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REVIEW

Therapeutic Potential of Nanomedicine in Management of Alzheimer's Disease and Glioma

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Abstract: Neoplasm (Glioblastoma) and Alzheimer's disease (AD) comprise two of the most chronic psychological ailments. Glioblastoma is one of the aggressive and prevalent malignant diseases characterized by rapid growth and invasion resulting from cell migration and degradation of extracellular matrix. While the latter is characterized by extracellular plaques of amyloid and intracellular tangles of tau proteins. Both possess a high degree of resistance to treatment owing to the restricted transport of corresponding drugs to the brain protected by the blood–brain barrier (BBB). Development of optimized therapies using advanced technologies is a great need of today. One such approach is the designing of nanoparticles (NPs) to facilitate the drug delivery at the target site. The present article elaborates the advances in nanomedicines in treatment of both AD as well as Gliomas. The intention of this review is to provide an overview of different types of NPs with their physical properties emphasizing their importance in traversing the BBB and hitting the target site. Further, we discuss the therapeutic applications of these NPs along with their specific targets. Multiple overlapping factors with a common pathway in development of AD and Glioblastoma are discussed in details that will assist the readers in developing the conceptual approach to target the NP for an aging population in the given circumstances with limitations of currently designed NPs, and the challenges to meet and the future perspectives.

Keywords: therapeutic potential, Alzheimer's disease, glioma, nanomedicine, blood–brain barrier

Introduction

Neoplasia and Alzheimer's disease (AD) comprise two of the most chronic psychological ailments. Age is a major risk factor associated with the deterioration of psychological functions in both diseases.[1,2] Multiple factors including uncontrolled proliferative signals, downregulation of growth suppressors, development of immortal characters, resistance to apoptosis, development of angiogenesis, activation of invasion and metastasis are a few hallmarks of neoplasm.[3] Further epigenetics alterations, genomic instability, avoidance of immune destruction, tumor microenvironment and inflammation associated with reactive oxygen species are other such markers associated with cancer.[4,5] Alzheimer's disease is one of the most common neurodegenerative disorders in the aged population, affecting about 36 million people around the globe and projected to impact 115 million people by the year 2050.[6] Clinical manifestations include progressive dysfunction and loss of neurons, histological alterations, marked by the presence of intracellular tangles of neurofibrils along with extracellular amyloid plaques with reduced cognition functions,[7,8] further characterized by loss of synaptic plasticity, misfold of amyloid β (Aβ) and Tau, hyperphosphorylated at various sites.[9,10] Progressive and spontaneous aggregation of Aβ forming oligomers and fibrils with final deposition of senile plaques are the main products responsible for memory deficit and synaptic damage in AD patients.[11,12] Along with Aβ proteins, metabolomics, proteomics and genomic studies have identified various markers that can predict disease development and progression from mild cognitive impairment (MCI) in AD.[13,14] The multivalent cations in the blood plasma, including zinc, copper and iron, are important factors besides markers in the diagnosis of AD.[15]

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Among all brain disorders from the family of cancer disease, Glioblastoma (GBM) (a type of Glioma) is one of the aggressive and prevalent types of malignant disease.[16] Overuse of statins,[17] hormonal including contraceptive pills and reproductive factors are associated with increased incidence of Glioma.[18] Compared to other malignant tumours, very little progress is made in its clinical outcome due to limitations in the effective drug delivery mechanism.[19] High invasiveness,[20] frequent recurrence [21] and increased mortality rates[22] made the treatment of Glioma a biggest challenge to neuro health scientists. The present therapeutic approach is limited to a combination of radiotherapy, chemotherapy and surgical resection.[23] Though researchers have tried cancer-selective cell killing by boron neutron capture therapy (BNCT) it is still in the juvenile phase before it can be completely used in humans.[24] Incomplete or ineffective treatment of Glioma can infiltrate the residual cells to penetrate the other parts of the brain, making the survival time-limited to 12–15 months. In one cohort study, Glioma (GBM) patients survive up to 5 years and only 0.7% of them can live to 10 years,[25] making treatment of GBM one of the non-competitive trials for researchers with advanced drug delivery technology. Many signaling pathways are associated with GBM but the most important among all is the signal transducer and activator of transcription 3 (STAT3) pathway,[26] involved in cancer proliferation, invasion and progression[27] along with evasion to the immune system.[28] The properties of evasion to the immune system and increased proliferation are assisted by cytokines like interleukin (IL)-6 and growth factors such as epidermal growth factor (EGF) and fibroblast growth factor (FGF) that can activate STAT3[29,30] through tyrosine phosphorylation.[31] The activated STAT3 increases the expression of all genes that are involved in cell proliferation, inhibition of apoptosis and metastasis.[32–34] Further, STAT3 is also associated with stemness and cell death of GBM.[35]

Inverse comorbidity between cancer and AD has been reported in many clinical and epidemiological studies. A transcriptomic meta-analysis of AD and cancer reported significant overlapping factors in association with genes enough to establish the relation between the two disorders.[36–38] Despite advancements in technology and mammoth efforts, present diagnostic and therapeutic options are limited and ineffective in the treatment and prevention of AD and Glioma, making them a high-risk disorder for pharmaceutical and health scientists. Effective and safe development of a new strategy is paramount to understanding the etiology and molecular physiology involved in pathogenesis that can target the new drug entity. The underlying factor for a limited option in the treatment of AD is the presence of the blood–brain barrier (BBB),[38] which protects the brain tissues from all toxic and perilous substances in the blood, retarding the activity of pharmaceutical compounds.[39] The protection and control of solute movement toward the brain are strictly governed by the BBB, composed of basal membrane, neurons, pericytes, astrocytes, tight junctions and microvascular endothelial cells.[40,41] The limitations of various molecules are very strict to cross the BBB including that the molecular weight should be <500 Da,[42] with a varying degree of brain to plasma partition coefficient,[43] high lipid solubility and non-charge at physiological pH.

The permeability to the BBB is dependent on the age factors and it is altered in AD both in structure and functions.[44] The limited options and age of the patients prompted health scientists to develop on an urgent basis a new and effective drug delivery mechanism, that can easily cross the BBB, have minimum adverse effects and maximum bioavailability for treatment of AD. To overcome the limitation of the conventional approach, nano drug carriers were designed to deliver the therapeutic agent at the required site.[45] This limitation of drug delivery therapy for AD and Gliomas can be overcome by nanotechnology in providing a better option and strategy in the field of CNS related diseases, and further the high biocompatibility, low toxicity and stability in the blood can be better hope in the field of therapeutics and for the pharmaceutical industry. Nanoparticles (NPs) facilitate the delivery of drugs to the brain with proper modification required by brain tissue. Table 1 details the selected NPs under investigation potential to cross the BBB. The present review provides some prospective application of nanomedicine in the treatment of AD and Glioma.

Overlapping Biological Molecules Between Glioma and Alzheimer Disease

Tumor suppressor p53 contributes to around 50% of all malignancies[46] including Glioma. The mutation in p53 facilitates angiogenesis,[47] genomic instability,[48] progression of cell cycle, cell survival and escape of cell death,[49–51] migration and invasion,[52] anchorage independence survival and growth.[53] Further, it alters impaired detoxification of reactive oxygen species (ROS) via decreasing Phase 2 ROS-detoxifying enzymes, quinone oxidoreductase 1 (NQ01) and heme oxygenase-1 (HO-1), thus resulting in imbalanced redox homeostasis.[54,55] In contrast to cancer, p53 expression increases in

Table 1 Summary of Application of Drug Nanoparticles Delivery System with Characteristics in Crossing the BBB to Various Brain Targets

S. No	Brain Target Sites	NPs	Characteristics		References
			Zeta Potential (mV)	Mean Size (nm)	
1.	Compromised Intracellular Calcium	Felodipine laden NPs	−25.7±2.52	651±2.10	224,225
		Capsulated Nimodipine in Chitosan	−17.60	119.54	226,227
		Amlodipine NPs	−13.46±0.31 to −23.45±0.33	31.1±8.2	228,229
2.	Regeneration of Neuron	SPIO-AuNPs	−25.1	20.8	230,231
		6-Mercaptopurine- SPIO-AuNPs-neuron-penetrating peptide	−25.8	24.6	232
		Fe_3O_4 NPs with NGF	NA	100	233
3	PPARs Agonist	PLGA-PEG Pioglitazone- loaded nanoparticles	−13.0±0.5	155.0±1.8	234–237
4	*Aβ* Plagues and Tau Proteins	NPs with functionalized *Aβ*1- 42 monoclonal Antibody	−20 to −30	125	238
		RVG@Met@VS	−36.8±0.29	110.25±3.29	239
		CS@Se	−41±3.5	89.1±4.5	240

Alzheimer's disease,[56] and promotes apoptotic neural cell death.[57,58] Accumulation of Aβ level with increased expression of mutated amyloid precursor protein/presenilin (APP/PS) strongly supports the correlation between p53 and AD[59] in the transgenic mice model. Further, functionally altered tertiary structure, called conformational mutant p53, is distinctly observed in AD patients.[60] It is reported that the expression of triggering receptor expressed on myeloid cells 2 (TREM2) in AD is regulated by an altered level of p53.[61] Impaired redox status of Superoxide Dismutase (SOD) and Glutathione Reductase in neurodegenerative diseases like AD[62] corresponds to an increase in the level of unfolded p53,[63] which strongly suggests a possible role of ROS in conformational changes of this gene in AD patients.

Cyclins, the cell cycle regulators in the dysregulated state, lead to cancer initiation and progression, through cyclin-dependent kinase (CKDs) in humans.[64,65] In addition to the cell cycle regulation, Cyclins also modulate and regulate the functions of terminally differentiated neurons, thereby imparting a significant contribution in the maintenance of the normal physiology of neurons.[66] Most extensively studied are Cyclins D, E, F and Y for their role in human diseases. Cyclin D acts as a checkpoint in the cell cycle,[67] controlling the entry of cells from the G0 to G1 phase in Glioma via CKD2/4/6.[67] Cyclin D mutant mice were resistant to cancer via inactivation of CKD 4/6.[68,69] Cyclin D knockdown induced oxidative imbalance in cancer cells by high ROS generation, which promoted the senescence of cancer cells, making it one of the essential targets for Glioma therapy,[70] and besides this, the brains of AD patients have demonstrated high levels of CKD4. Studies have reported that Cyclin D upregulation in AD patients is associated with tau and caspase 3 proteins in cultured hippocampal neurons that are responsible for apoptosis.[71] Recently, it has been deciphered that Cyclin D/CKD4-mediated ROS alters mitochondrial functions and facilitates neurodegeneration in AD.[72]

Cyclin E, a subunit of CDK2, is essential for DNA replication at G1/S checkpoints.[73] Its over-expression in breast cancer,[74] gastric cancer[75] and many other neoplasms[76,77] including Glioma[78] causes genomic instability.[79] Ubiquitin specific peptidase 27 (USP27), a novel therapeutic molecule, targets Cyclin E and retards the migration and metastasis of cancer cells.[80,81] Its expression in AD regulates synaptic plasticity and memory formation,[82] with induction of cell cycle activation in a *Drosophila* tauopathy model of AD.[83] However, deficiency of Cyclin E reduced spine volume and synapses and potentiated the memory impairment[84] key factors in AD pathogenesis.

Cyclin F (FBXO1), a motif of F box proteins, contributes to proliferation and invasion of cancer cells[85] and regulates genome stability through ubiquitin-mediated proteolysis, involved in the production of deoxyribonucleotide triphosphate, centrosome duplication and spindle formation in cancer cells.[86,87] Upregulation of Cyclin F under metabolic stress in Glioma inhibits tumorigenesis via mutation in isocitrate dehydrogenase-1,[88,89] which makes it a potential target for nanomedicine. Missense mutations in the Cyclin F gene are causative of amyotrophic lateral sclerosis (ALS) – a motor neuron disease characterized by a decline in motor functions, due to its binding with valosin, a protein essential for the normal activity of motor neurons;[90] with no specific underlying mechanism still to be deciphered, it is a potential candidate for further investigation to understand its relevance in AD and other neurodegenerative diseases.

Intercellular Communication Between Glioma and Alzheimer Disease

As discussed above, the intracellular molecules p53 and Cyclins have a significant contribution in maintaining a normal homeostatic pathway; any deregulation in these molecules may lead to Glioma and AD. Some research suggests that Glioma and AD can affect each other through intracellular molecules, which complicates the treatment of the two diseases. Recent studies demonstrated that Glioma cells secrete excessive glutamate via cystine/glutamate antiporter xCT,[91,92] thereby changing the microenvironment of neurons in the vicinity of Glioma, resulting in neuronal degeneration and death.[93,94] Glioma cells implanted in striata of experimental animals enhanced the release of glutamate causing rapid growth of Glioma and neuronal degeneration in the vicinity.[95] Neuronal degradation and Glioma formation was countered by blocking the glutamate and N-methyl-D-aspartate (NMDA) receptors with Memantine.[96,97] The whole phenomenon indicates a strong correlation between Glioma and AD. Many chemicals including transforming growth factor β (TGF-β)-1 induced anti-apoptotic factor (TIAF-1), associated with the microenvironment of Glioma forming protective peritumoral capsule, are known to be toxic to neurons.[98] TIAF-1 is also expressed in AD patients,[99] along with Aβ and tumor suppressors including Smad4 and WW domain-containing Oxidoreductases (WWOX or WOX1).[100] In research by Chou et al, a trio of TIAF1/WWOX/p53 tried to explain the tumor suppression; however, the combined effect of TIAF1/WWOX/p53 led to tumor progression, but may have caused brain protein aggregation due to functional antagonism of p53 to WWOX causing neurodegeneration.[101] Zinc finger-like proteins (Zfra) regulate apoptosis, but was able to suppress melanoma-mediated neurodegeneration and restore memory deficit in the hippocampus of mice with AD, via blocking the tau and Aβ protein aggregation[102] that suppresses melanoma-mediated neurodegeneration.[103] Underlying mechanisms behind inter-, intra- and extracellular communications in the brain could be a new benchmark for further studies. Nonetheless, intracellular mechanisms of TIAF1 and Zfra and their crosstalk between brain cancer cells and neuronal cells would be interesting as illustrated in Figure 1.

Therapeutic Targets of NPs in Alzheimer Disease

The advancement in medical science has increased the life expectancy and consequently the prevalence of neurodegenerative diseases including AD. All the present treatments available today are effective but with limitations, thus scaling the complications of AD with age. Multiple molecular and cellular pathways overlap with each other that ultimately lead to neuronal apoptosis.[104] Apoptosis, autophagy dysfunction, pathogenic proteins, impairment, oxidative damage and inflammatory processes are a few contributing factors for all neurodegenerative diseases.[105] Inflammation and oxidative stress are interdependent and linked together for neurodegeneration. Generation and elimination of reactive oxygen species (ROS) both from exogenous and exogeneous sources play a crucial role in maintaining the redox balance.[106] Inflammatory crosstalk between periphery and central nervous system via the blood–brain barrier is observed in Alzheimer's disease particularly involving cathepsin.[107] Activation and dysfunction of microglial disturbs the brain homeostasis, that directly enhances phagocytosis, increases proinflammatory cytokine secretion and increases the release of ROS.[108] It is observed that lipid dysfunction or dyshomeostasis disturbs the regulation of microglial cells due to alteration in phosphoinositides (PiPs), a key molecule in regulation of neuroinflammation. Further, PiPs also regulate the activities of proteins and enzymes essential for Toll-like receptor signaling, endocytosis, purinergic signaling migration and chemotaxis,[109,110] a possible reason for alteration in AD physiology. NPs with 1–100 nm of dimensions can easily traverse through the BBB and prevent aggregation of proteins, reduce inflammation and alleviate stress.

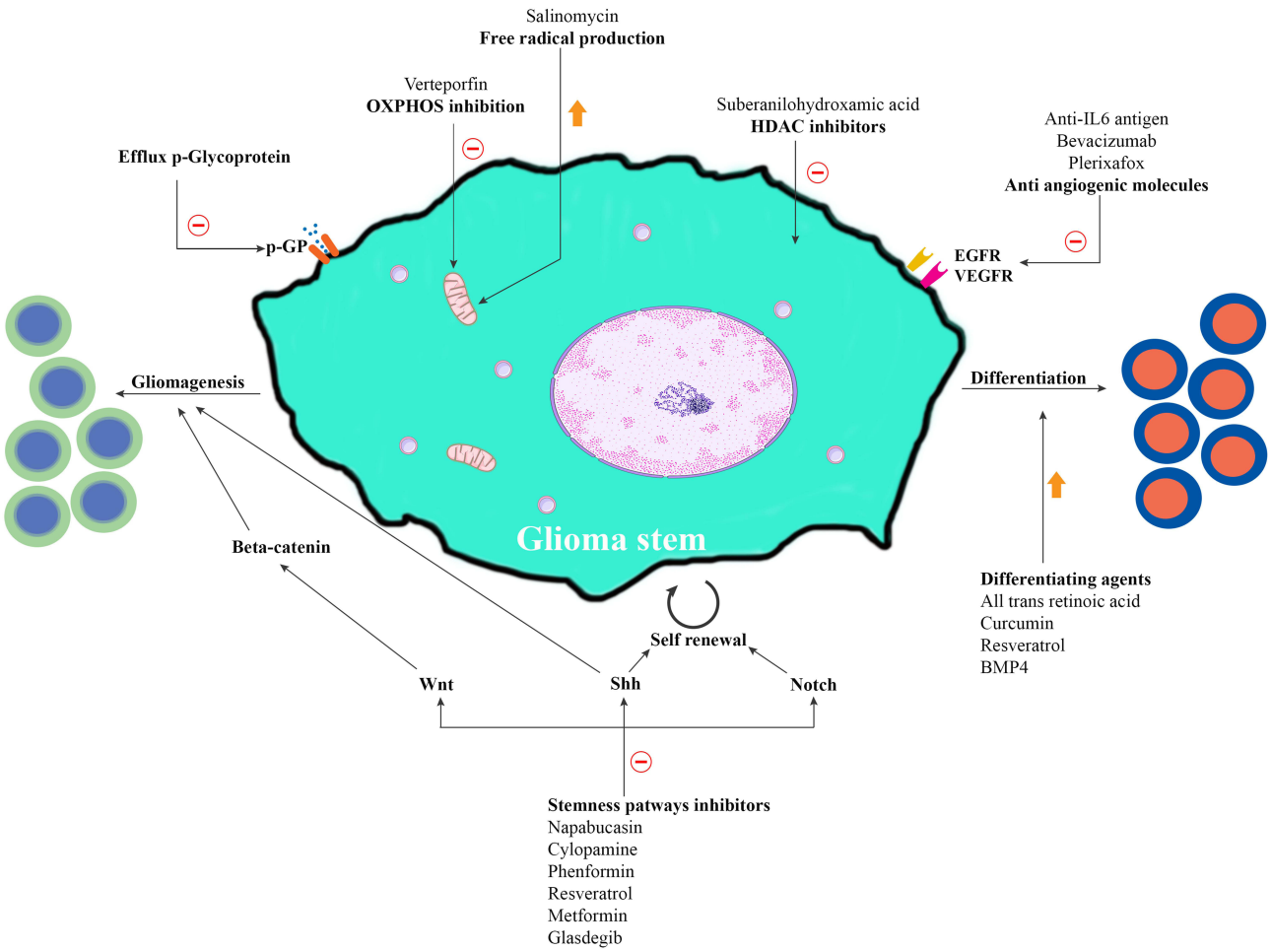

Figure 1 Possible approaches and their mechanisms that can probably eliminate Glioma stem cells. Glioma tumor cells and their metastases originate from stem cells possessing self-renewal and differentiation properties. Self-renewal is attributed to activation of alternative pathways like Wnt, Shh and Notch. Targeting these stemness pathways can eliminate Glioma stem cells. HDAC (Histone deacetylase) enzymes catalyze the deacetylation of histones, facilitate chromatin condensation and are associated with oncogenic transcription factors. HDAC inhibitors may target these enzymes and alter gene transcription. Cancer stem cells exhibit overexpression of OXPHOS (oxidative phosphorylation), which plays a key role in cellular energy. They use stored energy in mitochondrial ATP and generate free radicals, ROS (reactive oxygen species).

Specific Targets Linked to Aβ

Apart from the BBB, the brain parenchyma is the other major obstacle in the delivery of drugs in AD. The parenchymal cells reduce the effective drug concentration at the amyloid plaques, the specific target site in AD patients, thereby reducing its therapeutic value and efficacy.[111] Spontaneous aggregation of Aβ monomers leads to the generation of fibrils and oligomers,[112,113] a phenomenon causing neuronal malfunction and death.[114] The interaction or Aβ monomers aggregation may be prevented by drugs that block such reactions. NPs in the form of liposomes and PEG-PLA have been used as conjugates to prevent this aggregation.[115] KLVFF peptide is known to interfere with the Aβ aggregation,[116] but its inability to cross the BBB and poor bioavailability have retarded its use. However, when loaded in polymeric nanoparticles, KLVFF gave promising results in reversing Aβ-induced pathology in AD. Likewise, nano-forms of Epigallocatechin–gallate resulted in sustained release of the drug that significantly inhibited $A\beta_{42}$ protein and reduced cellular toxicity from metallic elements.[117,118] Liposomes have attracted great attention in transportation of drugs in AD. Curcumin embedded anti-TrF liposomes have shown a high affinity for amyloid deposits in brain samples of AD patients.[119] Similarly, in a mouse model of AD nasal administration of Quercetin,[120] liposomes attenuated degeneration of cortical and cholinergic neurons in the hippocampus.[121,122] Resveratrol is reported to exhibit the neuroprotective function in AD.[123] Liposome formulation of resveratrol, in the treatment of AD, is now well documented.[124] Immunotherapy using nano formulation with antibodies is receiving great attention in the treatment of AD.[125,126]

Immunoliposomes formulated as polyethylene glycol can act directly against the glial fibrillary acid protein.[127] Monoclonal antibodies that can target the Aβ protein in NPs are under the state of research and are showing some promising results in AD patients.[128] Graphene quantum dots (GQDs) and carbon nanomaterial are the two newly introduced nanomaterials which have shown some promising results in treatment of AD when combined with scavenging materials of peptide.[129,130] The charge on the graphene plays a vital role in inhibition of fibril formation, the charge may be transferred to the aromatic residue of protein amino acid.[131] Carbon dots (CDs) have demonstrated potential to cross the BBB, due to presence of amino and carboxylic acid group on their surface that can be conjugated with CNS drugs,[132] making them an ideal nanocarrier to deliver the drugs in CNS to treat glioma and AD. Yellow-emissive CDs and graphene quantum dots were able to prevent the aggregation of Aβ in neuronal cells linked to tramiprosate.[133,134] Similar results were obtained by Gong et al in glycine proline-glutamate loaded CDs to inhibit Aβ aggregation.[135] Identical results were observed when the branched PEI loaded CDs synthesized by Chung et al exhibited cationic surface and were able to suppress the aggregation of Aβ.[136] Preclinical and clinical research have demonstrated that some of the metallic ions including iron, zinc and copper play an important role in manifestation of AD[137] with increased concentration above a certain limit. This can increase the deposition of Aβ[138] and can promote the progression of disease.[139] Zinc loaded nanoparticles in wild type (WT) and APP23 mice model alters the pathological conditions in the mice model by significant effect on proinflammatory cytokines IL-6 and IL-18 and reduction in plague size.[140] Selenium-loaded nanoparticles with penicillamine can act as Aβ inhibitor, with no major toxicological effect on organs and systemic toxicity, making them an important product for biomedical use.[141] Naresh et al successfully developed patient-friendly long-acting donepezil nanocrystals formulation, with a high payload for i.m administration, detectable even after 18 days in blood with improved spatial memory learning.[142] Similar results were obtained for fabricated ApoE3 coated polymeric nanoparticles, enhancing the uptake of donepezil nanocarrier through oral delivery in treatment of AD.[143] Drugs like rivastigmine formulated in novel L-lactide polymeric NP[144] and Chitosan NP[145] were able to alter the beta amyloid proteins in AD model with enhanced brain uptake via oral route and intranasal route respectively.

Specific Targets Linked to Aβ Production

Deregulation or dysregulation of β and γ secretase can lead to overproduction of Aβ protein, making a significant contribution to the etiology of AD.[146] These enzymes can be appropriate pharmacological targets to develop new strategies for the management of AD. However, due to the broad range of proteolytic activity of these enzymes, the inhibition can favor the undesired adverse reactions or effects.[147] To target β secretase, a new concept of RNA interference small interfering RNA (siRNA) was developed with great promising results on AD in the nanoform.[148] They can directly block the causative gene expression with high targeting specificity, in low doses with a simple drug development process.[149] The major challenge for the siRNA in the treatment of AD is their delivery via systemic circulation that can cross the BBB, overcome enzymatic degradation, cell endocytosis and impaired cytosolic transport along with short circulation time. Present nano technology has great potential to overcome these barriers. In a recent study BACE1 siRNA to mouse brain through systemic injection has partially reduced AD neuropathology with low therapeutic efficacy.[150,151] The delivery was made through glycosylated NP siRNA, in transgenic mice targeting BACE1, which has a better potential for clinical translation. Exosomes are naturally occurring NPs with a diameter of 40–100 nm[152] and loaded with siRNA against BACE1, these exosomes altered the expression and production of Aβ proteins in a transgenic mice model.[153]

Specific Targets Linked to Aβ Dispensation/Clearance

Aβ plaques and neurofibrillary tangles are the hallmark of neuropathological lesions of AD. Aβ immunotherapy was able to reduce both extracellular Aβ plaques and intracellular accumulation also leading to a reduction in tau pathology,[154] indicating a direct correlation between accumulation of Aβ and tau[155], where clearance is mediated by the proteasome and is associated with phosphorylation.[156] In vivo antigens are prepared that can mimic the Aβ proteins, Abs targeting these antigens are products that can bind to cerebral Aβ and facilitate their dispense.[157] After obtaining promising results at a preclinical level in animals, its translation into humans resulted in severe adverse effects including vasogenic edema, intracellular microhemorrhages and T cell-mediated meningoencephalopathy.[158] Furthermore, Apolipoprotein (ApoE) and its isomeric forms APOE3 or APOE2 play a critical role in pathogenesis of neurodegenerative disease including AD

risk.[159] The incomplete structural information of ApoE limits its role in understanding the pathogenesis of AD. Single amino acid substitution of ApoE2 and ApoE4 differs from ApoE3, resulting in different impact on risk of disease and its outcome.[160] The binding or interaction of ApoE proteins with Aβ, tau, and α-synuclein alters the response of brain to these aggregates.[161,162] Lipidation of ApoE and the conformational changes that occurs in ApoE on the lipid surface is essential for its binding with the ApoE receptors.[163] The interdomain interaction within ApoE is an essential driving factor for specific isoenzyme difference of activity including Aβ, the biochemical data suggest and indicate non-lapidated ApoE undergoes dimerization and tetramerization at higher concentration for effective pathological activity.[164] Present techniques are insufficient to elucidate the exact interaction of ApoE with Aβ that can eliminate these proteins responsible for AD, however if isoform specific structures related to lipidation and non-lipidation of ApoE complex are solved then newer drugs can be designed that can directly modulate the ApoE–receptor and ApoE–protein interaction at the molecular and submolecular level.[165] Structure alteration of ApoE has already shown potential to alleviate the toxic effects of ApoE.[166] In order to counter the adverse effects of conventional immunotherapy, NPs could give a better advantage over it. Antibodies designed for Aβ are trapped in NPs, and deliver to specific targets.[167] The studies have demonstrated partial fragments of Aβ consisting of 15 amino acids formulated with PLGA have shown full response toward complete Aβ plague proteins via subcutaneous or intranasal route, with minimum toxicity.[168] Still, the delivery of antibodies or antigen for the treatment of AD is in the juvenile stage but gives better hope for AD patients if successful in human trials.

Therapeutic NPs in Management of Glioma/GBM

Preclinical studies on GBM models with NPs emerged with certain advantages compared to their soluble counterparts. Polymeric NPs can easily trap the drug molecule intended for GBM therapy and can exert the required effect on target tissue. NPs are either synthetic like PCL, PLA and PLGA with biodegradable and compatible properties[169,170] or can be natural, viz albumin, chitosan or gelatin.[171] The NPs are modified in order to generate the effective therapeutic concentration in the brain due to presence of macrophage in the liver and spleen that can engulf them.[172] Bioavailability and distribution of NPs in the brain is enhanced by use of hydrophilic surfactant with an increase in half-life.[173] Anticancer drugs like doxorubicin coated with Tween 80 as surfactant, in the form of NPs formulated from poly (n-butyl cyanoacrylate) (PBCA) (270±20 nm) exhibited potential therapeutic effect on GBM.[174] PBCA NPs loaded with doxorubicin have increased the survival time by 85% compared to the untreated control 24% where drug was administered in solution form without NPs, and further without the Tween 80 the survival rate was 38% only.[175] It was important to investigate the toxicological profile of DOX-loaded PBCA NPs (240±40 nm d.; injected IV) and DOX-loaded HAS (404±24 nm d.; injected IV) on healthy animals; both of the NP formulations were less toxic to cardiac and testicular tissues compared to DOX injection after 15 and 30 days respectively.[176,177] Drug concentration in the brain was enhanced many fold administered in PBCA NP form[176] compared to uncoated formulations. In spite of these encouraging results the specificity of the drugs to target the GBM remains a major challenge to health scientists.

Specific Target Sites in GSM

Targeted nanomedicines possess a unique advantage over a non-targeted form, increasing the amount of drug at cancer cells reducing the concentration at healthy cells.[178] The target site achievement can be initiated by addition of target agent in the form of an antibody or ligand that selectively binds to a specific site or receptor on the cancer cells[179] through endocytosis facilitating the cellular uptake of the cytotoxic agent.[180] In case of Glioma cells it is the CD133 receptor that can easily bind with the antibody[181] specific on them. The conjugation of anti-CD133 antibodies with polymeric dendrimers with mercapto-undecahydro-dodecaborate significantly increased the drug uptake.[182] Receptor-mediated targets have great importance in target site delivery of polymeric NP. Transferrin receptors (TfR) are over-expressed in multiple cancers. Anti-transferrin receptor antibodies (anti-TfR) conjugated with resveratrol liposomes reduced the growth of Glioma cells.[183] Paclitaxel loaded liposomes using arginine–glycine aspartic acid were able to initiate the excellent apoptosis on a Glioma cell line by binding to TfR receptor.[184] Although much advancement and effort has been made to specifically target the tumor cells in the brain, limitations of in vivo results made the development of CDs (CD-Asp) with D-glucose (Glu) and L-Aspartic acid (Asp) precursors demonstrated high selectivity

and target potential of CD-Asp towards C6 glioma cells.[185] Optimization of the ratio between Glu and Asp to improve target ability toward brain Glioma cells was the effort of Qiao et al[186] at a molar ratio of 7:3. Over-expression of transferrin receptor on tumor cells and endothelial cell in the BBB lead to the development of CDs conjugate with transferrin,[187] and further this design was modified by Hettiarachchi et al, a triple conjugated CDs based drug delivery system was designed with transferrin, epirubicin and temozolomide, with lot lower concentration that was able to reduce the cell viability of tumor cells, compared to a dual conjugated system.[188] Similar work with CDs conjugation with gemcitabine and transferrin was able to target CNS cancer cells at extremely low concentration with high potential to cross the BBB.[189] Laminin-411 over-expression is correlated with higher recurrence rate and short survival of GSM patients.[190] Antisense oligonucleotides conjugated with polymeric NPs can block the expression of Laminin-411 protein in Glioma cells with increase in the survival time of experimental animals.[191] The presence of specific and overexpressed receptors, particularly epidermal growth factor (EGFR) on the surface of many cancer cells,[192] has made the health scientists explore factors for anticancer activity particularly in the nano formulations. Anti-EGFR antibodies, particularly Cetuximab loaded with iron-bound NPs, gave promising results by enhancing the uptake in these cancer cells.[193] Although there are many limitations of therapeutic nanomedicine that can be practically implemented for humans, the advancement of science and technology in the field of nanomedicine have given health scientists a much needed boost. Using the endocytosis mechanism, expression of certain proteins on these cells has utilized the NPs to target these options. Further, the crossing of the BBB still remains a major limitation for delivery of any kind of drugs to brain tissue. Hence, most of the NPs are designed in such a fashion that they can overcome the limitations of the BBB. In this aspect a cyclic peptide of reduced density gradient (RDG) was conjugated with antisense nucleotide against TUG1 gene in Notch signaling and was targeted with micelles in experimental animals. The results of such experiments were able to give promising output in treatment of Glioma enhanced the slicing of TUG1 gene.[194] Temozolomide is Angiopep-2 a cell penetrating peptide conjugated NP, ingested by the cancer cells via surface modification of iron gold alloy NP a specific target for Glioma cells, a new cancer theranostics approach with minimal invasiveness, is under investigation for better treatment option.[195,196] Kim and colleagues utilized angiopep-2 conjugated liposomes encapsulating gamma secretase, a promising target on glioblastoma stem cells[197] with improved therapeutic effects. Furthermore, Angiopep-2 calcium arenite loaded liposomes in pH sensitive gave well calculated effects when used as anti-Glioma therapy,[198] and such types of formulations are able to reduce tumor volume significantly and prolonged survival of animals in vivo.[199] Activated curcumin and quinacrine loaded liposomes targeted with p-aminophenyl-α-D-mannopyranoside, and this combination was able to target both Glioma cells that can easily cross the BBB.[200] Such type of therapy has not only increased the median survival time but also retarded the tumor growth in experimental animals.[201,202] P53 encoding plasmid decreased the expression of 6-methylguanine-DNAmethyltransferase loaded with chemotherapy agent under Phase II clinical trial (NCT02340156), and the results gave much hope to Glioma[203] patients in time of need. Figure 2 and Table 2 detail the targets in Glioma stem cells and AD.

Multiple factors both intrinsic and extrinsic like high tumor heterogenicity, drug resistance, invasiveness, and targetable mutation are responsible for ineffective GB therapy; further, the design of drug delivery plays a major important role in crossing the BBB that can be specific to tumor site. In view to overcome these limitations Novel design of NPs has given new hope in effective treatment of GBM. Much of the NPs are already in various phase of clinical trials. Oligonucleotides (ONTs) are able to target the oncogenic mechanism delivered in the form of p53 mRNA or PTEN siRNA overcoming the limitations of tumor heterogeneity.[204] Integrins and ApoE are targeted by Dox due to common EGFR by EGFR(V) antibody conjugated to an EnGeneIC delivery vehicle (EDV), loaded with DOX (EGFR(V)-EDV-Dox).[205] A similar approach was reserved with *Pseudomonas* exotoxin with EGFR-targeted, convection enhanced delivery system.[206] Proteins such as Selectins are found to express both on brain endothelial and glioma cells, and NPs loaded with doxorubicin or other chemotherapeutic agent possess a tyrosine kinase inhibition potential,[207,208] that may improve treatment results with reduction in cell resistance.

It is still a topic of debate whether nano-formulations can eradicate Glioma and AD compared to conventional therapy.[45] This system of delivery is much safer with reduced toxicity compared to conventional therapy.[209] Drugs in the nano-formulation are known to improve saturation and maintain or enhanced permeability and retention effect (EPR) along with the concentration at the site of tumor with increase in retention time.[210] The underlying mechanism with EPR

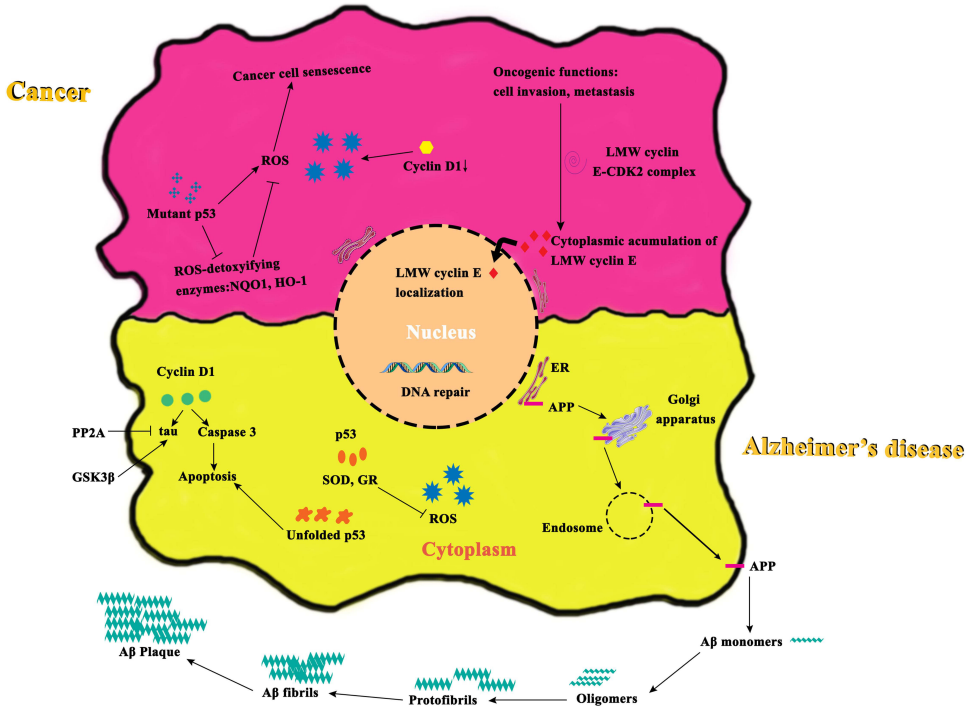

Figure 2 Mechanisms of overlapping fragments in cancer and Alzheimer's disease. Cyclin D1 endorses tau phosphorylation in presence of GSK3β (which is again dephosphorylated by PP2A), and induces apoptosis through a Caspase-3-mediated pathway. Reduced activity of SOD and GR tend to increase ROS production, which causes a conformational change in p53 by unfolding it. This unfolded p53 is also observed in Alzheimer's disease. Mutant p53 decreases the expression of NQO1 and HO-1, the ROS- detoxifying enzymes, and thus induces ROS production. LMW cyclin E forms a complex with CDK2 in the cytoplasm, and activates oncogenic functions like cell invasion and metastasis. APP produces Aβ proteins, Aβ fibrils and plaques.

Abbreviations: APP, Amyloid precursor proteins; Aβ, Amyloid β; CDK2, Cyclin-dependent Kinase 2; GR, Glutathione Reductase; GSK3β, Glycogen synthase kinase 3β; HO1, Heme Oxygenase 1; LMW, Low molecular weight; NQO1, Quinine-oxidoreductase 1; PP2A, Protein phosphatase 2A; ROS, Reactive Oxygen Species; SOD, Superoxide Dismutase.

is associated with rapid growth of tumor, blood vessels in a leaky state and low organized structure of blood vessels further the inefficient lymphatic drainage.[211] It is observed that enhanced potency of 1,3 β-Glucan as an outer shell to chitosan nanoparticles loaded with paclitaxel can prevent hemolysis enabling effective therapeutic advantage against glioblastoma, thus overcoming the systemic toxicities due to paclitaxel alone with increased bioavailability.[212] The safety profile of drugs in nano formulations provides additional advantage compared to free drugs,[213] and further the cancer therapeutic is always at risk and disadvantage due to radiation toxicity, drugs like baicalein in its oral nanoform in preclinical evaluation have modulated the radiation response.[214] Cytarabine loaded liposomes in phase I/II clinical trials have shown additional safety as compared to free drug[215] in patients with secondary glioblastoma. Further, the NPs in case of delivery to glioblastoma gives the protection from enzymatic degradation, metabolism especially in the case of delivery of siRNAs, miRNA and other forms of nucleic acids.[216] Therapeutic nucleic acids have been delivered in the form of polymeric NPs, lipid polymer NPs,[217] gold NPs[218] and superparamagnetic NPs of iron oxide.[219] Such types of formulations increase the efficiency of the target drug to the target gene through enhanced internalization that can easily slice glioblastoma related genes, thus prolonging the survival time period of the model animals. Further, it has been observed that such type of delivery has retarded the efflux of medicine by efflux pumps[220] in cancer cells including ABC proteins.

Future Direction and Limitations

The majority of these novel drug delivery system results available are only preliminary in vitro or in the mouse model. Many challenges may arise during clinical application of these NPs in humans. A poorly explored aspect is any change in the functional activities of a tissue or cell encountered by the nanoparticles while approaching their target. Also, it is not much reported whether and how the electrical impulse conduction of the neurons targeted by NPs are affected. Further,

Table 2 Summary of In Vivo and In Vitro with Drug Nano Formulation Demonstrating the Encapsulation Efficiency in Treatment of Glioma and AD

Drugs	Nano Formulation/ Product	Nanoparticle Encapsulation Efficiency (%)	Results		
			In Vivo	In Vitro	References
Mercapto-undecahydro-dodecaborate	Polyamide amine dendrimers	76.2±4.5	Xenograft model Anti-CD-133	SU2 U-87	241
Resveratrol	Liposomes	>90%	Xenograft mouse model of GBM anti-*TfR* antibody	U-87	183
Paclitaxel arginine– glycine aspartic acid	Liposomes	85.45±1.43	Transgenic male BALB/c mice initiate apoptosis	C6	242
Antisense oligonucleotides conjugated	Polymeric micelles	83.27±1.14	Xenograft model induces cytotoxicity through anti-EGFR mAb	U-87 patient derived cells	243,244
Cetuximab	Iron oxide NPs		Xenograft model Cetuximab induces cytotoxicity	U-87 patient derived cells	193,245
Antisense oligonucleotides conjugated	Polymeric micelles		Xenograft model induces apoptosis and enhances TUG1 silencing		194
Temozolomide	Liposomes	71±0.8%	Xenograft model increases cytotoxicity and alters tumor size	U-87 patient derived cells	196,246
Resveratrol	Nano capsules	99.89±1.3	Increases microglial and astrocyte accumulation with impaired memory and learning potential in *Aβ* graft model of AD rats		247–249
	SLNs	75–100		Improved passage is observed in human endothelial cells/pericytes model of BBB	
Apocynin	Polyanhydride NPs	0.029		Protective against oxidative stress in LUHMES cells Reduction in cytotoxicity of N27 prevention against oxidative stress	250,251
Curcumin	Nanogels	NA		Protection in SH-SY5Y cells against *Aβ* induced cytotoxicity	252–254
	Polymeric NPs	77.99±0.91		Protection in SH-SY5Y cells against *Aβ* induced cytotoxicity from oxidative damage	
	Liposomes	NA	In APP/PS1 mouse model: acted on *Aβ* aggregates		
Rutin	Lipid polymer hybrid NPs	68.06±1.50	In white male albino rats: biodistribution study confirmed brain accumulation	In erythrocytes separated from rat blood: hemolysis test confirmed biocompatibility	255

(*Continued*)

Table 2 (Continued).

Drugs	Nano Formulation/ Product	Nanoparticle Encapsulation Efficiency (%)	Results		
			In Vivo	In Vitro	References
Berberine	Multi-walled carbon nanotubes	NA	In *Aβ*-injected AD rat model: recovered memory performance, reduced *Aβ* aggregates and oxidative stress damages	In SH-SY5Y cells: efficient cellular uptake of the NPs	256
Ginsenoside Rg3	PLGA	65–70		In C6 cells: cellular uptake In THP-1 cells: reduced *Aβ*-induced amyloid plaques formation, oxidative stress damages and pro-inflammatory cytokine levels, reduced expression of gene encoding the β-amyloid A4 precursor In BMVECs/C6 cells BBB model: BBB crossing	257
EGCG epigallocatechin-3-gallate	PLGA	97.1±2.4	In APP/PS1 mouse model: increased synapses, reduced amyloid plaques and neuroinflammation, ameliorated spatial learning and memory abilities	In primary brain microvascular endothelial cells (BBB model): alterations of the BBB integrity through tight junctions' disruption	258
Anthocyanins	PLGA	60		In SH-SY5Y cells: increased cell viability against $A\beta_{42}$, abrogated ROS generation, attenuated AD and neuroapoptotic markers	259
	AuNPs	34	In *Aβ*-injected AD mouse model: prevented tau hyperphosphorylation, reduced microglia and astrocyte activation, reduced neuroinflammatory and neuroapoptotic markers, attenuated neurodegeneration In *Aβ*-injected AD mouse model: prevented tau hyperphosphorylation, reduced protein expression levels of apoptosis and neurodegeneration markers, mitigated synaptic dysfunctions and ameliorated memory impairments	In BV2 cells: prevented tau hyperphosphorylation, reduced protein expression levels of neuroinflammatory and neuroapoptotic markers	260

another important aspect to be considered is that nanomaterials may themselves be cytotoxic and their administration may cause neurotoxicity. Further, as these nanomaterials interfere with BBB integrity, they may create a passage not only for therapeutic drugs, but also favor the entry of toxic substances or pathogens to the brain. Additionally, NPs can interfere with normal cellular metabolism, resulting in increased ROS and altered gene expression. Alhough these challenges are still to be met, extensive research is going on, and every modification in nanotechnologies for drug delivery bypasses the presenting obstacles. Significance of nanoparticle driven drug delivery is increasing. New targets

like mutant genes, DNA synthesis, hypoxia, neuroproteins, neuropilin-1, novel therapies including virus-based NPs, protein based NPs and nucleic acid based NPs with more effective penetration across the BBB have a great potential to unfold a promising era in the treatment of AD, glioblastoma as well as other brain diseases. Furthermore, mRNA (particularly non-invasive PTEN mRNA[221]) targeting Orthotopic Glioblastoma[222] for prophylactic and therapeutics applications in the form of NPs have potential to change the course of many diseases including AD and Glioma.[223]

However, the bottom line still states that NPs need much more extensive research before they can be therapeutically used in humans, without any doubt of their drawbacks.

Conclusion

This article is crosstalk between nanoparticles with promising insight for the two diseases AD and glioblastoma with completely different pathology, where AD results from neuron degeneration while glioblastoma is characterized by rapid cell multiplication; however, the factor common in both is that their treatment is very difficult and unspecific. Development of nanoparticles loaded with drugs has provided a favorable approach to target and release the drugs at amyloid plaques, Aβ, the pathological site in AD patients. Similarly, the drugs in NPs can reach the brain parenchyma by EPR effect, an effective breakthrough in the treatment of glioblastoma. The particle size and physical properties of NPs are essential parameters that influence the penetration through biological membranes in order to obtain the best therapeutic effects of NPs.

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Disclosure

The authors declare that they have no competing interests.

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