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REVIEW

Controlled drug delivery systems for cancer based on mesoporous silica nanoparticles

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Abstract: The implementation of nanotechnology in medicine has opened new research horizons particularly in the field of therapeutic delivery. Mesoporous silica particles have emerged as biocompatible drug delivery systems with an enormous potential in the treatment of cancer among many other pathologies. In this review, we focus on the unique properties of these particles as chemotherapy delivery carriers. Here, we summarize the general characteristics of these nanomaterials – including their physicochemical properties and customizable surfaces – different stimuli that can be used to trigger targeted drug release, biocompatibility and finally, the drawbacks of these types of nanomaterials, highlighting some of the most important features of mesoporous silica nanoparticles in drug delivery.

Keywords: nanocarrier, drug release, targeted drug delivery, biocompatibility, biodegradability, tumor

Introduction

Chemotherapy, tog ether with surgery, are the most used cancer treatments in oncology. Unfortunately, chemotherapeutic agents are applied systemically destroying both tumor and healthy cells and resulting in many of undesirable side effects.[1] Encapsulated drug delivery systems offer the possibility to target therapies locally at adequate concentrations, maximizing the effect against cancer cells while reducing the side effects and cytotoxicity in healthy cells.[2] In this sense, nanotechnology can help with the design of target-specific and controlled delivery systems, capable of transporting enough therapies to specific cells, releasing the drug in a controlled manner.[2]

Different types of nanomaterials have been used as targeted carriers. Among others, the most employed are liposomes,[3,4] polymeric micelles,[5,6] carbon nanotubes,[7] dendrimers,[8–10] inorganic particles[11] and silica-based materials[12,13] (Figure 1). Recently, mesoporous silica particles (MSPs) have attracted much attention due to their singular properties.[14] Here we discuss some of their characteristics and advantages in cancer drug delivery.[15]

Physicochemical properties of MSPs

MSPs have a well-defined internal mesopore structure (from 2 to 10 nm of diameter) with a large pore volume (0.6–1 cm^3/g) and a high surface area (700–1,000 m^2/g). Their size, nano- (50 nm) to submicron-scale (500 nm),[16] as well as their shape[17] and surface[18] can be custom-designed offering many different possibilities for the loading of anticancer drugs such as docetaxel,[19] paclitaxel[20] or doxorubicin,[21] among many

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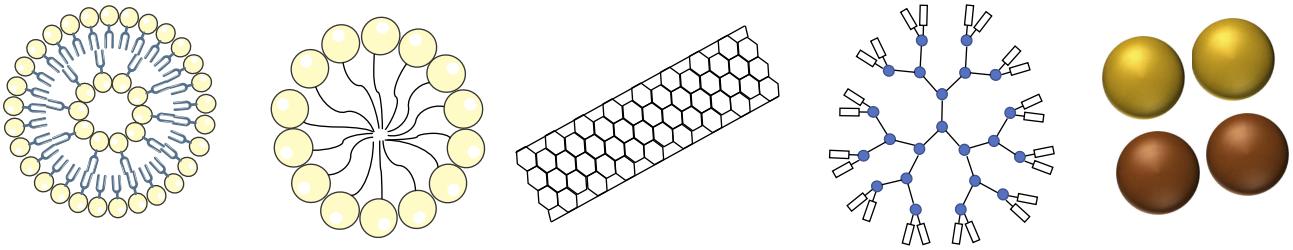

Figure 1 Schematic representation of different delivery systems. From left to right; liposomes, micelles, carbon nanotubes, dendrimer and gold (yellow) and iron (brown) nanoparticles.

others. Moreover, the cytotoxicity of these particles and cellular uptake have been demonstrated to be dependent on nanoparticle size and surface charge. Indeed, 15 nm diameter particles have been reported to trigger more cytotoxicity than 100 nm diameter particles in endothelial cells.[22] Lu and collaborators showed that 50 nm diameter particles are the optimal for cellular uptake.[23] When considering the particle surface charge, cationic silica particles appear to be more cytotoxic and have a faster cellular uptake than anionic or neutral silica particles.[24,25] Davila-Ibáñez and co-workers used magnetic silica nanoparticles with DNA attached to the silica network to show how charges at the surface of the nanoparticles is a key issue to guarantee the cellular uptake.[26,27] On the other hand, particles with a neutral charge do not appear to internalize the cell membrane of Caco-2 cells.

Targeting the cell/tissue of interest

One of the most important goals to achieve in drug delivery is the possibility of targeting nanoparticles to a specific cell or tissue. In this regard, most nanomaterials including MSPs, have been reported to passively target solid tumors. Typically, when a tumor reaches a certain size, the normal vasculature present in the tumoral organ cannot irrigate all the cellular mass. This effect generates intra-tumoral hypoxia triggering the segregation of growth factors that activate the rapid sprouting of new blood vessels from the surrounding capillaries.[28] This process known as angiogenesis generates irregular blood vessels displaying a discontinuous epithelium with an absent basal membrane.[29] When blood components reach these abnormal and discontinuous vascular networks, the fenestrations between the endothelial cells offer little resistance to the extravasation of nanomaterials inside of the tumor.[30] Particles/molecules smaller than 4 nm diffuse through the capillary endothelium back to the blood circulation and are reabsorbed,[31] but macromolecules and nanomaterials do not naturally return to the blood vessels, accumulating in the perivascular tumoral space. In the nanomedicine field, this phenomenon is known as the Enhanced Permeability and Retention effect or "EPR" effect (Figure 2). The study carried out by Lee and co-workers, showed how MSPs decorated with multiple magnetite nanocrystals loaded with Doxorubicin (DOX), induced efficient cell death in a melanoma model, confirming in vivo passive targeting and accumulation of the nanoparticles in the tumor site.[32] Huan and colleagues used MSPs functionalized with polyethyleneimine/polyethylene glycol (PEI/PEG) to carry doxorubicin together with P-glycoprotein siRNA. Their study demonstrated that these particles were effectively biodistributed, achieving an 8% of the enhanced permeability and retention effect at the tumor site in vivo.[33] But there are many more examples in the literature.

MSPs can also be functionalized to actively target tumors. One of the strategies used to reach this goal consists in the attachment of different ligand molecules – such as peptides, antibodies,[34] aptamers,[35] growth factors,[36] vitamins, etc. – on their surface, so the particles interact with receptors on the cellular surface (Figure 3).[37] This way, the entry mechanism of the nanodevice will be *via* receptor-mediated endocytosis, and the particle will be captured inside the endosomal membranes.[37] In the study carried out by Kayuan and colleagues, HB5 aptamer-functionalized mesoporous silica-carbon-based DOX-loaded systems (MSCN-PEG-HB5/DOX) were used in vitro for chemo-photothermal combined therapy in Human Epithelial growth factor Receptor 2 (HER2)-positive breast cancer cells. This study demonstrated how HER2-positive breast cancer cells uptake these particles with more avidity than normal breast epithelial cells (MCF-10A). Additionally, cytotoxicity experiments demonstrated that combined therapy induces highest cell killing effect compared to chemotherapy and photothermal therapy by itself.[38] Jianbin and colleagues showed how MSPs of 40 nm size, loaded with DOX and functionalized with selective αv-β3 integrin ligands on their surface displayed an enhanced targeting effect through the

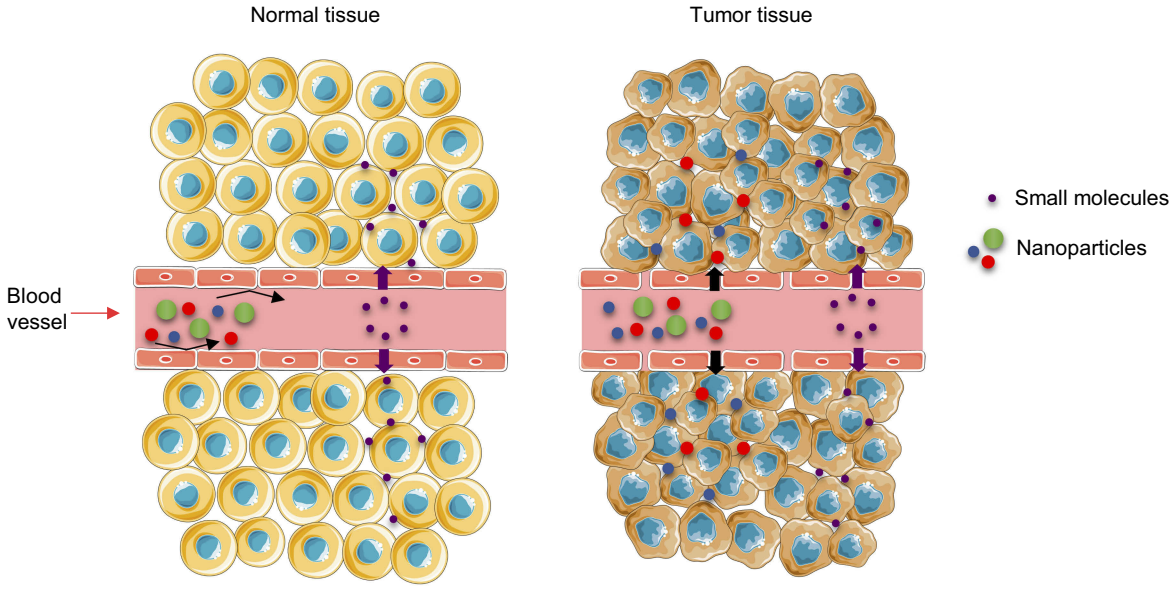

Figure 2 Image representing the blood transport mechanism of nanomaterials or molecules from normal tissue (left) and the enhanced permeability and retention effect in a tumor.

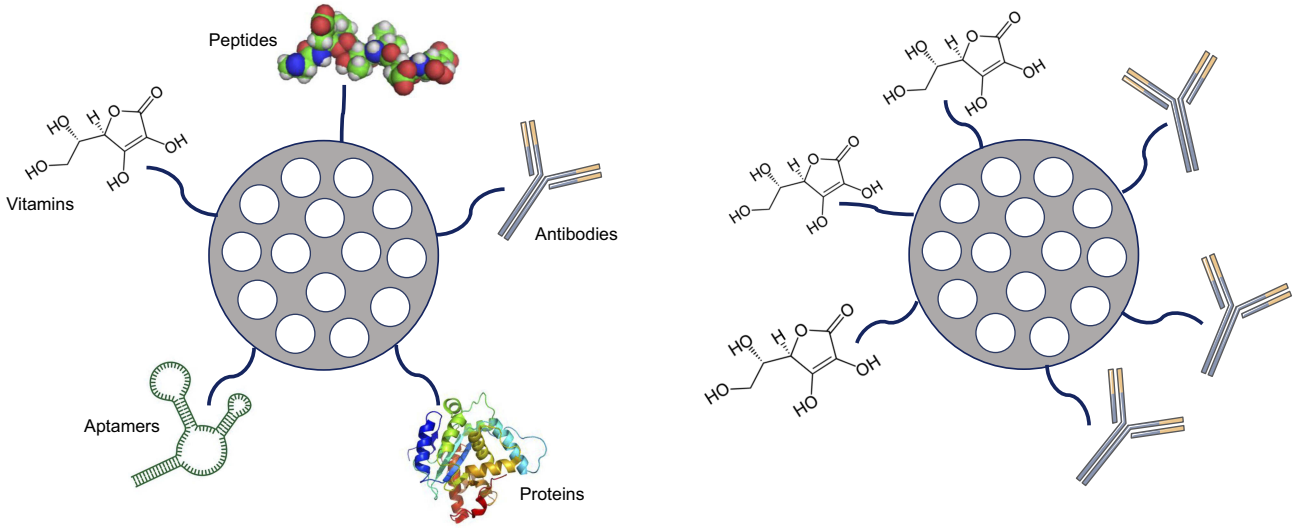

Figure 3 Schematic description of active targeting possibilities on mesoporous silica particles (left). Dual targeting example (right).

blood–brain barrier, penetrating glioblastoma cells. In summary, these targeted particles rapidly invaded cancer cells, delivering the drug intracellularly and improving the anticancer activity of the free drug. MSPs achieve satisfactory anti-glioblastoma efficacy avoiding toxic side effects in the healthy brain tissue thus, demonstrating active cell targeting.[39]

Controlling drug release: gatekeepers

Another challenge in the design of nanotransporters is delivering the drug at the precise moment when the carrier reaches the tumor, or alternatively, when a signal is provided. MSPs are useful carrier systems due to their high surface and tunable porous structure. Drugs can be loaded inside their mesopores through simple diffusion mechanism. But, one of the main advantages of MSPs is the possibility to design "zero release" nanosystems by blocking the MSP pores using gatekeepers.[13,40]

Once in the tumor, different internal or external stimuli can be employed to activate drug delivery. Some of the intra-tumoral stimuli used are the local pH conditions, the enzymes in the peritumoral tissue or the redox potential. In

Table 1 Different gatekeepers that can be used to maintain the "zero release" of the drug and to trigger drug release

External stimuli				**Internal stimuli**				
Magnetic field		**Light**		**pH Sensitive systems**		**Redox sensitive systems**		**Enzyme sensitive systems**
Magnetic particles	Magnetic nanocrystal	Gold nano-particles	Photolabile molecules	Polyelectrolytes	Ester bond	Acetal bond	Peptides	Disulfude bond

addition, external stimuli such as magnetic fields or light can also be applied to activate "on demand" drug release (Table 1, Figure 4).

Internal stimuli triggering drug delivery

The characteristics of the tumoral environment can help in the design of nanocarriers sensitive to internal or endogenous stimuli to ensure a controlled localized drug release.

- pH-sensitive systems

One general feature of solid tumors is the presence of acidity in the tumor environment due to the "Warburg effect". Healthy cells use the mitochondrial oxidative phosphorylation to produce energy. However, most cancer cells activate the glycolytic route.[41,42] This process, also known as anaerobic glycolysis, is less efficient in terms of energy (adenosine triphosphate) production and increases the generation of additional metabolites – mostly lactic acid – generating local tumoral acidosis which can be beneficial for tumor proliferating cells.[41,42]

An effective strategy to control drug release is blocking the MSP pores with noncovalently bonded pH sensible polymers. Different polymers can be selected so they detach from the particle at low pH, releasing the drug at the tumoral site. Among these systems, one of the most commonly used methods is based on polyelectrolyte multilayers. These gatekeepers are based on the layer-by-layer technique (Figure 5).[43–45] The

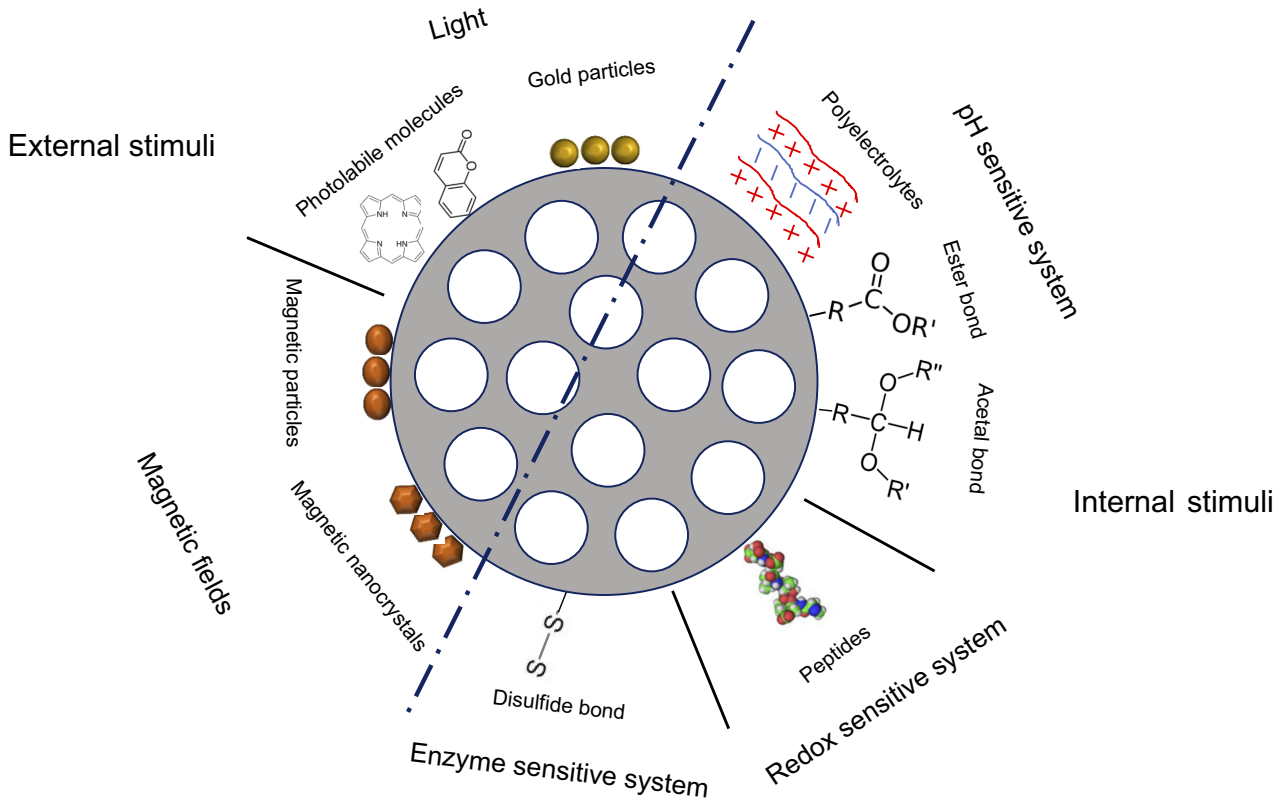

Figure 4 Examples of different gatekeepers that can be used to maintain the "zero release" of the drug inside mesoporous silica particles and to trigger on demand the release.

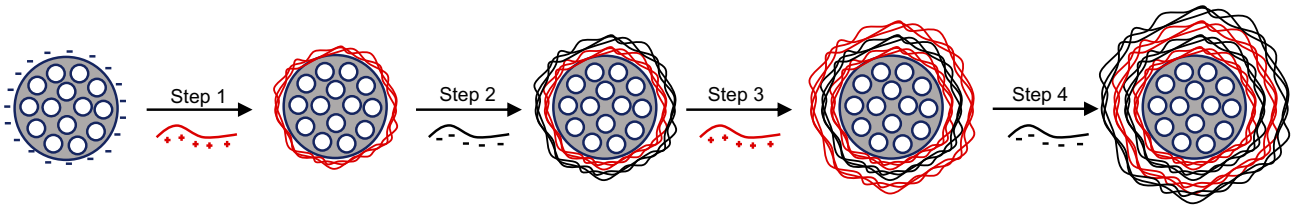

Figure 5 Scheme of the layer by layer technique in mesoporous silica particles.

composition, thickness or the molecular organization of the layers[46] and the permeability/elasticity of the polymers can be modified so the system can be easily "tuned".[47] Feng et al synthesized MSPs coated with multilayers of Poly(Allylamine Hydrochloride) (PAH) and Poly(Styrene Sulfonate) (PSS) polyelectrolytes, loaded with DOX inside the pores.[48] In this study, they demonstrated that the delivery of the drug was both pH and layer thickness dependent, and that the layer thickness has an exponential relationship with the number of polymer coats applied. This study also demonstrated that i) the biodistribution of the drug in vivo was smaller in major organs compared to that of free DOX, and that ii) these particles had lower systemic toxicity than free DOX, thus, concluding that these MSP-based nanoparticles were a good carrier system with high efficiency and low systemic toxicity. Also, Sun et al used multilayer-coated MSPs to load cisplatin and Rhodamine B (RhB).[49] The outer polyelectrolyte multilayer was assembled from the cationic polyelectrolyte PAH, and a second negatively charged polyelectrolyte, P(DMA-co-TPAMA), consisting of N,N-Dimethylacrylamide (DMA) and 3,4,5,6-Tetrahydrophthalic Anhydride functionalized N-(3-Aminopropyl) Methacrylamide (TPAMA) monomer units, that exhibited pH-induced charge conversion characteristics. This way, cisplatin and rhodamine B were released in the tumor microenvironment upon a pH reduction from 7.4 to 5–6, typical in malignant tumors. Other interesting gatekeeper systems are based on pH-sensitive linkers. These linkers are cleaved in acidic conditions, triggering the release of the cargo from the carrier. Acetal bonds,[50–52] hydrazine bonds,[53–55] hydrazone bonds[56,57] or ester bonds[58,59] are some examples that have been used worldwide. In a study carried out by Ze-Yong Li et al, DOX was conjugated to MSPs using hydrazine bonds.[60] They proved that when the particles were in vitro incubated at pH 6.5, a fast DOX release occurred due to the hydrolysis of the bonds. Lee et al were able to attach DOX to the inner wall of MSPs and release this drug in the endolysosomes of cancer cells in the liver.[61] The conjugation of the drug was done by hydrazone bonds that released the drug upon endo-lysosomal maturation when the pH of the vesicles decreased.

- Enzyme-responsive systems

Compared to healthy tissues or cells, many different enzymes, mostly proteases, are overexpressed by cancer cells.[62] This peculiarity can also be an interesting stimulus to trigger enzyme-mediated drug release.[63] The development of enzyme-released drug delivery systems based on MSPs has caught much attention. Liu et al used in their study a Matrix-Metalloproteinase (MMPs) responsive drug delivery system based on MSPs to reduce in vivo side effects of traditional chemotherapies.[64] MSPs were loaded with DOX and coated with bovine serum albumin as an end-cap to seal the mesopores of the nanoparticles, using lactobionic acid as the targeting motif. The in vivo experiments showed that the DOX delivery system could be used to inhibit tumoral growth in mice with minimal side effects.

- Redox-sensitive systems

Glutathione (GSH) is the most abundant non-protein thiol that acts as a reducing agent maintaining enzymes in an active state. In cancer cells, the intracellular concentration of GSH is three times higher than in normal cells.[65] Hence, this is a good tool to prompt the release of drugs. Disulfide bonds[66-70] (S-S) can be easily cleaved in the presence of GSH for being a redox-sensitive group, so they can be used to form capped systems with nanoparticles[71,72] or polymers[69,73,74] for instance. Gong et al were able to synthesize MSPs functionalized with polyethylene glycol using a disulfide bond linker.[74] These authors demonstrate drug release upon GSH rise, while low GSH concentrations blocked the release. Apart from PEG,[75,76] poly N-acryloxysuccinimide[77] has also been

used as an efficient method to deliver hydrophilic drugs to cancer cells improving the efficacy of the therapy.

External stimuli for drug delivery

Magnetic fields and light are external stimuli also used to control gatekeepers. Although these stimuli are less popular than endogenous stimuli, they are more reproducible and do not depend on the heterogeneous physiological conditions of the tumoral environment. Besides, these systems can be more precise in local drug release, minimizing toxicity and side effects.[78] The two main strategies of these drug delivery systems are based on magnetic fields and light.

- Magnetic fields

These drug delivery systems are based on the use of magnetic fields as external stimuli to guide the particles to the tumor environment and to locally increase the temperature, triggering cell death by controlled drug release and/or hyperthermia.[79] Superparamagnetic iron oxide nanoparticles are the most used magnetic nanoparticles. They exhibit an extraordinary capacity to convert magnetic energy into heat.[80,81] This ability allows the use of thermo-sensitive materials as gatekeepers capping the surface of MSPs, provoking the opening of the pores and the release of a drug using magnetic fields.[82,83] Baeza and colleagues used a nanodevice based on MSPs with iron oxide nanocrystals inside the silica matrix.[83] This device was coated with a copolymer of Poly(Ethyleneimine)-b-Poly (N Isopropylacrylamide) (PEI/NIPAM), which acts as a temperature-sensitive gatekeeper and retains proteins into the polymer shell linked by electrostatic forces or hydrogen bonds. Once these nanodevices are administrated into cancer cells, an alternative magnetic field is applied. The results demonstrate that the polymer can act as a gatekeeper, opening or closing the pores of the silica matrix, controlling the release of the macromolecules attached to the polymer branches. Moreover, Thomas et al used in their study DOX-loaded MSPs combined with magnetic nanocrystals that have been surface-modified with pseudorotaxanes.[84] After the application of a magnetic field, the nanocrystals generate heat, causing the disassembly of the pseudorotaxanes, triggering the release of DOX and consequently, a cytotoxic effect in breast cancer cells.

- Light

Among the external stimulus, light is a rapid, non-invasive, clean and efficient stimulus that can be used to control drug delivery with high spatial and temporal resolution.[85,86] Although most photoreactions used in drug delivery are induced by UV light,[85,87,88] the best wavelengths for good tissue penetration are those in the close IR, between 800 and 1,100 nm, which correspond to the so-called "water biological window".[89] The mechanism of these types of carriers to trigger drug release is based on the photo-sensitiveness of the gatekeeper that changes conformation upon light application. Guardado-Alvarez et al used MSPs with photolabile coumarin-based molecules capping the surface, noncovalently conjugated β-cyclodextrin to block the pores and rhodamine B inside the pores.[90] This way, 800-nm two-photon excitation triggered the release of the bond holding the coumarin to the nanopore releasing both the β-cyclodextrin cap and the cargo. Martínez-Carmona and colleagues carried another study in vitro using an MSP-based device with porphyrin-caps attached with reactive oxygen species (ROS)-cleavable linkages.[91] These bonds are sensitive to singlet-oxygen produced after exposure to visible light, releasing the cargo (Topotecan). The oxygen molecules produced by the porphyrin–nanocaps break the sensitive-linker uncapping the pores and releasing the entrapped drug. These particles have been used in osteosarcoma cancer cells demonstrating a controlled release of Topotecan inside the tumor cells. Another light-sensitive gatekeeper type is based on gold nanoparticles (AuNPs). These particles, combined with MSPs, are attractive devices for cancer cell imaging[92-94] and can also heat when irradiated with a laser producing a photothermal effect.[93] As for the magnetic nanoparticles, the heat generated upon light exposure can be used to release the anti-cancer therapy and/or trigger drug release. Wang and colleagues, for instance, designed a therapeutic delivery system, based on MSPs closed by AuNPs with RhB as the cargo.[95] This carrier was studied in vitro showing a good release of the RhB when temperature increased. In the study done by Vivero-Escoto et al AuNP-capped-MSPs were useful to release a chemotherapeutic such as paclitaxel in human fibroblast and liver cells.[96] This release could be easily controlled by low-power photoirradiation under physiological conditions.

Concerning the use of internal and external stimuli, it is important to mention the combination of both types of stimuli, light and alternating magnetic fields, to generate heat, to induce local hyperthermia increasing the pH[97] and the enzymatic activity[98] of the cells. Hence, this type of structured nanomaterials can be used as an interesting system for programmed site-specific drug delivery.

Triggering endolysosomal escape

Upon receptor-mediated endocytosis, MSPs are incorporated inside the endolysosomal membranes. Many nanoparticles after intracellular transit are eventually expelled from the cells by exocytosis.[99–101] Thus, to avoid therapy degradation in the lysosomal due to the hostile chemical conditions and/or, exocytosis, nanocarriers need to escape into the cytoplasm. Thus far, different strategies have been developed to trigger lysosomal escape among these, the proton sponge effect[102] and destabilization of the endosomal membrane are the most used.[103] The first mechanism is based on the swelling of the vesicle, and the second, in the creation of pores that enable therapeutic release into the cytoplasm.

The proton sponge effect

This effect relies on the rise of the proton concentration during hydrolysis that, in turn, causes an increase in the membrane potential, osmotic swelling and finally endo-lysosome bursting.[104] This phenomenon occurs when polyplexes such as PEI or PAMAM are endocytosed. The amine groups of these molecules capture protons that accumulate in endosomes, gradually increasing the membrane potential and breaking the lysosomal membrane equilibrium. The diffusion of Cl^- molecules into endosomes cause the increase of the osmotic pressure, swelling, expanding and finally tearing the lipid bilayer of the endolysosome, releasing the contents into the cytoplasm (Figure 6).[102] The MSPs used by Wu et al could release siRNA and DOX into the cytoplasm of breast cancer cells in vitro and in vivo using a Poly-β-amino ester coating to provoke endolysosome bursting.[105] The work carried out by Shen et al demonstrated that MSPs coated with PEI cannot only carry a siRNA but also deliver it to xenografted tumors, reducing the size of the tumoral mass.[106]

Destabilization of the endosomal membrane

Other mechanisms to trigger particle endo-lysosomal escape are fusion lipids, cationic polymers, peptides[107] or carbon nanotubes.[103] In the study performed by Zhang et al, they synthesized polymer-lipid supported mesoporous silica nanoparticles (PLS-MSPs).[108] These nanocarriers were able to release the anticancer drug (CPT -11) and maximize the effect of the treatment in MDR breast cancer cells. Apart from fusion lipids, many cell-penetrating peptides (fusogenic peptides) are being used based on bacterial or viral proteins. These peptides trigger vacuole-based endocytosis and/or to create discontinuities or pores on the cell membrane.[109,110] For instance, Li and colleagues used MSPs coated with PEI and a fusogenic peptide to deliver siRNA to a tumor model showing an inhibition of the tumoral cell proliferation.[111] Likewise, in some of our studies, we show how silica nanoparticles, when coated with multi-walled carbon nanotubes (MWCNT), can escape the endo-lysosomal route mimicking the viral spike fusion in lysosomes. The hypothesis is that proteins functionalizing the MWCNT surface are degraded in endolysosomes, exposing the surface of the nanotubes that are highly reactive and apolar. These stripped filaments now interact with the membrane of the endo-lysosomal vesicles, piercing and tearing it apart, triggering particle release into the cytoplasm (Figure 7).[103]

Biocompatibility

Last, but not least, one of the most important features of MSPs is their biocompatibility. Different studies have demonstrated that silica nanoparticles are not toxic when administrated to different cell types at different dosages.[99,112–114] Furthermore, there are several reports demonstrating that MSPs are degradable in water and in phosphate buffer saline.[13,14] There are different parameters that can trigger MSPs in vitro degradation including i) particle morphology,[115] ii) surface area[116] and iii) surface functionalization[117,118] among others. For instance, spherical particles are more degradable than with rod-shaped particles.[115] Similarly, particles that have a high surface area are more degradable.[116] Interestingly, the MSPs size is apparently not all that important in degradation in water or simulated body fluids.[119,120] Moreover, MSP and their fragments have also been reported to be eliminated by renal clearance, in urine, and/or feces.[113,121,122] Interestingly, positively charged MSPs are cleared faster than particles with a negative ζ potential. Also, PEGylated MSPs show a higher in vivo circulation time, since PEG avoids macrophage recognition and phagocytosis in the liver and spleen. Other studies are now developing to improve the interactions of nanomaterials with blood components. For instance, Roggers et al have demonstrated that the functionalization of MSPs with different lipids can be used to imitate red blood cell lipid membranes, improving their hemo-biocompatibility.[121]

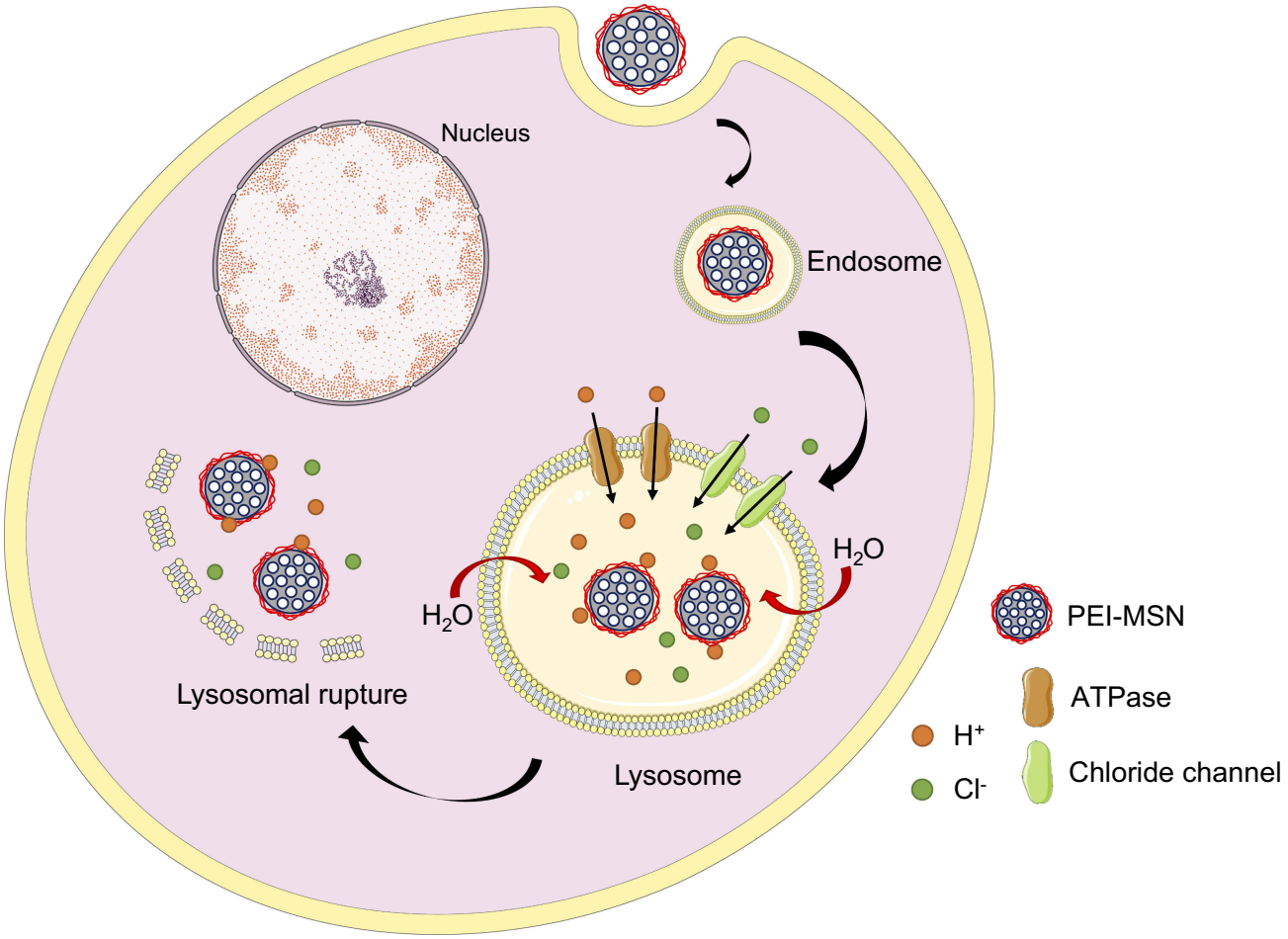

Figure 6 Diagram of the proton sponge effect: particles coated with polyethyleneimine (PEI) are captured in the endolysosomal route. Lysosomal membranes tear apart, releasing the particles in the cytosol.
Abbreviation: PEI-MSN, mesoporous silica particles coated with PEI.

Drawbacks of MSPs

Ideally, nanoparticles need i) to be stable, ii) to have a high loading capacity, iii) to be reproducible and iv) scalable in production. Reproducible MSPs synthesis is reasonably feasible when working at small scale, but the scaling up is not trivial therefore, reproducibility at industrial scale must be critically considered. Regarding the loading capacity of MSPs, not all drugs can be incorporated at an adequate concentration, and this critically influences the total concentration of nanoparticles that should be administrated to obtain an effective therapeutic effect. For instance, the tolerated dose of uncoated MSPs in murine models is ca. 50 mg/kg, but the human tolerance is so far unknown and needs to be evaluated.[122] Also, most biodistribution and excretion studies have been performed in mice[123] and must be reproduced in humans to understand the immune response and possible side-effects of these nanomaterials.

Another important point regarding the use of MSPs in clinical trials is the fact that the Food and Drug Administration and the European Medicines Agency must evaluate drug delivery nanocarriers before bench-to-bed translation, even if loaded with drugs already approved for clinical use. This is a slow procedure that significantly delays all new developments in nanodelivery. Hopefully, soon new requirements will be developed to accelerate the translation from research to the clinic.

Conclusion

The field of nanotechnology is gaining a high interest in cancer medicine. MSPs can be customized on demand in order to engineer nanocarriers that can i) target cells specifically, ii) release drugs inside the desired tissues/cells reducing the side effects of the treatment, iii) invade the cytoplasm by scaping the endo-lysosomal membrane, so that the cargo is preserved and finally iv) be biodegraded

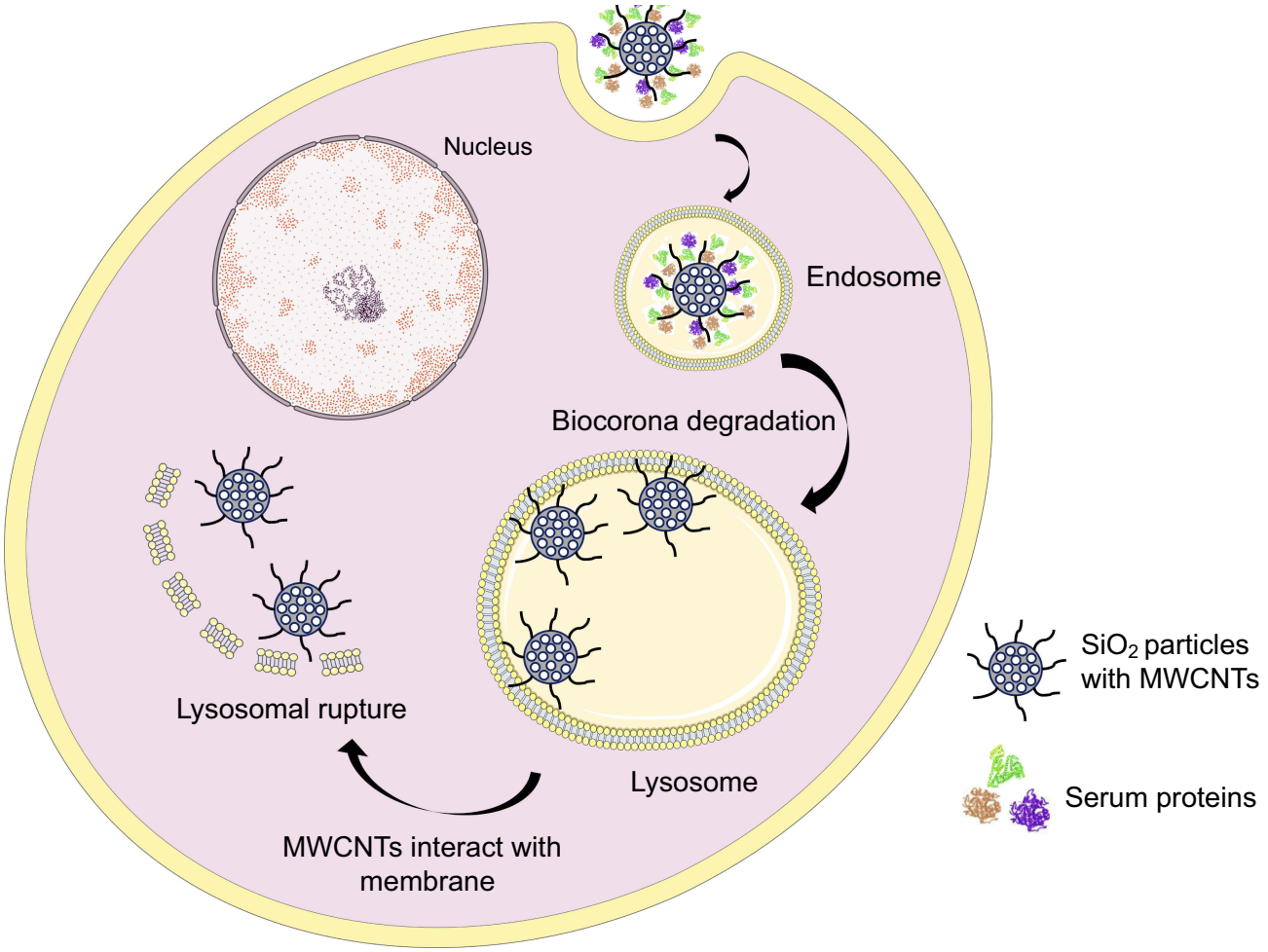

Figure 7 Diagram of how mesoporous SiO_2 particles with a multi-walled carbon nanotubes (MWCNT) coating, scape the endolysosomal route. When proteins of the biocorona are degraded, apolar MWCNTs interact with the membrane and help particles escape these vesicles.

or cleared from the organism to minimize toxicity. Although MSPs are being widely studied as nanocarrier systems in animal models to ensure they are safe, more research is needed in the field of nanodelivery in cancer.

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Images have been produced using the free software available at: https://smart.servier.com/.

Disclosure

The authors report no conflicts of interest in this work.

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