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Mesoporous Silica Nanoparticles: Synthesis, Modification and Applications

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Mini Review

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Abstract

Considerable technological success has been recently achieved in nanomedicine. Mesoporous silica nanoparticles (MSNs) are one of the most versatile and successful particles for biomedical applications. The large surface area, the aspect ratio between pore size and porosity, and tunability of these characteristics give MSNs advantages over other nanoparticles in the biomedical space. In this review, we outline the conventional synthesis methods for MSNs. In addition, the biocompatibility of MSNs is discussed with respect to the size, shape and surface properties. Emphasis has been placed on physical and chemical modifications that are utilized to enhance the biocompatibility and extend the biomedical applications of MSNs. Layer by layer self-assembly and chemical surface functionalization have been entirely discussed. Lastly, we demonstrate the potential of silica nanoparticles in biomedical applications including drug delivery, tissue regeneration, and bioimaging. The development of multifunctional MSNs able to exert the optimal therapeutic and/or diagnostic actions constitutes a significant challenge in nanomedicine. Recent advanced MSN-based platforms open new avenues in the application of nanoparticles in nanomedicine.

Keywords: Nanomedicine; Mesoporous Silica Nanoparticles; Drug Delivery; Biomedical Applications; Surface Modification

Introduction

Over the last decades, nanomedicine opened a vast field of biomedical research in improving human health due to the interaction with biological molecules at the nanoscale level [1]. These interactions can be monitored and tuned both in the extracellular medium and intracellular environment. The unique physical features of the nanoparticles such as the volume/surface ratio yield to several advancements in the fields of drug delivery, tissue regeneration, and bioimaging [2,3]. However, there are a number of risks associated with the biomedical application of nanoparticles including poor biocompatibility [4], colloidal instability [5], premature degradation of the nanoparticle before it reaches its site of action or loss of nanoparticles outside the tissue of interest [6]. In the case of drug delivery, tumor penetration, endosomal escape, and controlled drug release are yet to be addressed [7].

Mesoporous silica nanoparticles (MSNs) possess superior features compared with organic and inorganic nanostructures such as their tuneable porosity, pore size, particle size, excellent biocompatibility, and high specific surface area [8]. These unique characteristics have resulted in a broad range of applications of MSNs in different sub-areas of medicine such as diagnostics, therapy, and monitoring [9]. In bone regenerative medicine, MSNs exhibit superior osteo-conductivity and osteo-inductivity in comparison to the solid microparticle, and improved bioactivity versus conventional bioglass particles due to a faster release of Si ions [10]. The ease of synthesis using the sol-gel method and template removal has made MSNs accessible and favoured for biomedical applications.

In this review, we discuss the synthesis, biocompatibility, modification, and applications of MSNs. We specifically cover the physical and chemical modification methods that expand the use of MSNs in extracellular and intracellular delivery, dental and orthopedic regeneration, and bioimaging.

Synthesis

The most common silica source for the synthesis of MSNs is tetraethyl orthosilicate (TEOS) using the sol-gel method. Other tetraalkoxy silanes, particularly tetramethyl orthosilicate (TMOS) are rarely used because its reaction is fast and difficult to control [11]. The latter is usually utilized in the large-scale production of silica where the rapidreaction of TMOS enables the use of smaller-scale equipment [12].

Templates such as hexadecyltrimethyl ammonium bromide (CTAB) and n-octane are commonly utilized to form porous structures, initially reported in 1988 by Kuroda et al. [13]. Addition of these surfactants during the synthesis generates a structure with many small pores (mesoporous structure); these ranges between 2 and 50 nm, according to IUPAC notation [14]. More recently, it has been recommended to use templates such as chitosan due to its inherent amino and hydroxyl functional groups [15]. These functional groups facilitate further surface modification of MSNs, for instance with bioactive molecules, significantly increasing their range of applications.

Biocompatibility and Bioresorbability

In the context of biomedical applications, mesoporous silica nanoparticles are designed to perform a specific function, with minimal non-specific or adverse effects. Silica is generally considered as a biocompatible substance. However, MSNs biocompatibility needs to be assessed with regards to individual size, shape, and surface chemistries. Based on previous studies, the biocompatibility of MSNs remains inconclusive [16,17]. Here, we discuss the current advances in assessing the effects of size, shape, and surface properties on MSNs interactions with live cells.

Effect of Size

Controversy has arisen regarding the impact of particle size on the biocompatibility of MSNs [18]. Particle size can manipulate biological factors such as *in vivo* distribution, duration of blood-circulation, and excretion rate. With systemic (intravenous) delivery, MSNs were found to be mainly distributed in the liver and spleen, with a minority of them in the lung, and a few in the kidney and heart. A longer blood circulation lifetime was observed for particles with smaller size [19]. The excretion of MSNs from urine increased by the elevation of particle size may affect the degradation rate and therefore biocompatibility.

In vitro assays have suggested a degree of toxicity for spherical MSNs at the particle size of 1220 nm at >25 mg/ml concentration [20], while another study demonstrated the size-dependent hemolytic activity [21]. However, Hudson et al. showed no size-independent toxicity using an *in vivo* mouse model [17].

Effect of Shape

The morphology of MSNs influences the biocompatibility, biodistribution, and clearance. Huang et. al. have shown that Short-rod MSNs distribute mainly in the liver, while long-rod MSNs are easily trapped in the spleen and display a slower clearance rate than sort-rod ones using animal models [22]. The shape of MSNs also affects cellular uptake, which has been a major recent research focus. *In vitro* studies reported independency of shapeon endocytosis rates and dependency to endocytotic rate [23]. The large aspect ratio of MSN can result in a more extended circulation time and therefore, different biocompatibility.

Effect of Surface Chemistry

In addition to size and shape of nanoparticles, surface properties such as charge, functional groups and the presence of antifouling molecules can influence the biocompatibility of MSNs. Nanostructures with cationic charges on the surface induce more significant immune response and cytotoxicity than the neutral and anion counterparts [24,25]. However, they are beneficial for transvascular transport in tumors. MSNs with negative zeta potential can be associated with serum opsonin. They are rapidly removed from the extracellular or intracellular environments by macrophages in the reticuloendothelial system (RES). Another critical surface chemistry that might impact on the biocompatibility of MSNs is the number of silanol groups at the outer layer. These functional groups can negatively interact with biological molecules, such as cellular membrane lipids and proteins, and destroy the structure of these molecules [26]. Therefore, surface modification is an essential step in altering surface reactivity to enhance biocompatibility and further broaden the biomedical applications of MSNs.

Surface Modification

Physical and chemical surface modifications have been employed to expand the range of biomedical applications for MSNs. These can enhance biocompatibility, prevent non-specific adsorption, and provide functional groups for further biomolecule conjugation purposes. Layer by layer self-assembly (LSA) and chemical surface functionalization are the most common physical and chemical methods to modify the surface of MSNs, respectively.

Layer by Layer Self-Assembly (LSA)

Introducing functional moieties after the synthesis of the MSNs to the particles commonly occurs through the electrostatic interactions. The negative charges from the free SiO^- groups on the particle's surface can be triggered in the LSA [9]. For instance, cationic polymers such as polyethyleneimine functionalize the surface of MSNs to provide nucleic acid binding properties [27,28]. More recently, this technique has been utilized by Chen et al. to deposit negatively charged per-O-methyl-b-cyclodextrin-grafted-hyaluronic acid (HA-CD),and 5,10,15,20-Tetrakis(4- sulfonatophenyl)-porphyrin (TPPS4) were alternatively onto the surface of MSNs [29]. This nanocomposite was developed to fabricate a versatile tumor-specific theranostic nanoplatform based on self-assembled MSNs. The premature drug release from MSNs can be prevented by protecting the pore gates using biodegradable self-assembled layers of polymers [30] or stimuli-responsive polymers [31,32]. For instance, bis-aminated poly (glycerol methacrylate)s (BA-PGOHMAs) polymeric layers were successfully added to MSNs to control the release of anticancer drugs such as doxorubicin (DOX) [33]. In contrast, several studies showed significant clinical complications such as uncontrolled and excessive biocompound resorption due to the physical modifications of MSNs. Therefore there is a need to investigate the chemical modification methods to improve the biocompatibility of MSNs.

Chemical Surface Functionalization

The presence of silanol groups on the surface of MSNs provides the ability to chemically modify the nanoparticles surface. Common biological and chemical groups that have been conjugated to MSNs are listed in Figure 1 [34]. The modified surface of nanoparticles plays a vital role in drug delivery applications. That surface modification of MSNs has been found to improve the loading of drugs, DNA, and siRNAs [35]. Surface modification using long-chain organic molecules such as oligomers and polymers can enhance the selectivity of nanoparticles. This can lead to beneficial or detrimental decreases in the pore size, the wettability of the pore surface by aqueous solutions, and biological activity of the encapsulated biocompound [36].

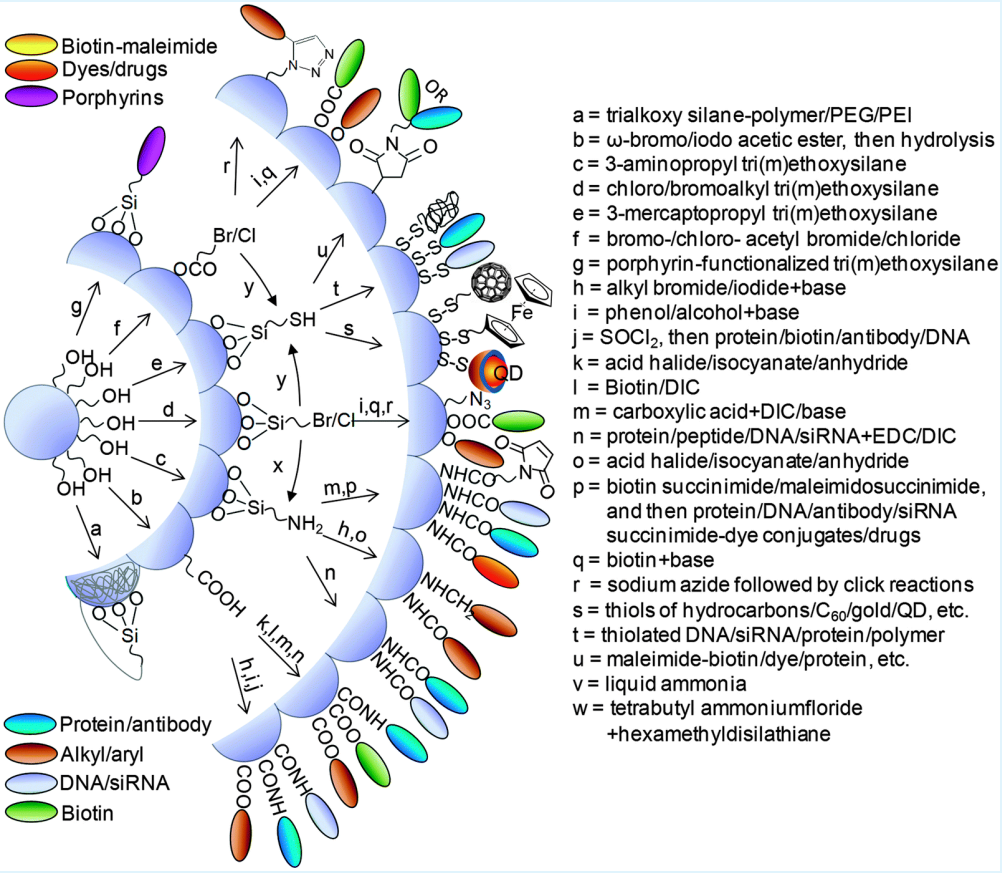

Figure 1: The typical chemical functionalization and bioconjugation methods pf MSNs. Reproduced from [34] with permission from the Centre National de la Recherche Scientifique (CNRS) and The Royal Society of Chemistry.

Biomedical Applications

Drug delivery

The ability to encapsulate different types of cargo molecules within pore channels of MSNs makes drug delivery their primary biomedical use. This encapsulation can prevent enzymatic degradation of therapeutic agents while it adds to the opportunity to deliver them to the desired location (Figure 2) [37]. Physical entanglement by soaking in a drug solution is the standard practice to incorporate drugs via diffusion, as driven by hydrogen bonding or electrostatic interactions. The loading efficiency is dependent on the surface areas of the specific materials [38], but can also be affected by the electrostatic interactions between the biocompound and the silica surface [39,40]. Low loading capacity and premature burst release can result from weak or insufficient interactions between the nanoparticles and drugs. It has been recently hypothesized that a functionalized MSN such as rituximab-conjugated and transferrin gated mesoporous silica could provide sustained release at the targeted diseased tissues with no premature release during their circulation within the bloodstream [41,42]. It can significantly broaden the efficacy of the MSN-based drug delivery systems by reducing the adverse side effects of the drug and increases the overall therapeutic effectiveness [37,43]. However, additional experiments are required to confirm the biological activity of a loaded drug after chemical modification.

The controlled release of drugs can be achieved based on physiological conditions, such as reducing intracellular environment or elevating pH in different organs or tumors. The most abundant redox coupler in mammalian cells is glutathione (GSH)/ glutathione disulfide (GSSG). The concentration of GSH reaches 2–10 mM in the cytosol and nuclei and only 2–20 μM in the extracellular matrix.

In vivo studies have indicated that tumors possess a GSH concentration of at least 4-fold higher than normal tissues. Small redox molecules like GSH or dithiothreitol (DTT) cleave disulfide bonds through thiol-disulfide exchange reactions. Based on that, reduction-sensitive materials containing disulfide groups have been used for controlled release of drugs [44]. Furthermore, the pH is considerably lower in organelles such as endosomes and lysosomes (pH 5.0–5.5) compared with blood and normal tissues (pH 7.4) [45]. Therefore, pH-sensitive bonds such as hydrolyzable Schiff base linkage can be designed to cleave between drug and nanoparticles specifically in the acidic environment of endosome and lysosome, resulting in site-specific drug release [46]. The pH-sensitive organic layer can also protect the bioactive compound in digestive system with different pH values [47]. These polymers can be employed to coat MSNs pores to act as gatekeepers to avoid premature drug exposure (Figure 2). Ultimately, surface functionalization of MSNs will have many applications for targeted drug delivery, enabling customization of release, and tissue targeting, but these have yet to be fully optimized.

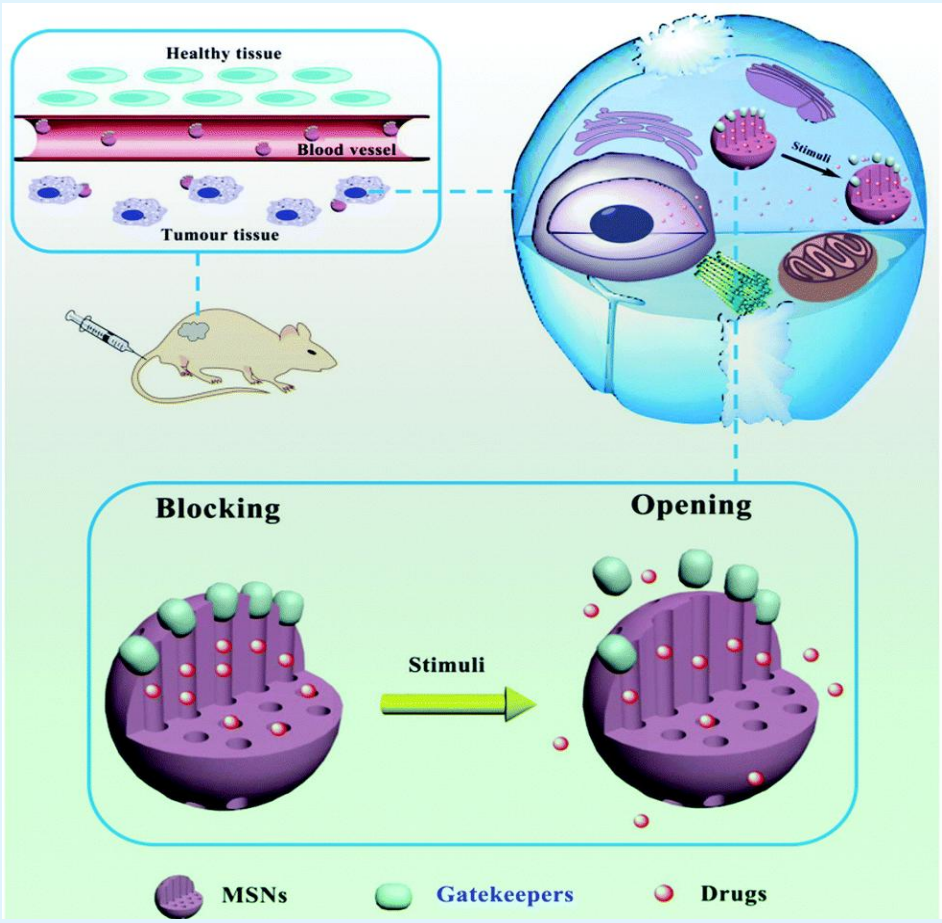

Figure 2: Schematic of prevention of enzymatic degradation and release of the drug in the desired place. Reproduced from [37] with permission from the Centre National de la Recherche Scientifique (CNRS) and The Royal Society of Chemistry.

Tissue Regeneration

Biomedical applications of MSNs are mainly focused on drug delivery and controlled release. However, the practical use of these nanoparticles in regenerative medicine is still in its infancy [48]. MSNs have the potential to serve as vehicles to carry growth factors, peptides, or stem cells to a tissue engineered scaffold to enhance tissue regeneration. The mechanical and nanotopographical features of the scaffolds can also be

tuned to modulate the chemical microenvironment of surrounding cells. Nanoparticles have been shown not interfere with stem cell differentiation and can thus provide a free-standing substrate for cell-directed drug delivery [49] (Figure 3).

The silanol groups on the surface of MSNs can be utilized for bone tissue engineering as they are able to react with the bone physiological environment to produce nanometer-sized carbonated apatite [50]. The bioactivity of MSNs can be improved by the incorporation of phosphorous ions and bioactive glass [51,52].

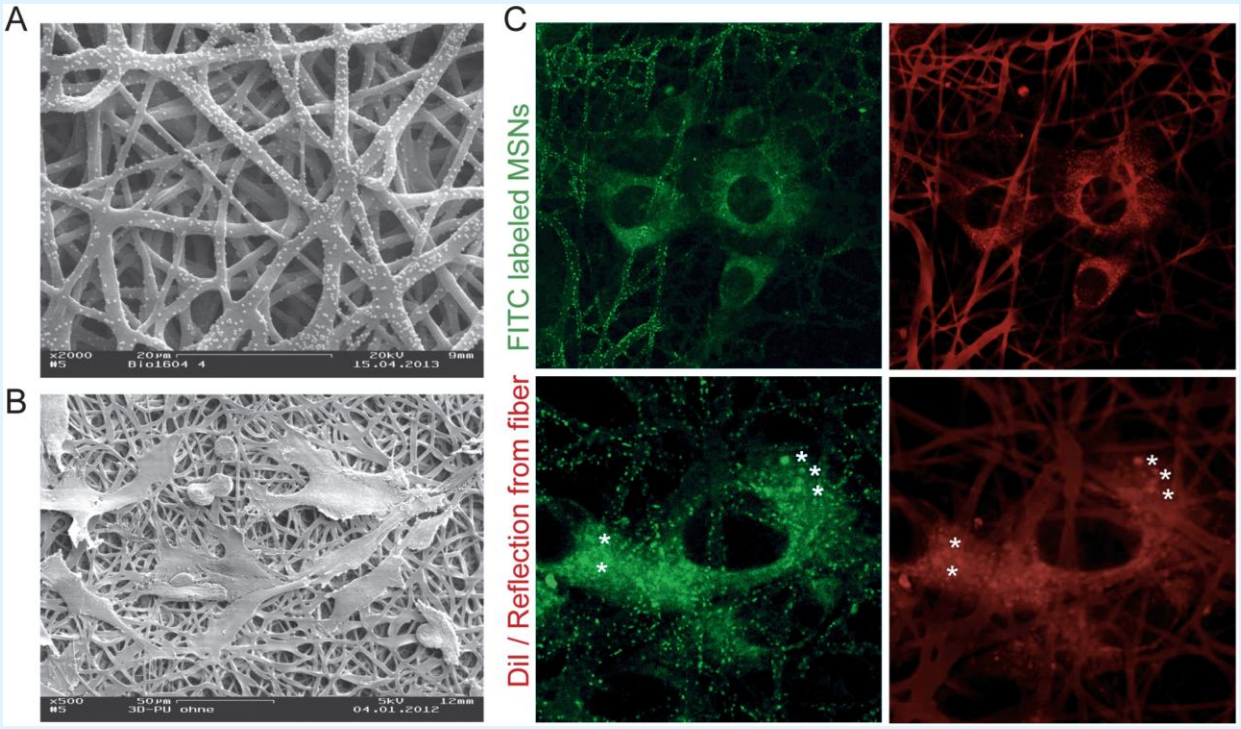

Figure 3: (A) SEM images of (A) scaffolds impregnated with MSNs, and (B) cells cultured on the scaffold. (C) Confocal microscopy images demonstrating particles decorating the polymer fibers (green dots along fibers), cells labeled (red), MSNs accumulated in intracellular vesicles (red and green vesicles marked with an asterisk), and the reflection image of the fiber structure (red fibers). Reproduced from [49] with permission from the Centre National de la Recherche Scientifique (CNRS) and The Royal Society of Chemistry.

Bioimaging

MSNs have three distinct domains: the silica framework, the nanochannels/pores, and the outermost surface [53]. Each region can behave differently and have independent utility. Fluorescent dyes or rare-earth elements can be incorporated into the silica framework for diagnostic and therapeutic applications as theranostics agents. For instance, magnetic mesoporous nanoparticles in the core/shell structure have been widely used to for MRI applications [54]. These nanoparticles can also be coated with gap-enhanced Raman tags allowing for high-speed Raman-based cell and tumor imaging [55]. The unique protection that MSNs provide results in the prevention of photobleaching of the built-in Raman reporters and therefore, the structure exhibits ultraphotostability as shown in Figure 4. These features of MSNs are favorable for long-term, high-speed, and real-time bioimaging under the continuous laser irradiation. The combination of MSNs, Fe3O4, and Au has been proposed for near-infrared biomedical applications [56].

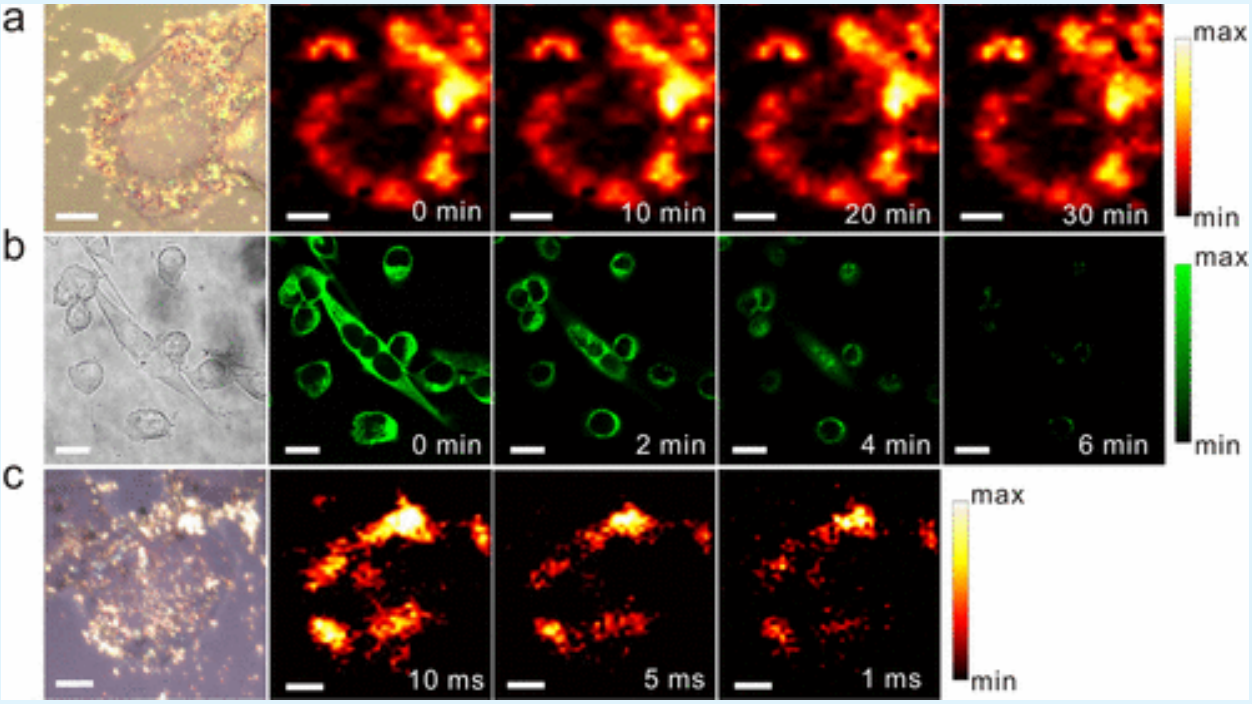

Figure 4: Raman and fluorescence images of H1299 cells stained with MSNs coated with gap-enhanced Raman tags. (a) Representative super stable Raman images obtained from a single cell: bright-field image (left) and Raman images at different irradiation times (t = 0, 10, 20, and 30 min). (b) Bright-field image (left) and corresponding cell fluorescence images at different irradiation times. (c) Representative Raman images obtained from a single cell: bright-field image (left) and Raman images acquired with different exposure times. The scale bars are 5 μm in panels a and c and 20 μm in panel b. Reprinted with permission from [55], Copyright (2018) American Chemical Society.

Conclusion

Nanomedicine is a rapidly progressing field, where the challenges and opportunities are only starting to be identified. Mesoporous silica nanoparticles have significant translational potential in nanotherapeutics. While an extensive array of studies have already been made in the application of MSNs in drug delivery, considerable research into fields of tissue regenerations and bioimaging have gained momentum recently. As a future perspective, the trends of new investigations on the MSNs are toward the production of theranostics agents for simultaneous diagnostic and therapy. In addition, understanding the mechanisms behind the effects of nanoparticles various aspects such as charge, shape, and size on cellular behaviors will aid in designing more effective diagnostic and therapy systems based on MSNs.

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