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DNA Aptamer Functionalized Nanomaterials for Intracellular Analysis, Cancer Cell Imaging and Drug Delivery

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1. Introduction

The advance in studying inter- and intra-cellular biochemical processes has made important contributions to our understanding of biology in the past several decades. Such fundamental advancement also has significant impact on cell imaging and drug delivery. Technologies such as fluorescent resonant energy transfer (FRET), single molecular imaging, and gene regulation have allowed unparalleled insights into cellular functions and mechanisms in drug delivery. An exciting development in this area is the combination of unique optical or magnetic properties of nanomaterials with high selectivity of DNA/RNA aptamers. Together these aptamer-functionalized nanomaterials have enabled novel analytical techniques that advance our understanding and treatment of disease, aging, and cancer [1–3]. This review highlights recent work on using DNA aptamer-nanomaterial hybrid platforms for the applications in cellular analysis, imaging and targeted drug delivery (Figure 1).

2. Overview of Nanomaterials and Aptamers

2.1 Nanomaterials for Cellular Applications

Metal nanoparticles have been used widely for the studies of cellular uptake and analysis due to their simple synthesis, easy modifications, and biocompatibility. For applications in cellular analysis, gold and silver nanoparticles have been especially common owing to their excellent plasmonic properties, which have enabled significant advances in localized surface plasmon resonance (LSPR) for applications such as surface enhanced Raman spectroscopy [4]. When in close proximity to the surface of a plasmonic metal, the Raman signal can achieve 10^{14} enhancements, due to electromagnetic enhancements from plasmonic “hot spots”. Nanoparticles [5], nanoshells [6], nanoflowers [7], nanorods [8], and many other nanostructures [9] have all been recently been explored for their plasmonic properties in cell imaging, uptake mechanisms, and detection of various analytes [10]. The reader is directed to other recent reviews that focus on SERS/plasmonic applications of nanoparticles for cellular analysis [11*].

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Other types of nanomaterials such as silica nanoparticles, quantum dots (QDs), and carbon based nanomaterials have also been applied in cellular applications [12–14]. Nanosized silica is widely known for excellent compatibility and has been used extensively in cellular studies [15]. More recently, mesoporous structures dramatically increased the surface area of silica nanoparticles and enabled high loading of cargo for cellular imaging and delivery [16]. Another material of interests is semiconducting QDs. Because of their fluorescence stability, broad absorption and narrow emission band, they are uniquely suited for high resolution [17] and multiplex imaging of cells [18*]. Carbon based nanomaterials such as carbon nanotubes, fullerenes, and most recently graphene and graphene oxide are also promising nanomaterials for cellular applications, including the use of stabilized graphene oxide in cellular imaging and drug delivery [19–21].

2.2 Aptamers

The above nanomaterials are promising in cellular applications as efficient reporters and carriers. However, the applications of non-functionalized nanomaterials have remained scarce due to limited functionality, lack of target specificity, and low intracellular stability. Aptamers are short single stranded DNA or RNA sequences that are selected and refined for highly specific binding to a target of interest by in vitro selection or systematic evolution of ligands by exponential enrichment (SELEX) [22–24]. In the past two decades, the technology has evolved quickly and has since found particular interest in environmental sensing, cancer imaging/diagnosis, and disease therapy [25–32]. Due to its automated synthesis, high stability, and well established selection process, DNA aptamers have become one of the most promising techniques for introducing target specificity to nanomaterials for intracellular imaging, diagnosis, and therapy [33**,34]. This review highlights recent work on using aptamer-nanomaterial hybrid platforms for the applications in cellular analysis, imaging and targeted drug delivery.

3. Aptamer-Modified Nanomaterials for Analysis of intracellular components and metabolites

Nanomaterials with good cell uptake, such as gold and carbon-based nanocomposites, can be modified by aptamers for the analysis of intracellular components and metabolites.

3.1 AuNP-aptamer Hybrid

Gold nanoparticles (AuNPs) are the most characterized nanomaterials for intracellular analysis. AuNPs exhibit high stability, good biocompatibility, excellent optical and electronic properties, and diverse surface functionalizations. In addition to cellular applications shown below, aptamer-modified AuNPs have also been extensively applied for detecting metal ion and biomolecular targets [35,36].

Mirkin and co-workers developed an aptamer-AuNP hybrid with fluorescent reporters, termed as “nanoflare”, which can quantitatively detect analytes inside living cells [37**]. The aptamer modified nanoflares are highly stable, readily taken by cells, and were used to detect intracellular ATP concentrations at 1~2 mM (Figure 2) [38]. Similar methodology have been applied to detect gene expression, message RNA in living cells by using antisense DNA strand or molecular beacon constructs [39,40].

3.2 SWCNTs and Graphene

Carbon-based materials, such as single-walled carbon nanotubes (SWCNTs) and graphene have attracted considerable interest due to their high surface area, mechanical strength, high electrical conductivity, and photoluminescence. These unique properties offer SWCNTs and graphene good opportunities for biosensing and bioimaging applications. For example, DNA

strands can be adsorbed onto SWCNT/graphene through strong π -stacking interactions and released through hybridization or structure switching [41]. By taking advantage of the high quenching efficiency of carbon structures, Cha et al. was able to develop an intracellular insulin sensor with wide detection range from 10 μ M to 2 mM [42].

Graphene derivatives featuring excellent optical and electrical properties recently emerged as another promising carbon-based nanomaterial for in situ analysis of small molecules in living cells. For example, Wang et al. reported the usage of graphene oxide nanosheet as quenchers for aptamer-based intracellular APT detection [43**]. They synthesized a nanocomplex with carboxyfluorescein (FAM) modified ATP aptamer strands absorbed on graphene oxide nanosheets (GO-nS) resulting in significant quenching of fluorescent intensity. They further demonstrated the effective uptake of aptamer-FAM/GO-nS nanocomplex into JB6 cells and fluorescence recovery after adding ATP molecules (Figure 3). They reported in situ intracellular ATP detection with a detection limit as low as 10 μ M.

4. Aptamer-Functionalized Nanomaterials for Cell-Specific Imaging and Drug Delivery

In addition to intracellular analysis, another exciting application of aptamer functionalized nanomaterials is toward cancer cell imaging and targeted drug delivery.

4.1 Cancer Cell Targeting and Imaging

Aptamers, as molecular probes with high specificity and selectivity, can readily distinguish between cancerous and healthy cells at molecular level. The combination of aptamers with nanomaterials as signal reporting groups therefore represents a powerful diagnostic tool for the detection of cancer and diseases in early stage.

Yin et al. reported a one-step method for the synthesis of DNA-aptamer templated fluorescent silver nanoclusters (AgNCs) [44]. The Sgc8c aptamer strands were immobilized onto AgNCs through cytosine-rich sequence, and the resulting Sgc8c-modified AgNCs showed specific targeting and fluorescent labeling capabilities to CCRF-CEM cancer cell over control cells. In addition to the fluorescence properties, the tunable LSPR properties of AgNPs were also utilized for cellular imaging. Chen et al. reported that the prion protein (PrP^c) aptamer modified AgNPs could be used as targeted contrast imaging agents for both dark-field light scattering and TEM imaging of SK-N-SH cells. They further observed that PrP^c-AgNPs could be internalized into plasma membrane, lysosome and endocytic structure through aptamer-mediated endocytosis [45].

Aptamer modified AgNPs were also used to specifically target and image the sub-compartments of live cells. In 2011, Sun and co-workers reported that by artificially adding tandem cytokines Sgc8c aptamer, they were able to generate an Ag cluster that targeted the nucleus of CCRP-CEM cells [46].

Kim and co-workers reported a cancer-specific multimodal imaging probe consisting of cobalt-ferrite nanoparticle protected by a silica shell and coated by fluorescent rhodamine. They demonstrated that the AS1411 aptamer-multimodal nanoparticle system not only enabled the targeted fluorescence imaging of nucleolin-expressing C6 cells, but also allowed radionuclide and MRI imaging *in vivo* and *in vitro* [47]. In addition, Colin et al. combined fluorophore-doped silica and silica-coated magnetic nanoparticles modified with highly selective aptamers to detect and extract CCRF-CEM targeted cells in a variety of mixtures [48**]. They also systematically studied the effect of nanoparticle size, conjugation chemistry, and aptamer sequences on the selectivity and sensitivity of the dual-particle assays.

Besides aptamer modified metal and silica nanoparticles, an extracellular supramolecular reticular DNA-QD sheath was reported by Zhang and co-worker in high-intensity fluorescence imaging [49]. At physiological temperature, the DNA-QD sheath readily recognized and bound to Ramos cells in a cell-specific manner, and was used to accurately quantify the Ramos cells within the range of 10 to 1000 cells. In addition, electrochemical sensors [50] and electrochemiluminescence methods [51**] have also been reported as detection methods for aptamer-QDs based cancer cell detection.

4.2 Cell-Specific Drug Delivery

Compared to conventional passive anticancer drug delivery system, targeted delivery attracts more attention and can be achieved by disease-specific recognition of tumor cells. Aptamer-functionalized nanoparticles have also been widely used for cancer cell specific drug delivery.

In 2011, Gao et al. reported the application of thrombin aptamer-functionalized TBA-tethered lipid-coated mesoporous silica nanoparticles (TBA-lipid-MSN) and demonstrated effective recognition of thrombin and suppression of Hela cell growth by extracellularly disturbing PAR-1 receptor signaling. Moreover, the efficient delivery of anticancer drug Dtxl also contributed to the effective cytotoxicity in the cytoplasm [52].

In collaboration with Wong and Cheng groups, our group recently reported cell-specific drug delivery system based on aptamer modified liposomes. Liposomes encapsulated with anticancer drug cisplatin were conjugated with AS1411 DNA aptamers that specifically bound to nucleolin overexpressed on the cancer cell membrane. We demonstrated that the aptamer-liposomes-cisplatin composite could be delivered into the target MCF-7 cancer cells but not into LNCaP cells as control. Moreover, the release of cisplatin was successfully controlled by introducing a complementary DNA strand of the aptamer as an antidote [53**]. Another type of biological vesicle, micelle, was also reported for aptamer-mediated targeted drug delivery by Wu et al., and the TDO5 aptamer modified micelle was found to exhibit specificity to Ramos cells [54**].

Aptamer-modified polymer nanoparticle is also a promising delivery system. For example, Jiang et al. developed a polymer nanoparticle based drug delivery system by conjugating AS1411 aptamers targeting the cancer cells and endothelial cells in angiogenic blood vessels to the surface of PEG-PLGA nanoparticles. In the tested C6 glioma cells, aptamer-nucleolin specific binding resulted in the cellular association of nanoparticles and thereby enhanced the cytotoxicity of the paclitaxel (PTX) delivery. They suggested the promise of utilizing Ap-PTX-NP as therapeutic drug delivery platform for gliomas treatment [55].

Moreover, novel nanostructures have also been explored as potential targeted drug delivery systems. Huang and co-workers reported using 3D DNA Icosahedral as a carrier for doxorubicin. MUC 1 aptamers were conjugated to distinct five-point-star and six-point-star motifs through DNA hybridization before the formation of DNA polyhedra. They demonstrated that aptamer-conjugated doxorubicin-intercalated DNA icosahedra showed a specific and efficient therapeutic effect for epithelial cancer cells [56**].

5. Perspective

The emerging demands for more in depth study of cellular mechanism and therapy has emphasized the importance of methodologies for cellular analysis and delivery. The recent development of nanotechnology has brought about many nanomaterials as signal reporters and delivery carriers that are more efficient than classic materials for cellular applications. Along with the advantages of nanomaterials, the functionalization of nucleic acid aptamers

as recognizing and targeting molecules onto these nanomaterials has successfully realized highly selective and efficient cellular analysis, imaging and targeted delivery. Within the past two years, a number of works shown above have revealed the promise of aptamer-functionalized nanomaterials in cellular analysis and delivery. These nanoconjugates will continuously play more and more important roles in cellular and many other applications.

Future exploration of other new nanomaterials with better cellular compatibility, optical property, and delivery efficiency is anticipated to advance this research field. Silica-based nanoparticles, quantum dots and mesoporous nanomaterials have been found to exhibit excellent biocompatibility, optical property and drug load, respectively. The combination of these materials into hybrid nanomaterials can yield ideal nanocomposites with all the desired properties. In addition, nanomaterials with multiple functions and controlled spatial distributions, such as Janus nanoparticles, can further expand their functions and cooperativity for potential cellular application [57,58].

On the other hand, the selection and evolution of new nucleic acid aptamers for more cellular targets are the basis to extend the applications of aptamer-functionalized nanomaterials in cellular analysis and delivery for studying more types of cells and their cellular processes. Beside in vitro selection from random nucleic acid pools, the introduction of unnatural nucleotides into the nucleic acid pools to improve the diversity of functional groups may further enhance the chance to obtain aptamers for more cellular targets [59].

Finally, to make even bigger impact on human health, the advance of these studies in cells needs to be translated into analysis, imaging and targeted delivery in animals or even human clinical trials. To achieve the goals, even more selective aptamer, more effective nanomaterials and better combination of the two are required and the safety of these nanomaterials in vivo needs to be carefully evaluated.

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Highlights

- DNA Aptamer-nanomaterials combine unique optical or magnetic properties of nanomaterials with high selectivity of aptamers.
- Together they have enabled novel analytical techniques that advance our understanding of health and treatment of diseases.
- Recent work on using DNA aptamer-nanomaterials for analysis of intracellular components and metabolites are reviewed.
- Their recent applications in targeting and imaging of cancer cells and in cell-specific drug delivery are also highlighted.

Figure 1.
A general illustration of the three cellular analysis and therapeutic applications of aptamer-functionalized nanoparticles.

Figure 2.

(a). Schematic view of the basic design and stimuli-responsive mechanism of aptamer nano-flare. (b). Fluorescence microscopy images of HeLa cells incubated with aptamer nano-flares and control particles. (c). Flow cytometry results of fluorescent intensity (Cy5) of cells treated with aptamer nano-flares and control particles. Adapted from [38].

Figure 3.

(a). Schematic illustration of in situ molecular probing in living cells by using aptamer/GO-nS nanocomplex. (b). JB6 cells specific uptake of ATP aptamer-FAM/GO-nS samples (b) and random DNA-FAM/GO-nS samples (c). Images were taken under differential interference contrast and wide-field fluorescence. Adapted from [43**].

Figure 4.

(a). Schematic view of self-assembly of aptamer modified, doxorubicin-loaded DNA icosahedra (Doxo@Apt-DNA-icosa). (b). Proposed MUC1 aptamer-mediated endocytosis mechanism of Doxo@Apt-DNA-icosa. Adapted from [56**].