Nanoparticle-programmed surface for drug release and cell regulation

Pinliang Jiang[1,2], Shihui Li[1], Jinping Lai[1], Hong Zheng[1,2], Changjian Lin[2], Peng Shi[1], Yong Wang[1]

[1]Department of Biomedical Engineering, Pennsylvania State University, University Park, PA

[2]College of Chemistry and Chemical Engineering, Xiamen University, China

Background

A surface directly connects the bulk of a material to the surrounding. The ability to regulate dynamically the surface without affecting the bulk of a material holds great potential for new applications.[1-3] The purpose of this work was to demonstrate that the surface can be dynamically changed using nanoparticles and oligonucleotides in a reversible and reiterative manner. A dual-functional nanogel has been synthesized as the model of nanoparticles using miniemulsion polymerization and click chemistry. The nanogel can adsorb drugs for sustained drug release and bind a surface functionalized with complementary oligonucleotides. Importantly, hybridization reaction and oligonucleotide degradation can drive reversible and reiterative nanogel binding to the surface for dynamic change, which in principle is unlimited. Moreover, nanogel-mediated dynamic change offers the surface with the drug-releasing function for inhibiting the growth of surrounding cells. Since nanogels can be replaced by any functional nanoparticles with a diverse array of properties, nanoparticle-programmed surface change constitutes a promising platform for various applications.

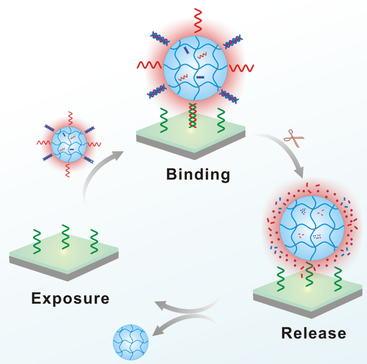


Figure 1. Nanoparticle-programmed dynamic surface.

Methods

The nanogel was synthesized via the inverse miniemulsion polymerization method. DNA sequences were conjugated to the nanogel via click reaction. After that, the nanogel with Dox was loaded onto the hydrogel surface by DNA hybridization. With the DNA degradation, the nanogel and Dox were released from the hydrogel surface. The released drug can induce the viability of smooth muscle cells.

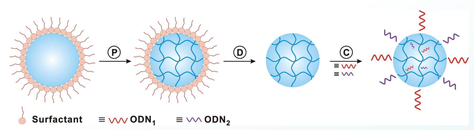


Figure 2. Schematic illustration. P: polymerization of nanodroplet in emulsion; D: dialysis for the removal of surfactant from the nanogel; C: click chemistry for conjugation of oligonucleotide (ODN) to nanogel.

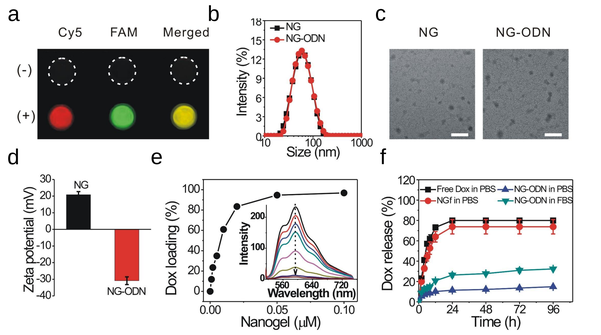
Acknowledgements

This work was supported by the Grace Woodward grant and NSF INSPIRE Award (DMR 1322332).

Reversible nanogel adsorption and release for dynamic surface change

The nanogels had two functions. One of them was to load drugs for drug release and cell regulation. The other was to bind the hydrogel surface for dynamic change. This binding function was also realized using intermolecular hybridization reaction. Two complementary oligonucleotides, ODN_1 and chemically modified $cODN_1$, were used to functionalize the nanogels and the hydrogel surface, respectively. With the degradation of ODN_1, the nanogel was released from the hydrogel surface. After that, the surface was treated with the fresh nanogel solution at the end of day 3. The procedures for nanogel adsorption and release were the same as the initial treatment. The same trend as observed in the first cycle of test occurred in the second cycle of test .

Figure 3. (a) Fluorescence images of nanogels functionalized with DNA via click reaction (+). (b) Dynamic light scattering analysis. NG: native nanogel; NG-ODN: nanogel conjugated with ODN_1 and ODN_2. (c) TEM images of nanogels. Scale bar: 100 nm. (d) Zeta potential of nanogels. (e) Quantification of Dox loading into nanogel. (f) Dox release from ODN-functionalized nanogels. Free Dox: release of free Dox from the Dox solution. NGf: release of Dox after Dox was mixed with nanogels that were free of ODN. NG-ODN: release of Dox from the ODN-functionalized nanogels.



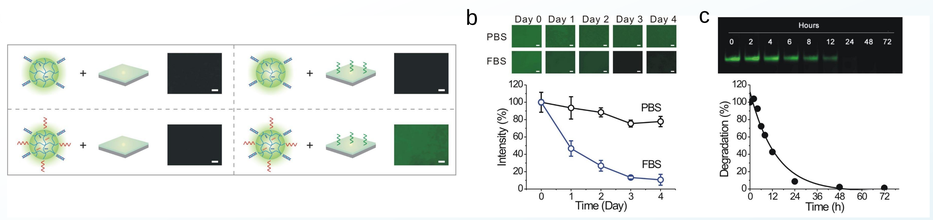


Figure 4. Nanogel adsorption and release on the surface. (a) Binding of ODN_1-functionalized nanogels on the $cODN_1$-functionalized surface. Scale bar: 100 μm. (b) Kinetics of nanogel release from the hydrogel surface. Scale bar: 100 μm. (c) Electrophoretic gel images of free ODN_1 incubated in the FBS solution.

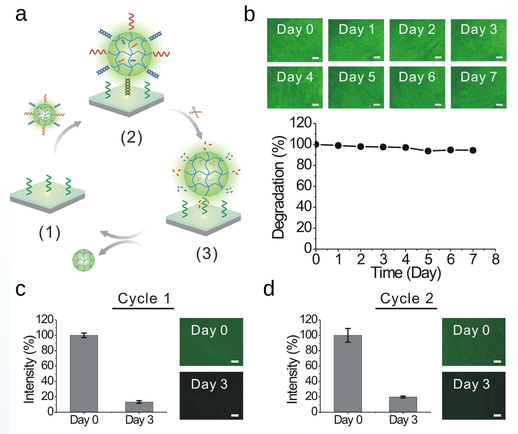


Figure 5. Evaluation of reversible and reiterative nanogel adsorption on the surface. (a) Illustration of programmable change of the surface via reiterative nanogel attachment and release. (b) Fluorescence images of $cODN_1$-functionalized hydrogel surface immersed in the FBS solution. Scale bar: 100 μm. (c) Examination of programmable surface change in a two-cycle test. Scale bar: 100 μm.

Examination of drug release and cell Regulation

We used drug release and cell inhibition as an example to demonstrate the potential applications. The hydrogel surface with the nanogel solution was examined for two cycles to achieve the Dox release in FBS solution. Smooth muscle cells were used to show the cell response to the dynamic surfaces.

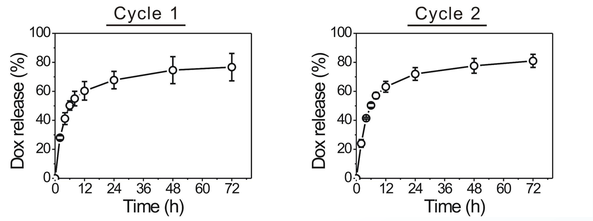


Figure 6. Nanogel-programmed surface change for sustained Dox release in a two-cycle test.

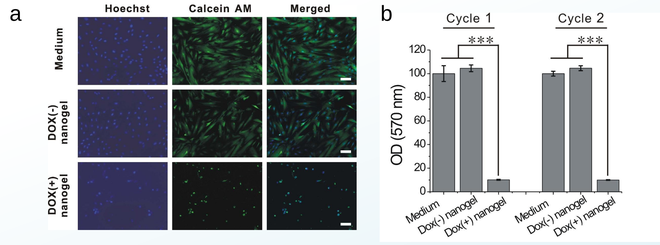


Figure 7. Fluorescence images of SMCs that were stained with Hoechst 33342 and Calcein AM after 72-h incubation with the dynamic surface. Scale bar: 100 μm. (c) Analysis of cell viability using MTT assay. Error bar: standard deviation (n = 3). *** indicates $p < 0.001$.

References

1. Robertus, J.; Browne, W. R.; Feringa, B. L. Dynamic control over cell adhesive properties using molecular-based surface engineering strategies. *Chem. Soc. Rev.* **2010,** *39*, 354-378.
2. Li, S.; Gaddes, E. R.; Chen, N.; Wang, Y. Molecular Encryption and Reconfiguration for Remodeling of Dynamic Hydrogels. *Angew. Chem. Int. Ed.* **2015,** *54*, 5957-5961.
3. Zhang, Z.; Chen, N.; Li, S.; Battig, R.; Wang, Y. Programmable hydrogels for controlled cell catch and release using hybridized aptamers and complementary sequences. *J. Am. Chem. Soc.* **2012**, *134*, 15716-15719.