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MESOPOROUS SILICA NANOPARTICLES FOR BRAIN CANCER THERANOSTICS

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ABSTRACT

Emerging theranostic nanomedicines or nanocarriers has been considered as a promising therapeutic paradigm that combines therapeutics with diagnostics. These nanocarriers have a brilliant capacity to load both imaging and therapeutic agent onto or into them. The resulting nanosystems are able to diagnose, delivery of drug and monitor the therapeutic response which permit the delivery of therapeutics and concurrently allow the detection modality throughout the entire treatment regimen. In recent years, due to their unique attributes, mesoporous silica nanoparticles (MSNPs) have been extensively studied in the area of cancer theranostics. MSNPs have many desirable features such as mesoscopic arrangement, tunable pore dimensions, a large pore volume, surface area, controllable surface functionalization as well as morphology. These special characteristics make these nanoparticles specific to modular design, in which functional moieties and features may be interchanged or combined to produce multifunctional nano delivery systems suitable for targeting, diagnostic, and therapeutic actions. The functionalization of MSNPs with variety of targeting and imaging agent makes it able for controlled release of loaded drugs, molecular identification and detection. This review covers the latest developments related to the use of mesoporous silica nanoparticles (MSNPs) as a theranostic agent with special focus on brain cancer therapy and diagnostics.

KEY WORDS: Theranostic nanomedicines, mesoporous silica nanoparticles, brain cancer, imaging.

INTRODUCTION

Recent advances in nanomedicines are having a major impact on cancer therapy and diagnosis. With the development of nanotechnology, theranostic nanomedicines have attracted increasing attention in drug delivery, diagnostic and medical imaging. Theranostics refers an integrated nontherapeutic system which combines diagnostic contrast agent with the therapeutic. Initially nanomaterial-based diagnosis and treatment have been done separately but the successful collaboration of molecular imaging and nanotechnology advancement has given a fundamental contribution to the birth of a new, highly

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interdisciplinary research field called theranostics (Xie et al., 2010; Terreno et al., 2012; Muthu et al., 2013; Muthu et al., 2015). It is assumed that a combined technique will result in the acceleration of drug development, improved disease management, reduced risks and reduced cost. Cancer is a disease which needs immediate detection and treatment and hence suitable theranostic approaches are expected to develop. For cancer treatment, nanocarriers as theranostic agents have many favorable physicochemical properties like size, shape, surface area and easily modified structure which results in numerous advantages like longer duration of circulation time, enhanced permeation and retention time, reduced toxicity and higher safety profile (Muthu et al., 2014; Singh et al., 2017; Sonali et al., 2018). By molding nanomaterials into vesicles, various theranostic nanocarriers have been developed to securely deliver drugs and diagnostic agents specifically into targeted sites. Few of the conventional nanomedicines such as liposomes and polymeric nanoparticles have received FDA approval and many are under later stages of clinical trial (Muthu et al., 2012; Muthu et al., 2014; Wicki et al., 2015; Yao et al., 2016, Jo et al., 2016)

Over the last two decades, the development of synthesis and characterization techniques has led to the emergence of new drug delivery systems such as inorganic nano delivery system for therapeutic and diagnostic applications. These are iron oxide nanoparticles, gold nanoparticles, carbon nanotubes, polymeric nanocomposites and mesoporous silica nanoparticles Many nanomaterials are already having imaging properties which are helpful to readily "upgrade" these nanomaterials to theranostic agents by mounting therapeutic functions on them (Muthu et al 2009; Singh et al 2016a; Muthu et al 2016). For example, nanocarriers like quantum dots (QD), gold nanoparticles have excellent optical property that can be used for imaging purposes, in connection with increased biocompatibility and stability. Magnetic nanoparticles MNPs also got marketed attention due to their unique magnetic properties (Rosenholm et al., 2011; Chen et al., 2013; Singh et al., 2016b).

Recently, MSNPs have considered as strong and versatile delivery platforms for theranostic applications. Various studies show that MSNPs provide unique opportunities for simultaneous diagnosis and therapy not only as drug delivery system but also as an imaging modality due to their highly ordered structure, uniform and adjustable pore size, enormous surface area (near 1000 m^2g^{-1}), pore volumes (near 1.0 $cm^3g\text{-}^1$) and versatile functionalization. Their unique properties and siloxane chemistry allow researchers to develop desired functionalized surface with desired ligand for diagnostic imaging and therapy (Slowing et al., 2006; Tarn et al., 2013; Zhang et al., 2016). MSNPs can be easily functionalized with contrast agent for traceable imaging of diagnostic targeting, drug payload for therapeutic effect and biomolecular ligand for targeted delivery of both therapeutic and diagnostic cargos which are well suited to theranostic application. Furthermore, MSNPs can be incorporated with a high concentration (over 30%) of number of cargos like various imaging agents, e.g. fluorophores for optical imaging, superparamagnetic IONPs or paramagnetic gadolinium (Gd)-chelate for MR imaging and therapeutic drugs like anticancer drugs or drugs for other diseases. The high drug load potential of MSNPs makes them efficient tools for multidrug

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delivery, a desirable feature in cancer therapy given the complexity of oncogenic activities (Rosenholm et al., 2012; Wang et al., 2016; Zhang et al., 2017).

MSNPs surface can be modified with various polymers either chemical interaction (through covalent bonding) or physical interaction (by physical adsorption). In addition, the surface of MSNPs can also be functionalized with targeting ligands, for example, antibodies, aptamers, peptides etc. In summary, due to the changeable silane chemistry, many functional moieties could be conjugated to the MSNPs surface easily. Thus, many desired surface properties for theranostic applications could be easily obtained using MSNPs (Choi et al., 2012; Gary-Bobo et al., 2012; Mekaru et al., 2015). In a previous research, Slowing *et al.* investigated the effect of surface functionalization of MCM-41-type MSNPs on the endocytosis by human cancer cells. They synthesized a fluorescein-functionalized, MCM-41-type MSNPs material (FITC-MSN). Three functional groups, 3-aminopropyl (AP), N-(2-aminoethyl)-3-aminopropyl (AEAP), and N-folate-3-aminopropyl (FAP), were grafted onto the external surface of the FITC-MSN. They demonstrated, the uptake of MCM-41-type mesoporous silica nanoparticles by HeLa cells can be regulated by different surface functionalization. Study results indicated that these surface functionalities could also affect MSNPs ability to escape endosomal entrapment, which is an important factor in designing effective intracellular delivery vehicles (Slowing et al., 2006). Another side, in 2010, Cheng et al., reported the development of the first trifunctionalized MSNPs in which they attached a fluorescent reporter (ATTO647N) within the nanoparticle's silica framework for tracking, a peptide (cRGDyK) on the outermost surface for targeting avb3integrin receptor, and a photosensitizer (Pd-porphyrin) within the nanochannels of MSNPs for photodynamic therapy. It was found that in vitro evaluation of the theranostic platform showed not only excellent targeting specificity and minimal collateral damage, but a highly potent therapeutic effect as well (Cheng et al., 2010).

MSNPs FOR BRAIN CANCER THERANOSTICS

Brain cancer is considered as a large unsolved clinical problem while significant advancements have been achieved in the treatment of other cancer. Glioblastoma multiforme (GBM), a high-grade malignant glioma, is the most horrible form of brain cancer characterized by fast-growth and damaging of surrounding brain parenchyma. Intense frequency of recurrences, high resistance to chemotherapy, fast neurological damage, and very low survival rates make brain cancer one of the most dreaded cancers (Rozhkova et al.,2011; Wang et al., 2013; Sonali et al., 2016a; Agrawal P et al., 2017a). Currently available treatment includes surgical removal of tumor followed by radiotherapy or chemotherapy or both. But after getting treatment, the expected median survival of patient with brain cancer is only 14.6 months. It was found that less than 5% of patients live longer than 5 years. This poor condition is primarily due to: A) fast-growth and infiltrative nature of brain tumors result in incomplete removal; B) Presence of blood-brain barrier (BBB) which excludes most of therapeutic agents; and C) development of chemotherapeutic resistance which results in tumor recurrence. As well as, even in patients with strong initial responses to standard treatment regimen,

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most of the patients show tumor recurrences. Hence, it is resulted that available conventional chemotherapy is largely ineffective for treating brain cancer. Thus, there is a critical need for means to overcome the limitations and improve the efficacy of brain cancer therapies (Hernández-Pedro et al., 2013; He et al., 2014; Sonali et al., 2016b: Agrawal P et al., 2017b).

Nanomedicine offers promising therapeutic potential for brain cancer theranostics. The day by day development in nanomaterials has open lots of ways to get rid of various limitation of brain cancer treatment. These nanomedicines which have merged quality of diagnosis and therapy can be promising candidate for better treatment of brain cancer at preliminary stage. During last some years, varieties of delivery systems have been evolved like liposome, polymers, and inorganic nanoparticles (NPs) etc. Many of them have got FDA approval for cancer therapy. Doxil is a first FDA approved nano-drug which is Doxorubicin (DOX) encapsulated liposomes, have shown prolonged circulation time and enhanced bioavailability of DOX, and also reduced adverse effects to heart muscles and other normal tissues. Currently, inorganic NPs have received immense attention for cancer theranostic application due to their unique physicochemical properties (Farokhzad et al., 20016; Choi et al., 2012; Fan et al., 2014; Sonali et al., 2016c; Singh et al., 2016c).

Among them, MSNPs have been realized as one of the most promising platforms for theranostic application in cancer treatment. MSNPs are the multifunctional drug delivery system due to their big surface area with desirable chemical properties, their controllable and fine-tune porous structure for entrapping various moieties, and their biocompatibility (Mekaru et al., 2015). The *in-vivo* behavior of MSNPs has also been fully discussed, and it has been noted that the integral characteristics of the MSNPs and its functionalization with chemical moeity deeply influence the biodistribution, biodegradation, and definitive clearance of cancer tissue. Although there are a few adverse reports, MSNPs are commonly seen as suitable platforms for use in brain theranostics and numerous studies have been carried out using these materials (Rozhkova et al., 2011; He et al., 2014). Moreover, in 2011, the first silica-based tumor diagnostic nanoparticles- Cornell dots (C-dots) were approved by FDA for stage I human clinical trial. C-dots are dye-entrapped silica nanoparticles with ultra-small size (<10 nm), which can be utilized as diagnostic tools to assist surgeons in identifying tumors (Mekaru et al., 2015).

Recently, Mo et al. designed the MSNPs with suitable particle sizes to overcome the blood-brain barrier and antagonize the glioblastoma. They synthesized cRGD peptide conjugate doxorubicin loaded MSNPs of different sizes i.e. 20, 40, and 80 nm. It was resulted that the functionalized nanosystem selectively recognizes and binds to the U87 cells with higher expression level of αvβ3 integrin, sequentially enhancing the cellular uptake and inhibition to glioma cells, especially for particle size of 40 nm. This particle could rapidly enter cancer cells and was difficult to excrete outside the cells, thus leading to high drug accumulation. Furthermore, doxorubicin loaded MSNPs exhibited much higher selectivity and anticancer activity than free Doxorubicin and induced the glioma cells apoptosis through triggering reactive oxygen species (ROS) overproduction. It was observed that doxorubicin loaded MSNPs at about 40 nm

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exhibited stronger permeability across the BBB, and could disrupt the VM-capability of glioma cells by regulating the expression of E-cadherin, FAK, and MMP-2, thus achieving satisfactory antiglioblastoma efficacy and avoiding the unwanted toxic side effects to normal brain tissue. These results suggest that modifying or reducing the particle size of MSNPs nanosystem could be an effective strategy to antagonize glioblastoma and overcome BBB (Mo et al., 2015). In another study, Liu et al. designed the PEGylated SiNPs (PSiNPs) of three different sizes to transport across the BBB and evaluated it in vitro and in vivo. In vivo animal experiments were performed by noninvasive in vivo imaging and ex vivo optical imaging after injection via carotid artery. Confocal fluorescence studies showed that the BBB transport efficiency of PSiNPs is inversely dependent on the size both in vitro and in vivo (Liu et al., 2014).

Due to their versatile multifunctional properties MSNPs have been investigated for application in stimuli-responsive controlled drug release (pH-triggered, temperature triggered, biomolecule triggered etc.) to achieve concentrated dosage release to targeted sites and prevent premature cargo leakage which results in improved drug efficacy and reduced drug side effects (Zhao et al., 2014). In a recent research, Li et al., synthesized pH triggered MSNPs loaded with camptothecin (CPT) and doxorubicin (DOX) (CPT@MSN-hyd-DOX) for synergistic chemotherapy of glioblastoma. It was observed that at pH 6.5 (analogous to the pH in tumor tissues), a fast DOX release was observed that was attributed to the hydrolysis of the hydrazone bonds. In addition, a further burst release of DOX was found at pH 5.0 (analogous to the pH in lyso/endosomes of tumor cells), leading to a strong synergistic effect. In all, CPT and DOX could be delivered simultaneously into tumor cells, and this intelligent nanocarrier has great potential for tumor-trigged drug release for use in the synergistic chemotherapy of tumors (Li et al., 2015).

As a theranostic agents, MSNPs are widely studied for cancer application. In spite of few studies performed for brain cancer theranostics, MSNPs has established itself a very good candidate for brain cancer theranostic applications. Yu et al synthesized fluorescein-doped magnetic mesoporous silica nanoparticles (FMNPs) to evaluate the effect of surface functionality on cellular uptake by glioma cells which possess extremely high optical intensity, superparamagnetism, easy bio conjugation and good biocompatibility. This nanosystem have not only shown tremendous potential in visualizing and simultaneously treating various diseases, but have also shown potential in cell tracking and magnetic resonance imaging (MRI). In this study, second-generation (G2) PAMAM dendrimers were covalently attached to the surface of FMNPs. These surface modified FMNPs can simultaneously act as imaging and drug reservoirs. The research results suggest that these surface functionalized magnetic silica nanoparticles with PAMAM dendrimers might serve as excellent candidates for future studies on intracellular delivery and cell tracking (Yu et al., 2009).

In an advanced study, Bertucci et al., synthesized MSNPs of 100 nm in size, incorporating a Cy5 fluorophore within the silica framework, and loaded with the anti-cancer drug temozolomide (TMZ), used in the treatment of gliomas. The surface of the particles is then decorated with a polyarginine-peptide nucleic acid (R8-PNA) conjugate targeting the miR221 microRNA. Results showed that the multi-functional

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nanosystem is rapidly internalized into glioma C6 or T98G cells. The anti-miR activity of the PNA is retained, as confirmed by reverse transcription polymerase chain reaction (RTPCR) measurements and induction of apoptosis is observed in temozolomide resistant cell lines. The TMZ-loaded MSNPs show an enhanced pro-apoptotic effect, and the combined effect of TMZ and R8-PNA in the MSNPs shows the most effective induction of apoptosis (70.9% of apoptotic cells) thus far achieved in the temozolomide-resistant T98G cell line (Bertucci et al., 2015). Thus, it is clear from the above discussed examples that functionalizing or activating the MSNPs surface with capping reagents, targeting ligands or diagnostic agents can originate very effective drug delivery system with controlled/targeted release and cell identification properties, which present valuable advantages over other drug delivery systems for brain cancer theranostics. In spite of advanced research in the theranostic applications of MSNPs-based drug delivery nanosystems, some important challenges still need to be discussed for achieving clinical success. This suggests that more comprehensive and detailed toxicity studies are imperative before MSNs are used in patients and must have a particular focus on the toxicity induced by different administration routes or MSN particle sizes.

CONCLUSION AND FUTURE PROSPECTS

In this review we highlighted theranostic application of MSNPs especially for brain theranostic applications. Numerous studies have shown significant in vitro and in vivo tumor suppression effects by mesoporous silica nanoparticles, and achieved imaging and cancer therapy concurrently. With the high loading capacity, good biocompatibility, tunable particle and pore size and multifunctional surface properties, MSNs are considered as an ideal drug delivery system. Moreover, MSNs-based drug delivery systems can be conjugated with versatile molecules to bring forward multifunctional capabilities simultaneously, which offer a multifunctional delivery platform including drug delivery, optical imaging and controlled-release for treatment. However, despite the significant progress in MSNPs as theranostic nanomedicine, there are several challenges that need to be addressed and investigated to enable the development of clinical cancer theranostics. In the future, to create MSNPs, suitable for clinical applications without undesirable side effects, better and more extensive in vivo testing is necessary for this new and rapidly expanding field of nanomedicine.

CONFLICT OF INTEREST

Authors have no conflict of interest.

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