Coordination Chemistry Reviews 319 (2016) 86–109

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

The application of mesoporous silica nanoparticle family in cancer theranostics

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Contents

ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form 29 April 2016
Accepted 30 April 2016
Available online 13 May 2016

ABSTRACT

Cancer is among the most serious diseases characterized by uncontrollable cell growth and spread of abnormal cells. Cancerous cells form tumors that negatively impact the functions of the body, inducing serious malfunctioning leading to fatalities in most cases. Up to now, the effective diagnosis and treatments of cancer have remained a big challenge. Nanotechnology is an emerging field encompassing science, engineering and medicine, which has attracted great attention for cancer therapy in recent years. Among

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http://dx.doi.org/10.1016/j.ccr.2016.04.019
0010-8545/

Keywords:
Mesoporous silica nanoparticles
MCM-41
SBA-15
ORMOSIL
Drug delivery
Stimuli

the numerous nanomaterials, mesoporous silica nanoparticles (MSNs) have attracted great attention and are being considered as promising biomedical materials for the development of cancer therapies because of their size tunability, surface functionality, optically transparent properties, low toxicity and high drug loading efficiency. In this review, we first outline the properties and structure of different configurations of MSNs and their subsequent application in the field of cancer theranostics. Thereafter, the potential of MSNs as multifunctional delivery platforms for therapeutic agents and their significance in next generation cancer therapy is discussed.

1. Introduction

Cancer is characterized by abnormal and uncontrollable cell growth. With malignant phenotypic behavior such as metastasis and invasion, cancer adversely affects different parts of the body and is considered among the most chronic diseases all over the world [1,2]. In recent years, worldwide incidence and mortality rates of cancer have been rising sharply. Based on the 2004 World Health Organization (WHO) statistics, cancer stands as the primary factor of death in developed countries. In developing countries, it is the leading cause of fatality second only to cardiovascular disease. The number of worldwide deaths due to cancer is increasing at an alarming rate, from 10 million (13% of all deaths) in 2000 to 12 million in 2020 [3,4]. Based on the different stages of cancer, patient age and health status, cancer treatments need to be customized and combined with several other therapies. Contemporary cancer treatment modalities such as surgery, chemotherapy, radiotherapy and photodynamic therapy (PDT) are able to prolong patient's lives to some extent. Although physical methods like surgery are effective for patients with non-metastatic cancer, other systemic therapies are required in cases where the cancer has entered metastasis and spread throughout the body. Radiotherapy is the common alternative for surgery which utilizes high-energy rays to cause damage to cancer cells, followed by apoptosis. Nevertheless, radiotherapy can pose serious side-effects including the risk of secondary malignancy in the irradiated area and severe damage of normal and healthy tissues. Another method, chemotherapy, involves the use of one or more chemotherapeutic agents to destroy cancer cells. Most chemotherapeutic agents lack cell specificity, resulting in damage of normal cells with irreversible systemic side-effects. Besides the non-specificity, the development of multi-drug resistance (MDR) by cancer cells is a critical limitation for the low therapeutic index of chemotherapy [5]. More selective methods such as PDT, which is relatively new, use photosensitizing agents to kill cancer cells upon light activation. Photosensitizing agents are effective only if they have been activated by a specific type of light precisely directed at the cancer cells, thus making PDT more selective and less toxic than chemotherapy [6]. The limiting factor of this method, however, is the low efficiency of light penetration for deeply located tumors within the body and the development of MDR toward the PDT agents in the treated cancer cells [7]. As a consequence, tumor recurrence, metastasis, resistance to chemotherapy and side effects caused by radiotherapy and chemotherapy remain the major bottlenecks in cancer therapy. Well-designed diagnostic, therapeutic and prognostic strategies are urgently needed for the effective treatment of cancer.

Nanomedicine is an emerging field, integrating nanotechnology and biomedicine, which offers promising therapeutic potential for various diseases including cardiovascular disease, diabetes, tissue engineering and cancer theranostics. The rapid development of new nanomaterials has provided great opportunities to overcome chemotherapeutic side-effects while promising the diagnosis of cancer at preliminary stage. The first Food and Drug Administration (FDA)-approved nano-drug, Doxil, is a typical example, where doxorubicin (DOX) is encapsulated in liposomes for prolonged circulation time and bioavailability of DOX, and diminished side-effects to heart muscles and other normal tissues [8]. 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 [9]. Subsequently, tremendous efforts have been devoted toward functionalized nanoparticles for cancer theranostics. Christopher Loo et al. have pioneered this field through the engineering of immune-targeted nanoshells to detect and destroy breast carcinoma cells, by demonstrating bioimaging coupled with cancer therapy [10]. Another group has utilized anti-epidermal growth factor receptor (EGFR)-gold nanorods (AuNRs) to treat malignant oral epithelial cells, developing AuNRs as reagents for cancer cell diagnostics and selective photothermal therapy [11]. Similarly, MSNs bear enormous potential as functionalized nanomaterials. The earliest examples include the synthesis of folic acid (FA) modified-MSNs for targeted delivery of the hydrophobic anticancer drug camptothecin (CPT) [12,13]. These studies have shown significant *in vitro* and *in vivo* tumor suppression effects by mesoporous silica nanoplexes, and achieved imaging and cancer therapy concurrently [12,14]. With further progress in nanomaterial research, nanomedicine is envisaged to hold a strong stake in cancer diagnosis and therapy.

Silicon dioxide (SiO_2), also known as silica, is among the most abundant naturally available minerals on earth and a crucial component for human health, especially for skin, bones, hair and nails. Classified by the FDA as "Generally Recognized as Safe" (GRAS), SiO_2 is widely used in food additives, cosmetics and pharmacy. Due to the biosafety and easy synthesis of silica, silica-based nanomaterials occupy a prominent status in biomedical research. In recent years, MSNs have attracted increasing attention for optical imaging, magnetic resonance imaging (MRI), PDT and drug delivery [15–20]. Since the proposal of MCM-41 type MSNs as nanocarriers for delivering therapeutics in 2001 [21], a variety of MSNs such as MCM48 [22], SBA-15 [23,24], TUD-1 [25], HMM-33 [24] and FSM-16 [26] have been engineered and applied as drug delivery systems extensively. As drug delivery vehicles, MSNs offer several advantages: (i) large internal surface area and pore volume enabling MSNs an effective drug delivery vehicle for a range of therapeutic agents, (ii) tunable particle size (50–300 nm) permitting facile endocytosis across living animal and plant cells with minimal cytotoxic effects, (iii) a tunable porous structure with controllable narrow pore size distribution, allowing the loading of different therapeutic agents with highly precise drug release kinetics, (iv) a highly hydrophobic and rigid matrix structure facilitating MSNs to remain uniformly dispersed in water and resist changes due to pH, heat, mechanical stress and hydrolysis-induced breakdown, (v) the internal and external surface can be selectively functionalized, enabling MSNs to offer targeted delivery and controlled release, (vi) a uniquely porous structure preventing premature release of its loaded components even when its pores are not fully capped [19,20,27–29]. MSNs exhibit incredible advantages over other drug delivery nanocarriers and provide promising opportunities for simultaneous cancer diagnosis and therapy.

In this review, we focus on the current advances of MSNs as drug delivery systems for cancer theranostics. The structure and properties of different types of MSNs such as nanoparticulate MSNs, hollow/rattle MSNs and organically modified silica (ORMOSIL)