Controlling Cellular Function with Multifunctional Mesoporous Nanoparticles

Thomas Bein
Department of Chemistry, Nanosystems Initiative Munich (NIM) and Center for Nano Science (CeNS), University of Munich (LMU), Butenandtstr. 11, 81377 Munich, Germany.

Over the years, numerous intriguing types of multifunctional mesoporous nanoparticles have been developed as carriers for targeted drug delivery, for example in the context of cancer therapy. In our recent work, we have addressed several key challenges related to the development of multifunctional mesoporous silica and other mesoporous nanoparticles, including stimuli-responsive release systems, targeting ligands for specific cellular receptors, biodistribution and biocompatibility.

For example, folate and epidermal growth factor (EGF) have been used for successful cell targeting with MSNs. Considering triggered release in the endosome, a novel pH-responsive system has been created based on genetically modified carbonic anhydrase (CA) gatekeepers. A pH-dependent CA inhibitor was covalently attached to the surface of the MSNs, resulting in the desired opening mechanism caused by the endosomal pH change. Addressing endosomal escape, we have covalently attached a red-light sensitive phthalocyanine photosensitizer to the MSN, surrounded by a lipid bilayer, which releases cargo upon illumination. Moreover, we have exploited the proton sponge effect during acidification of the endosome with polymer-functionalized MSNs to achieve endosomal release. Taking advantage of overexpressed matrix metalloproteinases in cancer tissue, we have also achieved spatially selective extracellular release of bioactive molecules.

To expand the scope of bioactive cargo molecules that can be released from MSN systems, we have developed organically functionalized large-pore and medium-pore MSNs that can reversibly adsorb oligonucleotides such as siRNA at high loading and with high cellular activity upon release. Moreover, cellular uptake of proteins such as small

antibody fragments was successfully achieved using a novel release mechanism from MSNs. These antibodies were used to target cellular organelles with high specificity.

Recently, we have expanded the scope of mesoporous materials to mesoporous metal phosphates with very high surface area and the ability to dissolve in the acidic cytosol (surface area of 900 m2 g-1, very narrow pore size distribution with a maximum at around 5 nm, and cumulative pore volume of 1.0 cm3 g-1).(1) Their intracellular behavior is complimentary to that of MSNs, opening new vistas in targeted drug release with porous nanoparticles. Specifically, we will discuss a novel synthesis method for spherical, amorphous mesoporous calcium phosphate-citrate nanoparticles (CPCs) with an average size of 50 nm. Internalized CPCs dissolve once the endosomal pH turns acidic. This leads to a rapid release of Ca2+ ions into the cytosol. Remarkably, mesenchymal cancer cell lines are much more strongly affected by the Ca2+ shock and induce apoptosis at lower IC50 values than epithelial cancer cells, while healthy cells are not affected. These nanoparticles show promising therapeutic activity in a malignant pleural effusion (MPE) mouse model. Our results strongly suggest the possibility to efficiently treat certain lung tumors while at the same time dramatically reducing side effects.

(1) T. Bein, H. Engelke, H. Feckl, C. von Schirnding (2015), PCT/EP2016/068231.