



Cover Story

Smart nanobombs for inducing traumatic death of cancer cells

Smart hydrogel nanoparticles (nanogels) that exhibit volume transition behaviors in response to various external stimuli, such as temperature, pH, light, and enzymes, have been used widely in drug delivery and molecular imaging. The smart nanogels that are normally synthesized by chemical crosslinking of water soluble polymers in a nano-sized spherical structure are different from self-assembled micelles and polyelectrolyte complexes. Recent studies on biomedical applications of smart nanogels were mostly focused on enhancing the extent of cellular uptake for anti-cancer drugs, including small interfering RNA (siRNA).

It was demonstrated previously that the smart nanogels could be exploited for destabilizing sub-cellular vesicular compartments, such as endosomes, by thermally triggered volume expansion [1]. Cationic nanocapsules composed of polyethylenimine (PEI) and poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO, Pluronic™) were synthesized for facile cytosolic delivery of siRNA by cold-shock-induced rupture of endosomes after cellular uptake. The smart nanocapsules exhibited an abrupt volume expansion from ~100 nm at the body temperature to ~350 nm at room temperature. Such a volume transition was large enough to physically disrupt the membrane integrity of sub-cellular endosomes, resulting in enhanced gene silencing effect of siRNA. However, the volume expansion of nanocapsules alone showed no significant cytotoxicity to cancer cells.

In an article in this issue [2], the same group reported for the first time that a new class of smart nanogels exhibiting a thermally reversible volume transition behavior from nano- to micro-scale dimension could be used to induce traumatic death of cancer cells by physical rupture of whole cell organizations. The smart “nanobomb” was synthesized by lightly crosslinking oligo(L-lactic acid) end-capped Pluronic copolymers and PEG-grafted poly(L-lysine). The abrupt intracellular nano- to micro-scale explosion of the smart nanobomb occurred upon a brief cold-shock treatment. This abrupt explosion induced necrotic cell death by severely damaging sub-cellular self-assembled network architectures including cytoskeleton, and by

physically rupturing plasma membrane structures. The smart nanobomb which could be detonated by a brief cold-shock treatment could effectively kill the cells.

The smart nanobomb can be further engineered to produce even smarter “targeting nanobomb” by modifying the surface with various cancer cell targeting ligands and concomitantly loading with anti-cancer drugs. It is also anticipated that various smart nanobombs, exhibiting nano- to micro-scale volume transition responsive to other stimuli such as light, pH, and specific enzymes of target cancer cells, could be similarly fabricated using other types of stimuli-sensitive polymers. Considering the fact that many subcellular compartments have pH lower than 7.4, a number of pH-sensitive nanobombs can be developed. The abundant presence of a certain enzyme on the target cancer cell membrane can also be exploited for developing enzyme-triggered nanobombs. The study of Lee et al. opens a new and exciting venue for developing the next generation nanovehicles possessing multiple functions.

References

- [1] S.H. Lee, S.H. Choi, S.H. Kim, T.G. Park, Thermally sensitive cationic polymer nanocapsules for specific cytosolic delivery and efficient gene silencing of siRNA: swelling induced physical disruption of endosome by cold shock, *J. Control. Release* 125 (2008) 25–32.
- [2] Y. Lee, S.Y. Park, C. Kim, T.G. Park, Thermally triggered intracellular explosion of volume transition nanogels for necrotic cell death, *J. Control. Release* 135 (2009) 89–95, doi: 10.1016/j.jconrel.2008.12.008.

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