Design and application of mesoporous carbon nano-drug delivery systems in cancer therapy

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Abstract: Cancer therapy has been the focus of attention in the medical field. Conventional chemotherapy has many disadvantages such as low bioavailability, short cycle time, and off-target toxicity. In the last decade, nanotechnology has provided efficient and versatile therapeutic means for tumor treatment with reduced side effects and improved targeting. Mesoporous carbon nanomaterials (MCNs), known for their high drug-carrying capacity and photothermal conversion properties, have attracted much attention in the biomedical field. In this paper, the cutting-edge advances of mesoporous carbon nanomaterials as four drug delivery systems and their applications are highlighted in cancer therapy.

1 Introduction

Cancer therapy has always been a very challenging field. Traditional chemotherapy drugs often find it difficult to curb the development trend in the process of tumors and suffer from defects such as low bioavailability and poor targeting, which lead to a variety of toxic effects. This is mainly due to the diversity of cell types and cytokines in the tumor microenvironmental, which makes it difficult for drugs to effectively penetrate the tumor and reach the tumor cells. Concurrently, cytokines and additional molecules inherent within the tumor microenvironment contribute to the proliferation and persistence of tumorous cells, ultimately bolstering their resilience against chemotherapy medications. To overcome these challenges, drug delivery systems have achieved encouraging results in cancer therapy. In the realm of pharmaceutical science, the implementation of sophisticated methodologies for the precise and effective delivery of diverse drug types, encompassing proteins, peptides, nucleic acids, as well as small molecule drugs, directly to tumor cells, coupled with the successful execution of their intended release, has ushered in a new era for drug delivery systems. These sophisticated systems have proven instrumental in elevating the overall efficiency of drug utilization, thereby enhancing therapeutic outcomes. Additionally, they offer significant cost savings while concurrently mitigating the occurrence of toxic side effects, representing a substantial advancement in the field aimed at optimizing treatment protocols and enhancing patient outcomes. [1].

In recent years, the rapid development of nanotechnology in the field of medicine has brought new opportunities and breakthroughs for the diagnosis and treatment of diseases. As an innovative drug delivery method, nano-delivery systems use nanotechnology to prepare drugs into nanoscale particles and can significantly improve drug solubility effectively increase the permeability of drugs to biological membranes, and achieve targeted drug delivery through the targeting groups on its surface, which has gained widespread adoption in the treatment of tumors and other diseases [2]. Common nano-drug delivery systems include liposome polymer nanoparticles, nanoemulsion, inorganic nanoparticles, etc. MCNs are a new kind of inorganic nanocarriers composed of mesoporous structure and carbon, which have good biocompatibility and physicochemical stability. Compared with other carbon-based materials, their extensive surface area and substantial pore volume are favourable for drug loading, their surfaces are easy to be modified to improve drug targeting, and they have excellent thermal conversion capabilities in the near-infrared (NIR) region, providing a greater possibility for tumor photothermal therapy (PTT).

2 Mesoporous Carbon

Mesoporous carbon constitutes a category of non-silicon-derived mesoporous materials, characterized by pore dimensions spanning between 2 nm to 50 nm, featuring uniform pore diameters and possessing an extensive pore surface. Its properties include (1) high specific surface area improving the material transport efficiency; (2) tunable pore structure meeting the needs of different applications; (3) large pore size facilitating the transport and adsorption of macromolecules; (4) good chemical stability with good corrosion and wear resistance; (5) unique photothermal properties for real-time monitoring and therapeutic diagnosis in vivo. It has been found that MCN has better performance than mesoporous silica nanomaterials (MSN) in terms of drug loading efficiency and drug release. In addition, MCN has better near-infrared absorption than MSN and is more effective in

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chemotherapy and phototherapy when loaded with DOX [3]. At present, the common methods for the synthesis of mesoporous carbon materials include catalytic activation, organogels carbonization and template method. However, carbon nanomaterials have highly hydrophobic surfaces and are often modified by oxidation or surfactants to prepare drug delivery systems. In addition to these conventional approaches, in recent years, synthesis methods for mesoporous carbon have evolved significantly. For instance, the single micelle assembly approach has emerged, allowing for the fabrication of mesoporous carbon materials with diverse structures. By incorporating various surfactants, different micelle structures can be achieved, offering enhanced tunability. This advancement provides a novel pathway for the synthesis of multifunctional mesoporous carbon materials. [4]

3 Four drug delivery systems

Drug delivery systems are engineered platforms designed to transport therapeutic agents to specific sites in the body with controlled release kinetics. Due to the disadvantages of conventional cancer chemotherapy, such as low bioavailability, low improvement index of therapeutic effect, and unclear side effects, the development of a drug delivery system (DDS) provides a new therapeutic strategy for cancer therapy. Currently, four drug delivery systems are used for cancer therapy, namely immediate drug delivery systems (IDDSs), sustained-release drug delivery systems (SDDSs), controlled drug delivery systems (CDDSs), and targeted drug delivery systems (TDDSs).

3.1 IDDSs

IDDS is a drug delivery method that rapidly releases the active ingredient after administration, thus achieving rapid onset of drug effect. Oral drug delivery is the most convenient mode of IDDSs. However, most antitumor drugs are difficult to administer orally due to the tumor microenvironment and/or low gastrointestinal absorption. In IDDSs, mesoporous carbon can protect loaded drugs from degradation by gastric acid and significantly improve the solubility of insoluble drugs. The particle size and pore size of mesoporous carbon and the drug loading method affect the drug loading and drug release. For example, hollow mesoporous carbon (HMC) has a larger hollow void and low density so that more drugs can be encapsulated in the cavity, and thus exhibits superior performance than traditional MCNs [5]. Fan et al. [6] successfully synthesized oxidized mesoporous carbon nanoparticles (oMCNs) utilizing a gentle oxidation technique, yielding nanoparticles with notable characteristics such as an elevated drug loading capacity, favorable biocompatibility, and remarkable cellular internalization. Specifically, when loaded with resveratrol (RES), these oMCNs drastically enhance the saturation solubility of the drug and its in vitro release profile, making them promising candidates for the treatment of triple-negative breast cancer. This advancement underscores the potential of such tailored nanoparticles to revolutionize therapeutic strategies targeting this aggressive cancer subtype. (Figure 1). In addition, Bhosale et al. [7] developed mesoporous carbon@tungsten oxide nanocomposite as a drug carrier with good drug-controlled release ability and loaded with Adriamycin to achieve good anti-tumor effect.

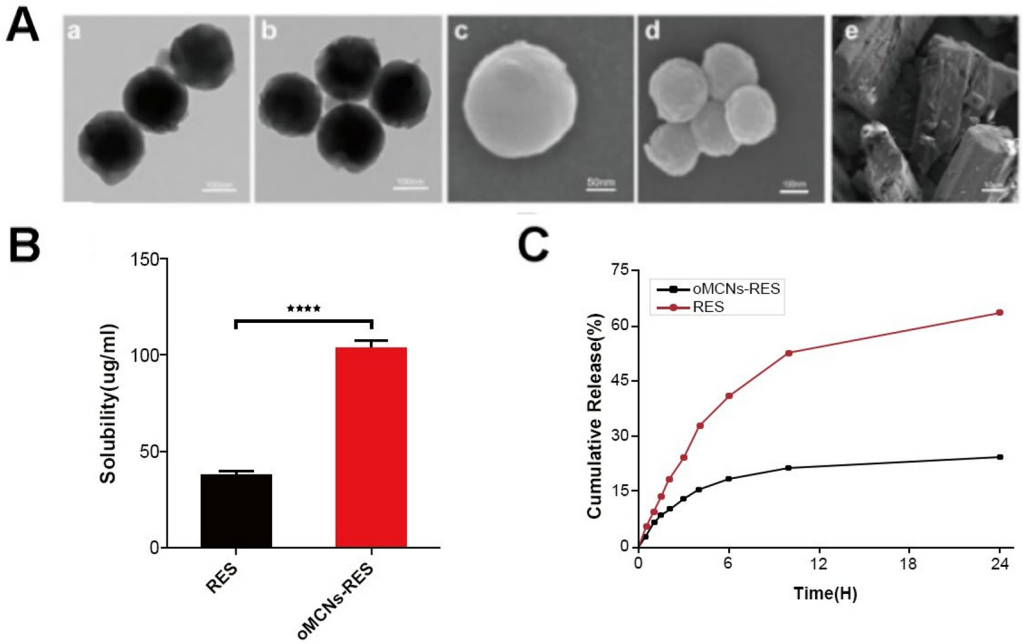

Figure 1. Oxidized mesoporous carbon nanoparticles (oMCNs) significantly improved the solubility and in vitro release performance of resveratrol (RES). (A) transmission electron microscopy and scanning electron microscope images of oMCNs (a, c), oMCNs-RES (b, d), and pure RES (e). (B) Saturated aqueous solubility of pure RES and oMCNs-RES. (C) In vitro release profile in phosphate buffer saline (****$P < 0.0001$) [6].

3.2 SDDSs

SDDS refers to the ability to release drugs slowly in the organism after administration so that the concentration of the drug within the bloodstream or at a targeted site remains within the therapeutically effective range for an extended duration, our approach diminishes the necessity for frequent dosing and minimizes the likelihood of adverse reactions, thereby lowering the risk associated with toxic side effects. This refinement in drug delivery methodology promotes sustained therapeutic levels while optimizing patient safety and comfort. The design of SDDSs usually needs to take into account the effects of these several factors, including the pore size and pore length of the MCNs, the interaction forces between the drug and the MCNs, and the drug diffusion hindering forces. For example, choosing longer pore lengths or chemically modifying the surface of MCNs can delay drug release. Luo et al. [8] used poly(N-isopropylacrylamide-co-allylamine) (P(NIPA-AL17)) and poly (styrene sulfonate) (PSS) functionalization to construct photothermal responsive controlled-release hollow mesoporous carbon nanoparticle systems and further studied the effects of drug loading of HMCNs, temperature-sensitive polymer properties and drug release conditions on drug release behaviour. Zhang et al. [9] designed carboxymethyl chitosan/phospholipid bilayer capped mesoporous carbon nano-matrix (CCS/PL/MC) with good pH sensitivity and prolonged release capability, where the positively charged phospholipid (PL) coating releases the drug in an effective and controllable manner, and the carboxymethyl chitosan protects the PL layer and prevents premature release of the drug in an acidic stomach.

3.3 CDDSs

Stimuli-responsive CDDS can release loaded therapeutic agents in a controlled manner in response to various stimuli such as physical (e.g., light, sound, and heat), chemical (e.g., pH and redox potentials), and biological (e.g., enzymes, nucleic acids, and biomolecules) at the site of the lesion or under pathological conditions to improve the accuracy and safety of drug delivery. For example, the disulfide bond acts as a linker between mesoporous carbon and gated modifier, which can be broken for further drug release when stimulated by high GSH concentrations in the tumor microenvironment. Wang et al. [10] designed graphene quantum dots (GQDs) as a gating control, linked to MCNs via disulfide bonds, and loaded doxorubicin (DOX) to form a drug delivery system (DOX/MCN-SS-GQD), which can be stimulated by multiple responses of pH, GSH, and NIR for synergistic chemo-photothermal therapy. In a similar design, a drug delivery system (MC-ss-CDS) was obtained by gating long-wavelength emitting carbon dots (CDs) on a long wave and connecting mesoporous carbon nanoparticles (MC) via disulfide bonds. In addition, Lin et al. achieved synergistic chemo-photothermal therapy by pH/thermal-bi-responsive poly (N-isopropyl acrylamide) (PNIPAM) coated hollow mesoporous carbon nanoparticles (HMCs) to obtain an effective nanocarrier (PNIPAM@HMCs), which was further loaded with DOX to achieve pH/thermal dual-responsive release to improve tumor therapy. Wang et al. synthesized polyethene glycol (PEG)-modified mesoporous carbon nanoparticle delivery platforms embedded with iron (C/Fe-PEG NPs) can be used to generate H2-induced oxidative stress in specific acidic tumor sites and exert H2 therapy and photothermal therapy. Wang et al. established the M@C-HA/ICG platform by loading the photosensitizer indocyanine green (ICG) on hollow mesoporous carbon (C) nanoparticles modified with hyaluronic acid (HA) to modify macrophages. When this platform migrated to the tumor tissue, the polarized macrophages secreted cytokines to kill the tumor cells, achieving the combination of PTT, PDT, and immunotherapy. Corresponding case studies are shown in Table 1.

Table 1. Case studies of stimuli-responsive mesoporous carbon nano-drug delivery systems

Delivery system	Model drug	Release mechanism	Therapeutic means	Ref.
DOX/MCN-SS-GQD	DOX	pH/GSH/NIR	PTT/ chemotherapy	[9]
DOX/MC-ss-CDs	DOX	GSH/NIR	PTT/ chemotherapy	[10]
DOX/PNIPAM@HMCs	DOX	pH/NIR/ temperature	PTT/ chemotherapy	[11]
C/Fe-PEG NPs	/	pH/NIR	PTT/H2 therapy	[12]
M@C-HA/ICG	ICG	HA/NIR	PTT/PDT/ immunotherapy	[13]

3.4 TDDSs

TDDS is a preparation in which a drug or carrier is selectively concentrated in target tissues/organs/cells after entering the circulation. It is usually divided into active targeting and passive targeting. Active targeting is the coupling of a probe molecule (folic acid, hyaluronic acid, antibody, etc.) that specifically binds to the target molecule to the surface of the drug or its carrier to achieve the targeting effect. Passive targeting is based on the body's natural response to the physicochemical properties (light, heat, pH, magnetic field, etc.) of the nanocarrier and the encapsulated drug to induce the carrier to act at the site of disease. Wang et al. constructed a mesoporous carbon nano-platform (M27-39@FA-MCN) modified with a biologically active peptide (M27-39) and folic acid (FA), which can target both mitochondria and the colon while increasing the accumulation and residence time of M27-39 in colon tumors, thus improving its biosafety and targeting. In a similar case of FA modification, Liu et al. proposed to synthesize the nano-platform Fe3O4@carbon(C)/ZnO-DOX-FA by using pH-responsive ZnO as a gatekeeper, mesoporous carbon as a photothermal agent, and Fe3O4NPs as a passively targeted magnetic targeting

agent loaded with DOX that achieved dual-targeting, controlled chemotherapy and photothermal therapy (PTT). Vinothini et al. successfully coupled FA to oxidized mesoporous carbon nanospheres (Ox-MPCNPs), and then DOX bound to the Ox-MPCNPs via hydrogen bonding and π-π interaction to prepare DOX/Ox-MPCNP-Cys-PAsp-FA, which offered a great opportunity for targeted therapy of breast cancer. In addition, Xin et al. synthesized the DOX/MCN-CP-HA system by electrostatically adsorbing copper peroxide nanoparticles (CP NPs) onto the surface of MCNs, then loading DOX into the nanocomposite (MCN-CP) and coating the surface with HA for targeted therapy of breast cancer cells. Corresponding case studies are shown in Table 2.

Table 2. Case studies of target-controlled mesoporous carbon nano delivery systems

Delivery system	Model drug	Targeting technique	Therapeutic means	Ref.
M27-39@FA-MCN	M27-39	active targeting	PTT/bioactive peptides	[14]
Fe3O4@carbon(C)/ZnO-DOX-FA	DOX	active/passive targeting	PTT/ chemotherapy	[15]
DOX/Ox-MPCNP-Cys-PAsp-FA	DOX	active targeting	PTT/ chemotherapy	[16]
DOX/MCN-CP-HA	DOX	active targeting	CDT/PTT/ chemotherapy	[17]

4 Conclusions

In this paper, we mainly summarized the design of four drug delivery systems based on MCNs and their applications in cancer therapy. However, although studies with MCNs have shown significant therapeutic advantages, they still have some limitations. The very small size of the nano-drug delivery systems can cross the biofilm to affect the normal function of cells, and their safety needs to be further investigated. In addition, the complexity of the preparation process of nano-drug delivery systems leads to high costs, and the regulatory issues have not yet been clarified, which may hinder the clinical application of nanodrug delivery systems. In summary, nano-drug delivery system relied on MCNs has broad application prospects in the field of cancer therapy, and it is necessary to further strengthen related basic research and clinical application research in the future to promote the development of nanomedicine.

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