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Bioresponsive Controlled Release Using Mesoporous Silica Nanoparticles Capped with Aptamer-Based Molecular Gate

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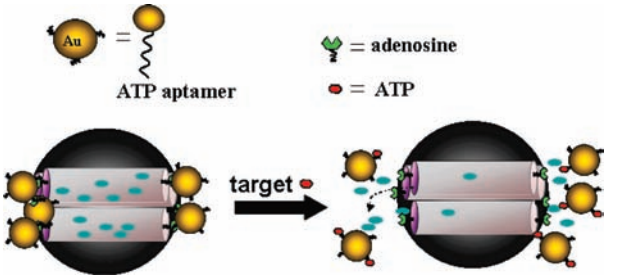
Supporting Information

ABSTRACT: This communication describes the design of a novel and general bioresponsive controlled-release mesoporous silica (MS) nanoparticles system based on aptamer−target interactions. In this system, the pores of MS were capped with Au nanoparticles modified with aptamer (ATP aptamer in this case). By a competitive displacement reaction, the Au nanoparticles were uncapped in the presence of ATP molecule, and the cargo was released. Our results demonstrated that the aptamer−target interaction may be a promising route for the design of custom-made controlled-release nanodevices specifically governed by target biomolecules. Since aptamers have been obtained for a broad range of targets, including several cancer biomarkers, we believe that this aptamer-based controlled-release system should have an equally broad spectrum of applications.

Due to its nontoxic nature, high surface area, large pore volume, tunable pore size, and chemically modifiable surfaces, mesoporous silica (MS) has been used as a promising carrier system for drug delivery.[1−4] Recent reports on the design of capped and gated MS derivatives have shown promise in the generation of controlled-release systems. For example, inorganic nanoparticles,[5a−5d] polymers,[5e,5f] and larger supramolecular assemblies[5g,5h] have been used as the blocking caps to control opening/closing of pore entrances of MS. Different stimuli, such as pH,[6a−6c] light,[6d−6f] redox potential,[6g−6j] and temperature,[6k] have been applied as "triggers" for uncapping the pores and releasing the guest molecules from MS. Most recently, designing MS-based systems to trigger the release of guest molecules involving biomolecules became an important field. Some biomolecules, such as enzymes,[7a,7b] antibodies,[7c] glucose,[7d] and nucleotides[7e] have been used as stimuli to uncap the MS. Despite these burgeoning developments, it is still a challenge to develop more general and practical bioresponsive controlled-release MS systems.

In this communication, we report the construction of a novel and general bioresponsive controlled-release MS system that is based on MS nanoparticles capped with aptamer-modified gold nanoparticles and is stimuli responsive to the aptamer−target interaction. Aptamers are single-stranded oligonucleotides that can specifically bind to their targets with high affinity and specificity.[8]

Scheme 1. Schematic Illustration of Aptamer−Target Interaction Responsive Controlled-Release System[a]



[a] AuNPs-aptamer was capped on the MSA surface due to the binding reaction of ATP aptamer to the adenosine molecule. The delivery of the entrapped guest (fluorescein) was selectively triggered by an effective displacement reaction in the presence of the target molecule (ATP).

In comparison with antibodies, aptamers, particularly DNA aptamers, are relatively easy to obtain, more stable to biodegradation, less vulnerable to denaturation, and flexible to modification. After more than a decade's development, aptamers have shown ample potential and have a promising future in the fields of bioassay, biotechnology, and nanotechnology.[9]

The working principle of the aptamer−target interaction responsive controlled-release system is illustrated in Scheme 1. In this work, the solid MCM-41 nanoparticle tailed by the $-NH_2$ group was selected as support, and the adenosine triphosphate (ATP) molecule was demonstrated as target. A derivative of the ATP molecule (adenosine-5′-carboxylic acid, denoted as adenosine-COOH) was immobilized on the outer surface of the MS through amidation reaction (denoted as MSA). Meanwhile, Au nanoparticles (AuNPs) were functionalized with ATP aptamer through Au−S bond (denoted as AuNPs-aptamer). Detailed DNA sequence, modification, and linkages are shown in the Supporting Information. Because the ATP aptamer recognizes the adenine and ribose moieties and not the phosphate moiety,[10] when mixing AuNPs-aptamer with MSA, AuNPs would be capped on the pores of MSA, owing to the binding reaction of ATP aptamer with adenosine. The obtained products were denoted as MSA-Au particles. The release of the guest molecule from MSA-Au could be triggered by challenge with ATP molecules. The addition of ATP resulted in a competitive displacement reaction

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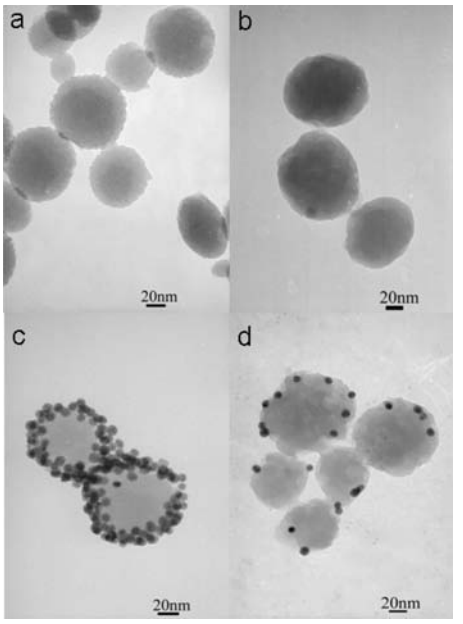

Figure 1. TEM of (a) MS-NH_2, (b) MSA, (c) Au-capped MSA, and (d) Au-capped MSA in the presence of ATP (8 mM).

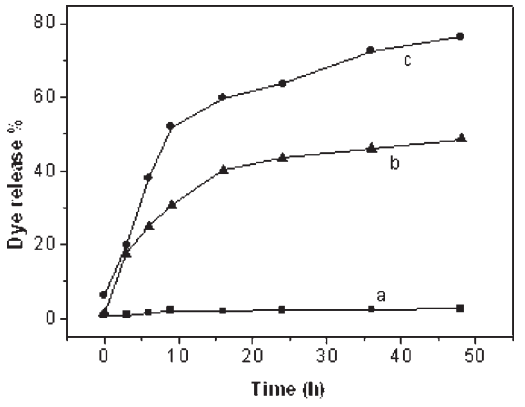

Figure 2. Time course of fluorescein release from MSA-Au in the absence (a) and in the presence of 8 mM of ATP (b). The control test for MSA-FITC is also shown in (c).

to the adenosine−aptamer interaction. Therefore, the AuNPs could be uncapped from MSA surface, and the cargo molecule could be released.

We first synthesized aminopropyl-functionalized mesoporous silica particles (MS-NH_2) with an MCM-41-type channel-like mesoporous structure shown in Figure 1a using a method reported previously.[11] The obtained MS-NH_2 particles have a surface area of 1047 $m^2\ g^{-1}$ and an average pore size of 3.1 nm. The quantity of amine group on the MS surface was determined to be 35.58 μmol/g MS by a fluorescamine test. Then, the adenosine-COOH molecule was immobilized on the MS-NH_2 surface through the amidation reaction, giving rise to the MSA particles (see Supporting Information). The interaction between MSA particles and AuNPs was confirmed by TEM microscopy, as shown in Figure 1. In the case of Au-capped MSA (Figure 1c), dark spots on the outside edges of the mesopores were observed, representing the aggregation of AuNPs on the exterior surface of MSA. In contrast, by addition of ATP molecule, Au-uncapped

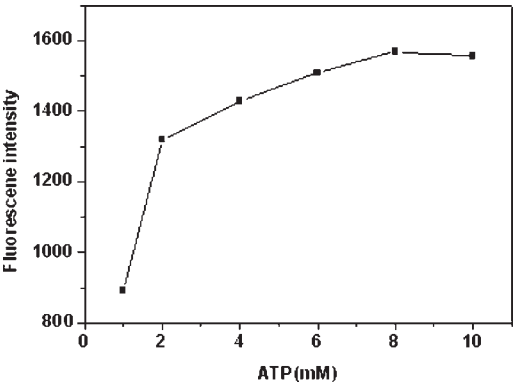

Figure 3. Controlled release of FITC from the MSA-Au system triggered by ATP as a function of concentration, measured after 24 h.

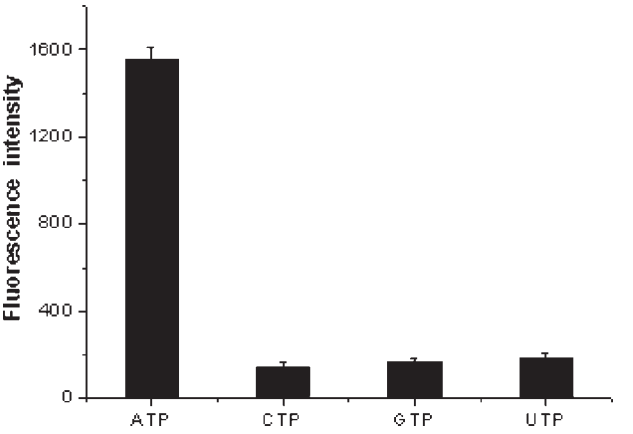

Figure 4. Selectivity release profiles for aptamer−target-responsive controlled-delivery system triggered by ATP, CTP, GTP, and UTP, respectively (8 mM, 24 h).

MSA particles could be observed in Figure 1d. The results indicated that the AuNPs really could be capped and uncapped from the MSA by the aptamer−target interaction.

To investigate the aptamer−target-responsive release behavior of MSA-Au system, fluorescein isothiocyanate (FITC) dye was loaded as a guest by soaking MSA in a PBS solution (pH 7.4) of FITC (MSA-FITC). The loading of FITC was determined to be 0.67 μmol/g of MSA as described in the Supporting Information. To examine the capping efficiency, the MSA-Au sample loaded with FITC was first dispersed in PBS solution without target molecules. The intensity of released FITC is essentially constant, indicating no obvious leakage of the entrapped dye molecules (Figure 2a), whereas the uncapped MSA-FITC sample exhibits a rapid dye molecular transport in Figure 2c. This result indicated that the capping strategy was successful with good efficiency. The trigger release of fluorescein was investigated by addition of ATP molecules to the MSA-Au system. In the presence of target molecules, the linkage between MSA and the Au-aptamer could be dissociated through a competitive displacement reaction, and the AuNPs would be uncapped from the MSA system. Therefore, it was expected that the release of FITC would be sensitive to the ATP molecule. A considerable FITC release from the MSA-Au system was indeed observed in the presence of ATP molecules (Figure 2b). The amount of released FITC from the MSA-Au system was dependent on the

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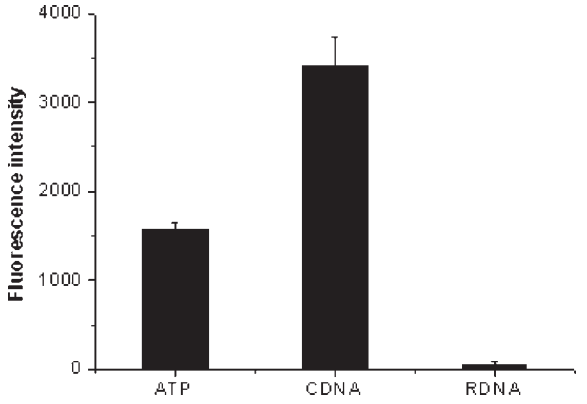

Figure 5. Fluorescence intensity for MSA-Au system on the aptamer–target-responsive release toward ATP (8 mM), cDNA (CDNA, 8 μM), and random DNA (RDNA, 8 μM) for 24 h.

added amount of ATP (shown in Figure 3). The maximum release was observed at 8 mM of ATP.

In addition, to these delivery studies for the MSA-Au system, further control experiments were carried out to evaluate the effect of the aptamer on the selective delivery process. The ATP analogues, such as cytosine 5′-triphosphate (CTP), guanosine 5′-triphosphate (GTP), and uridine 5′-triphosphate (UTP) did not induce a characteristic release similar to the release for ATP, as shown in Figure 4. This observed high selectivity was attributed to the high specificity binding of the ATP aptamer to the ATP molecule. To further examine the applicability of this delivery system, we also examined the uncapping ability of the complementary oligonucleotides (CDNA) and the random oligonucleotides (RDNA) to the ATP aptamer. The delivery profile of fluorescein in the presence of CDNA and RDNA is displayed in Figure 5. A remarkable release of dye was observed with CDNA, whereas the presence of RDNA induced negligible dye delivery, displayed in Figure 5. This result demonstrated that this controlled-release system could also be stimuli-responsive to the complementary oligonucleotide of the aptamer. Additionally, a difference in delivery dye was observed between the ATP molecule and CDNA. The high delivery efficiency toward CDNA could be explained by its high binding ability to ATP aptamer in comparison with that of ATP ($K_{d\ CDNA}$: ~1 nM; $K_{d\ ATP}$: 0.7–0.8 μM).[10]

In summary, we have demonstrated for the first time that the aptamer–target interaction could be used as a stimuli-responsive mechanism in controlled-release systems. The capping and release profile is strongly dependent on the high affinity and specificity between the aptamer and target. We believe that the aptamer–target-responsive method may be a promising route for the design of custom-made controlled-delivery nanodevices specifically triggered by target molecular guests. Due to the specificity and diverse application in biomedicine of aptamers, the system reported here is promising for biosensor and in vivo site-specific drug delivery.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details for the synthesis of MSA and the modification of gold nanoparticles by ATP aptamer; X-ray data for MSA-Au. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Slowing, I. I.; Trewyn, B. G.; Giri, S.; Lin, V. S. Y. *Adv. Funct. Mater.* **2007**, *17*, 1225.

(2) Trewyn, B. G.; Slowing, I. I.; Giri, S.; Chen, H.-T.; Lin, V. S. Y. *Acc. Chem. Res.* **2007**, *40*, 846.

(3) Vallet-Regi, M.; Balas, F.; Arcos, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7548.

(4) Vallet-Regi, M.; Ramila, A.; del Real, R. P.; Perez-Pariente, J. *Chem. Mater.* **2001**, *13*, 308.

(5) (a) Lai, C.-Y.; Trewyn, B. G.; Jeftinija, D. M.; Jeftinija, K.; Xu, S.; Jeftinija, S.; Lin, V. S.-Y. *J. Am. Chem. Soc.* **2003**, *125*, 4451. (b) Giri, S.; Trewyn, B. G.; Stellmaker, M. P.; Lin, V. S.-Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5038. (c) Aznar, E.; Marcos, M. D.; Martinez-Manez, R.; Sancenon, F.; Soto, J.; Amoro, P.; Guillem, P. *J. Am. Chem. Soc.* **2009**, *131*, 6833. (d) Vivero- Escoto, J. L.; Slowing, I. I.; Wu, C.; Lin, V. S.-Y. *J. Am. Chem. Soc.* **2009**, *131*, 3462. (e) Liu, R.; Zhao, X.; Wu., T.; Feng, P. Y. *J. Am. Chem. Soc.* **2008**, *130*, 14418. (f) Zhu, C. L.; Song, X. Y.; Zhou, W. H.; Yang, H. H.; Wang, X. R. *J. Mater. Chem.* **2009**, *19*, 7765. (g) Nguyen, T. D.; Liu, Y.; Saha, S.; Leung, K. C. F.; Stoddart, J. F.; Zink, J. I. *J. Am. Chem. Soc.* **2007**, *129*, 626. (h) Liu, R.; Zhang, Y.; Feng, P. Y. *J. Am. Chem. Soc.* **2009**, *131*, 15128.

(6) (a) Angelos, S.; Yang, Y.-W.; Patel, K.; Stoddart, J. F.; Zink, J. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 2222. (b) Park, C.; Oh, K.; Lee, S.; Kim, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1455. (c) Liu, R.; Zhang, Y.; Zhao, X.; Agarwal, A.; Mueller, L. J.; Feng, P. Y. *J. Am. Chem. Soc.* **2010**, *132*, 1500. (d) Nguyen, T. D. K.; Leung, C. F.; Liong, M.; Liu, Y.; Stoddart, J. F.; Zink, J. I. *Adv. Funct. Mater.* **2007**, *17*, 2101. (e) Ferris, D. P.; Zhao, Y.; Khashab, N. M.; Khatib, H. A.; Stoddart, J. F.; Zink, J. I. *J. Am. Chem. Soc.* **2009**, *131*, 1686. (f) Lin, Q. N.; Huang, Q.; Li, C. Y.; Bao, C. Y.; Liu, Z. Z.; Li, F. Y.; Zhu, L. Y. *J. Am. Chem. Soc.* **2010**, *132*, 10645. (g) Hernandez, R.; Tseng, H.-R.; Wong, J. W.; Stoddart, J. F.; Zink, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 3370. (h) Nguyen, T. D.; Tseng, H.-R.; Celestre, P. C.; Flood, A. H.; Liu, Y.; Stoddart, J. F.; Zink, J. I. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10029. (i) Nguyen, T. D.; Liu, Y.; Saha, S.; Leung, K. C.-F.; Stoddart, J. F.; Zink, J. I. *J. Am. Chem. Soc.* **2007**, *129*, 626. (j) Kim, H.; Kim, S.; Park, C.; Lee, H.; Park, H.; Kim, C. *Adv. Mater.* **2010**, *22*, 4280. (k) Schlossbauer, A.; Warncke, S.; Gramlich, P. M. E.; Kecht, J.; Manetto, A.; Carell, T.; Bein, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4734.

(7) (a) Patel, K.; Angelos, S.; Dichtel, W. R; Coskun, A.; Yang, Y.-W.; Zink, J. I.; Stoddart, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 2382. (b) Park, C. Y.; Kim, H.; Kim, S. H.; Kim, C. H. *J. Am. Chem. Soc.* **2009**, *131*, 16614. (c) Climent, E.; Bernardos, A.; Martínez-Máñez, R.; Maquieira, A.; Marcos, M. D.; Pastor-Navarro, N.; Puchades, R.; Sancenón, F.; Soto, J.; Amorós, P. *J. Am. Chem. Soc.* **2009**, *131*, 14075. (d) Zhao, Y. N.; Trewyn, B. G.; Slowing, I. I.; Lin, V. S.-Y. *J. Am. Chem. Soc.* **2009**, *131*, 8398. (e) Climent, E.; Martínez-Máñez, R.; Sancenón, F.; Marcos, M. D.; Soto, J.; Maquieira, A.; Amorós, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 7281.

(8) (a) Ellington, A. D.; Szostak, J. W. *Nature* **1990**, *346*, 818. (b) Tuerk, C.; Gold, L. *Science* **1990**, *249*, 505. (c) Shamah, S. M.; Healy, J. M.; Cload, S. T. *Acc. Chem. Res.* **2008**, *41*, 130.

(9) (a) Willner, I.; Zayats, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 6408. (b) Bunka, D. H. J; Stockley, P. G. *Nat. Rev. Microbiol.* **2006**, *4*, 588. (c) Famulok, M.; Hartig, J. S.; Mayer, G. *Chem. Rev.* **2007**, *107*, 3715. (d) Lu, Y.; Liu, J. W. *Acc. Chem. Res.* **2007**, *40*, 315. (e) Fang, X.; Tan., W. *Acc. Chem. Res.* **2010**, *43*, 48. (f) Nutiu, R.; Li, Y. *J. Am. Chem. Soc.* **2003**, *125*, 4771.

(10) (a) Huizenga, D. E.; Szostak, J. W. *Biochemistry* **1995**, *34*, 656. (b) Diechmann, T.; Butcher, S. E.; Sassanfar, M.; Szostak, J. W; Feigon, J. *J. Mol. Biol.* **1997**, *273*, 467.

(11) Lai, C.-Y.; Trewyn, B. G.; Jeftinija, D. M.; Jeftinija, K.; Xu, S.; Jeftinija, S.; Lin, V. S.-Y. *J. Am. Chem. Soc.* **2003**, *125*, 4451.