstract

The progression of Alzheimer's disease (AD) is characterized by the accumulation of amyloid plaques and tau protein aggregates in the brain. While amyloid plaque has been the focus of much research and drug development for AD, recent studies have suggested that tau protein may be a more promising target for therapeutic intervention because of its more closely associated pathology with cognitive decline and neuronal death than amyloid plaque. Tau protein is a microtubule-associated protein that plays a key role in stabilizing the cytoskeleton of neurons. In AD, it gets hyperphosphorylated and aggregates into neurofibrillary tangles, which disrupt the normal health and functioning of neurons.

Several approaches have been undertaken to target tau proteins including immunotherapy, gene therapy and nanotechnology where nanotechnology has been explored as a potential strategy for its management. One promising area of research is the use of biomimetic nanoparticles (BNPs) for drug delivery to the brain. BNPs are eco-friendly, sustainable and better than traditional nanoparticles since they resemble biological things with increased biocompatibility and stability. However, targeting molecular accessibility, drug loading capacity and determining long-term safety are the challenges. Thus to successfully translate these nanofabrications into clinical applications, it is crucial to address the above adversities.

Keywords: Alzheimer's disease (AD), Biomimetic nanoparticles, Neurofibrillary tangles (NFTs), Tau protein.

Introduction

In AD, beta-amyloid protein and tau protein accumulate in the brain, resulting in the death of brain cells and a progressive decline in cognitive abilities[1,7,14]. It is anticipated that the incidence of this condition will increase four-fold by the year 2050[3]. In addition to genetic factors, environmental factors and lifestyle factors are believed to contribute to AD. There are many risk factors for AD including age, family history, genetic mutations, head injuries and chronic conditions such as high blood pressure, diabetes and heart disease. Although Alzheimer's disease has no cure at present, research is being conducted to identify the underlying mechanisms of the disease and develop treatments to slow down or to stop its progression.

Tau, a microtubule-associated protein, in an aberrant state results in neurofibrillary tangles (NFTs), which affect cellular transport. It happens when protein gets hyperphosphorylated and forms aggregates, which interfere with synaptic transmission and normal brain functioning, ultimately impairing cognition. The brains of Alzheimer's patients also show two histopathologically different lesions, NFTs, which are composed of hyperphosphorylated versions of the microtubule-associated protein tau3, in addition to the loss of neuron and synaptic connections[11,21]. To create tau-targeting treatments and to stop or halt AD's growth, it is essential to comprehend this mechanism.

Changes in lifestyle, pharmaceutical therapies and various innovative therapeutic techniques have been investigated to delay the start of AD. A nutritious diet, regular exercise and cognitive stimulation are a few lifestyle improvements that have shown promising benefits in lowering the chance of developing AD. Indeed, the root causes of disease, especially the abnormalities of tau, are the focus of pharmaceutical therapies, however, additionally, cutting-edge therapeutic approaches are being also researched for their ability to stop or delay the progression of AD illness including gene and immunotherapy. One of the most promising approaches to drug delivery and therapy involves nanoparticles, particularly biomimetic nanoparticles.

An essential part of Alzheimer's pathophysiology is played by the peptide beta-amyloid (Aβ). Alzheimer's disease begins when the brain begins to develop Aβ which causes the formation of toxic species like dimers, oligomers and fibrils that induce synaptic dysfunction and cell death. Aβ toxicity further worsens tau phosphorylation and its somatodendritic buildup making synapses more susceptible to plaque toxicity[20]. Fully established Alzheimer's disease is linked to higher tau levels in the dendritic compartment which increase neuronal vulnerability to the damaging effects of Aβ at the postsynaptic compartment[12]. A direct connection between Aβ and tau in producing toxicity in Alzheimer's disease has also been shown by researchers in humans, mice and *in vitro*, but the molecular basis of this interaction is still unknown[4,12,25].

Mechanism of p-Tau in Alzheimer’s

Structure wise Tau protein is composed of four domains which are referred to as the N-terminal domain, the proline-rich domain, the microtubule-binding domain and the C-

terminal domain. Tau protein at its N-terminus region has some phosphorylation sites and is regarded to regulate the functions and stability of tau protein. The area rich in proline contains different sequences rich in proline which are hypothesized to be for protein-protein interactions. Microtubule-binding domain is the largest domain of the tau protein and is responsible for its interaction with microtubules. The domain contains an amino acid sequence of 31 repeats which bind to microtubules. At the C terminus, there are many phosphorylation sites found on tau protein which seem to play a role in its function as well as stability[8].

Tau's exact role in Alzheimer's disease remains unclear, but it is critical for the advancement of the illness. Microtubule-associated tau protein binds microtubules in neurons and stabilizes their cytoskeleton. In AD and other tauopathies, however, this protein aggregates to form neurofibrillary tangles, thereby interrupting normal neuronal activities. Besides, there are also changes in its structure as well as interactions with different proteins that are part of this transformation.

When tau aggregates due to inappropriate phosphorylation, NFTs are created inside neurons leading to detachment of tau from microtubules and aggregation. Thus, these NFTs contribute to the cognitive decline that comes with Alzheimer's disease because they result in abortive functioning and eventually death of neurons. In Alzheimer's disease, there are therapeutic drugs targeting the abnormality of tau pathology that can help ameliorate negative effects, terminate many subsequent reactions and may be useful in the treatment of AD.

Nanoparticles Approach: The most significant problem for AD treatment is the capability of drugs to cross the blood-brain barrier (BBB) and access the brain (Figure 1). Small size, high surface area and capacity to encapsulate drugs are some of their unique properties that have made NPs a target of research in drug delivery[6]. However, NP-based approaches for treating AD have been probed owing to these facts. This challenge can be overcome by making NPs that can encapsulate drugs and deliver them to the brain.

Biomimetic Nanoparticles: Biomimetic nanoparticles (BNPs) are nanoscale particles that imitate or mimic the traits of biological molecules. They mimic biological materials by drawing inspiration from natural processes as well as architecture to enhance their functionality and biocompatibility. Exemplary ones include membrane-coated nanoparticles for example RBC-coated with curcumin containing nano-particles[9]. The latter has higher stability, prolonged circulation time *in vivo* as well as improved targeting. Various materials such as lipids, polymers, or proteins could be employed in their fabrication including endogenous membrane fragments like extracellular vesicles or cell membranes obtained from other cells[5].

The most prevalent kind of nanocarriers are found in cell membranes, which are also present in RBCs, platelets, neutrophils, NK cells, macrophages and cancer cells[2]. In addition to having a variety of functional changes, these nanoparticles can inherit intrinsic features from their parent cells such as immune evasion and tumor tropism[15]. Clinical transformation of conventional nanoparticles is constrained by factors including immunogenicity and probable toxicity hazards of carrier materials, early drug leakage at off-target sites during circulation and drug load concentration.

Using simple synthesis methods, biomimetic nanoparticles can add many capabilities to conventional nanoparticles by employing membrane coverings from cells of various origins. They can dodge the immune system, reducing unintended interactions with healthy tissue and specifically attacking particular cell types or areas of the brain[26]. These nanoparticles can replicate the surface characteristics of cells owing to their biomimetic coatings which help them to interact with the target site and boost drug delivery effectiveness. They can be designed to have increased biocompatibility with focused administration, prolonged efficacy and minimal side effects.

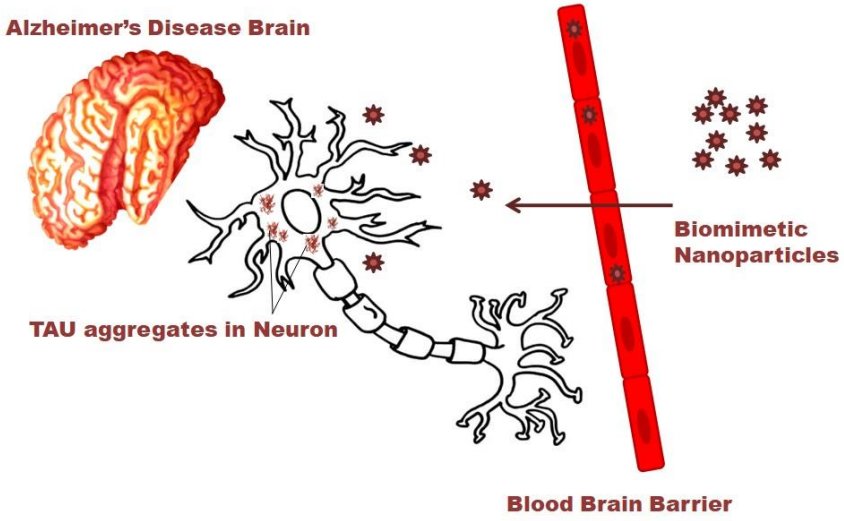

Figure 1: Biomimetic Nanoparticles and Blood Brain Barrier

Table 1
Role of Biomimetic Nanoparticles in neurodegenerative diseases

Membrane source	Type of nanoparticles	Properties of these nanoparticles	Applications
RBCs	Curcumin-loaded RBC membrane-coated PLGA nanoparticles	Low immunogenicity, Long half-life circulation, BBB transportation, Good biocompatibility	Inhibition of tau hyperphosphorylation and accumulation by activation of PKB/GSK-3B pathway[9]
RBCs	Curcumin-loaded Rabies viral polypeptide modified RBC membrane PVP nanocrystals	Prolonged blood circulation, BBB crossing	Reversal of mitochondrial deregulation and inhibition of α-synuclein aggregation[17]
RBCs	Cu_XO loaded pentapeptide modified RBC membrane-coated gold nanozyme	Low immunogenicity, Long half-life circulation, no systemic toxicity	Inhibit Aβ induced oxidative damage and protein corona formation[18]
Exosomes	Rabies viral glycoprotein-modified gold nanoparticles	BBB crossing	Neuronal targeting via acetylcholine receptor[13]
Exosomes	Curcumin-loaded Exosome coated nanoparticles	Increased solubility and bioavailability of curcumin and increased drug penetration across the BBB	Inhibition of Tau hyperphosphorylation through AKT/GSK-3β pathway[24]
Exosomes	Quercetin loaded Exosome coated nanoparticles	Enhanced bioavailability enhanced accumulation in brain region	Inhibition of formation of phosphorylated tau-mediated neurofibrillary tangles via reducing apoptosis of neuron cells[19]
Macrophages	Using this method, rabies virus glycoprotein (RVG29) and triphenyl-phosphine (TPP) molecules are added to cell membranes of peritoneal macrophages of c57BL/6J mice via lipid insertion. A SLN core loaded with Genistein was then coated with the modified membrane.	Crossed the blood-brain barrier	Prevention of abnormal glial activation and neuro-inflammation, lessening neuronal damage and delaying the disease progression[10]

Hybrid membranes, which combine the capabilities of different cell types, also fall under this category since single-cell types are restricted in their ability to perform certain functions[27]. Several findings by various researchers suggested the potent role of biomimetic nanoparticles in treating neurodegenerative diseases (Table 1).

Challenges and Limitations

While biomimetic nanoparticles have many potential benefits, several challenges need to be addressed before they can be widely used in clinical practice. Currently, biomimetic healthcare drugs denoted by cellular membrane BNPs are still in their formative years and have many restrictions associated with them. First, biomimetic nanoparticles are often less stable in terms of long-term storage. They have a lesser shelf life than synthetic NPs because they are made from natural materials that can degrade over time. For example, cell membranes can be sensitive to changes in temperature, pH and other environmental factors which can affect their structure and function. This decrease in the effectiveness and safety of NPs may be due to their clustering and breakdown.

The researchers currently studying new strategies are using cross-linking agents and encapsulating the BNPs in protective coatings to overcome these constraints[28]. Furthermore, compared with synthetic counterparts, BNP fabrication also has challenges of uniformity and scalability. This is majorly because we depend on naturally occurring materials that are highly heterogeneous both in composition as well as in quality like cell membrane lipid and protein compositions. Moreover, the complexity of the technology makes it difficult to apply clinically, due to its innate difficulties. However, this barrier is being reduced by new methodologies implemented for standardizing the manufacturing processes of BNPs with stringent quality control measures[22].

Additionally, after they have been administered into the physiological milieu, BNPs can be recognized as foreign bodies by the immune system thus triggering an immunological response that may compromise their therapeutic efficacy. Furthermore, this can also lead to the manifestation of toxicity and various other adversities. The possible reason for this could be credited to the irregular

encapsulation of nanoparticles. To tackle this, current investigations aimed at mitigating the immunogenicity of biomimetic nanoparticles via practicing stealth coatings or the surface modification of the nanoparticle by incorporating immune-modulating molecules[16,27].

Thus comprehension and optimisation of BNPs' functionality as well as the ability to anticipate their *in vivo* performance can be quite tough. Employing sophisticated imaging and analytical methodologies may further help to design and to optimise their properties in a targeted and customized manner for the enhancement of stability, mitigation of immunogenicity and augmentation of reproducibility[23].

Conclusion

The subject of attention right now is the prospective treatment of AD with biomimetic nanoparticles in the future. Biomimetic nanoparticles may be potent candidates in developing targeted treatments for AD with further developments in nanotechnology and a better understanding of disease pathology. To ensure that these nanomedicines are successfully translated into clinical treatment, or at least a portion of it, issues like cellular penetration mechanism and long-term safety must be addressed. Further, translational studies of biomimetic nanoparticles essentially required reproducibility at a larger scale.

In conclusion, biomimetic nanoparticles give hope for a variety of biomedical applications including the treatment of AD. However, elaborate and conclusive research is needed to optimize their design and efficacy for clinical use and a deeper insight into their physiology and mechanistic profiling will be beneficial to work progressively in the required direction. The management and treatment of Alzheimer's disease could be revolutionized with further research and development in this field.

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