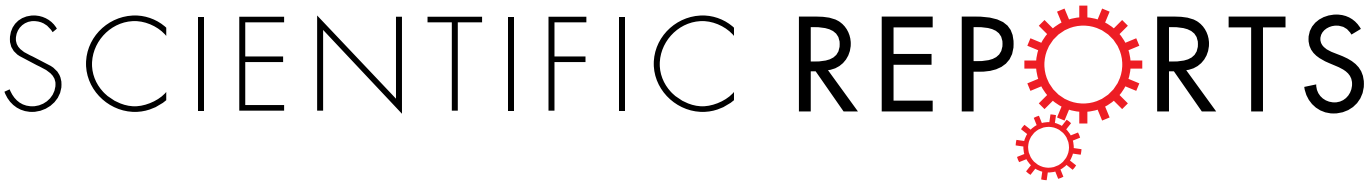

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A Targeted DNAzyme-Nanocomposite Probe Equipped with Built-in Zn^{2+} Arsenal for Combined Treatment of Gene Regulation and Drug Delivery

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As catalytic nucleic acids, DNAzymes have been extensively used in the design of sensing platforms. However, their potentials as intelligent drug carriers for responsive drug release in gene therapy and chemotherapy were rarely explored. Herein, we report a dual-functional probe composed of gold nanoparticles (GNPs), catalytic Zn^{2+}-dependent DNAzyme, anticancer drug doxorubicin (Dox), targeted AS1411 aptamer and acid-decomposable ZnO quantum dots (ZnO QDs) to achieve intracellular gene regulation and drug delivery in a controlled manner. By means of aptamer-guided targeting and receptor-mediated endocytosis, the probes were specifically internalized into the HeLa cells and trapped in the acidic endo-/lysosomes, where the ZnO QDs as the built-in Zn^{2+} arsenal were promptly dissolved to offer Zn^{2+}, leading to the activation of DNAzyme to cleave the substrate strands, and subsequent drug release. Meanwhile, as designed, one part of the cleaved substrate, hybridized with the overexpressed miR-21 in the target cells, thereby declining its intracellular level. Taken together, the down-regulation of miR-21 has a synergistic effect with Dox to efficiently eradicate the cancer cells. Thus, the favorable biocompatibility, cancer cell specificity and combined treatment make the probe promising for therapy of multidrug-resistant cancer and *in vivo* application.

MicroRNAs (miRNAs) are a category of small noncoding RNA molecules of ~22 nucleotides that regulate gene expression in a wide range of physiological processes including cellular development[1], differentiation[2], proliferation[3], apoptosis[4], hematopoiesis[5], etc. In recent years, accumulated evidence has showed that aberrant expression of miRNAs is closely correlated with the initiation, development, and metastasis of various cancers, where they can function as tumor suppressors or oncogenes, highlighting their significance in human cancer[6]. miR-21, an oncogenic miRNA, has been found overexpressed in various cancers[7,8]. The inhibition of miR-21 expression by delivering antisense sequence can down-regulate antiapoptotic genes such as Bcl-2, resulting in the decrease of cell proliferation and increase of apoptosis[9]. Thus, chemical tools developed for either detection or regulation of endogenous miR-21 may provide great potential for cancer therapy.

Deoxyribozymes, denoted as DNAzymes, are a class of artificial single-stranded DNA molecules with catalytic activities[10–12], whose functions are performed by recruiting cofactors such as metal ions or organic molecules. Particularly, many metal-dependent DNAzymes have high affinities for specific metal ions. In the presence of corresponding metal ions, the specific DNAzymes fold into compact structures to activate catalytic function of cleavage[13], making themselves widely applicable in the detection of metal ions such as Pb^{2+} [14–17], Cu^{2+} [18,19], Zn^{2+} [20] and UO_2^{2+} [21,22]. Compared with RNA- or protein-based enzymes, DNAzymes are more stable against nuclease degradation and less susceptible to hydrolysis, which endow them with unique applicability in the fields

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