Bioconjugate Chemistry

Article

pubs.acs.org/bc

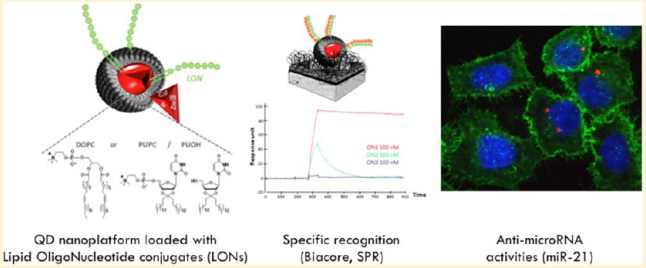
Quantum Dot Lipid Oligonucleotide Bioconjugates: Toward a New Anti-MicroRNA Nanoplatform

Ahissan Aimé, Nataliia Beztsinna, Amit Patwa, Alexander Pokolenko, Isabelle Bestel,* and Philippe Barthélémy*

Universite Bordeaux, ARNA laboratory, F-33000 Bordeaux, France, and INSERM, U869, ARNA laboratory, F-33000 Bordeaux, France

Supporting Information

ABSTRACT: The construction of new nanotools is presented here using the example of fluorescent semiconductor nanocrystals, quantum dots (QDs). In this study, the implementation of the new lipid oligonucleotide conjugate-functionalized quantum dots (LON-QDs) is realized in four steps: (i) the synthesis of the lipid oligonucleotide conjugates (LONs), (ii) the encapsulation of QDs by nucleolipids and LONs, (iii) the study of the duplex formation of LON-QDs with the complementary ON partners, and (iv) the cellular uptake of the LON-QD platform and hybridization with the target ONs (microRNA and miR-21).



INTRODUCTION

A fundamental objective in biology is to elucidate the role and the fate of biomolecules in living cells, which still requires new approaches, technologies, and tools. To address these bioimaging issues, nanocrystalline semiconductors, namely quantum dots (QDs), are promising nanosystems.[1−3] QDs, which are inorganic (CdSe, CdS, CdTe, etc.) nanomaterial (2−6 nm), possess remarkable optical, electronic, magnetic, and even chemical features.[4,5] Their properties have been investigated in various scientific domains, including biology[6−8] and biomedicine,[9] computing and memory,[10] electronics,[11] optoelectronic devices,[12] lighting and lasers,[13] and sensor applications.[14]

Despite the numerous functionalization strategies investigated so far, the surface coating of QDs with biomolecules remains a challenge in many cases.[15] Functionalized QDs have been widely constructed via ligand exchange with thiol- or histidine-bearing molecules and covalent linkages involving surrounding QD ligands (lipids[16] and copolymers).[17] Considering the functionalization of QDs with oligonucleotides, different approaches have been reported, including covalent coupling,[18,19] high-affinity ligand−receptor recognition (biotin/streptavidin),[18,20−22] and noncovalent interactions using mainly electrostatic adsorption.[23,24] Among the main drawbacks observed for the QDs functionalized via electrostatic interactions, one can mention the instability of the systems caused by the variation of pH and/or ionic strength, the relative weakness of the adsorption, and the limited number of copies of adsorbed oligonucleotides per QD.[23] Less common, although highly promising, the insertion of modified oligonucleotide via hydrophobic anchoring in a QD nanoplatform encapsulated with lipids could overcome these drawbacks.

Here we demonstrate that lipid oligonucleotide conjugates (LONs)[25] targeting microRNAs can be used to functionalize QDs. We show that the combination of the solubilization−functionalization strategy with optimized amphiphilic oligonucleotide functionalities and lipids is an efficient approach for providing oligonucleotide-based QDs with recognition and detection properties.

RESULTS AND DISCUSSION

New nanoplatforms based on QDs hold great promise for the development of biological labeling applications, intracellular sensors, deep-tissue and tumor imaging agents, and sensitizers for photodynamic therapy or drug delivery by virtue of their unique optical properties.[1] Nevertheless, biological exploitation of QDs involves several steps of functionalization. Because of the fluorescent behavior of QDs,[4,5] several strategies mainly based on covalent linkers[18,19] or electrostatic adsorption[23,24] were developed. The first one requires surface chemistry that is not trivial; the second is highly dependent on pH, and a low rate of functionalization is encountered.[23,24] In this context, the anchoring of LON at the QD hydrophobic surface, a strategy very promising for functionalization in terms of robustness and ease of handling, has never been investigated. The implementation of our ON-based nanoplatform was realized by a procedure achieved in three steps. First, LONs were synthesized via two different approaches: 1,3-dipolar cycloaddition click and phosphoramidite reactions. In a second step, QDs possessing a native hydrophobic shell [trioctylphosphine

Received: March 28, 2013
Revised: July 2, 2013
Published: July 26, 2013

dx.doi.org/10.1021/bc400157z | Bioconjugate Chem. 2013, 24, 1345−1355