

Chapter 14

The Application of Nucleic Acid Amplification Strategies in Theranostics



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Abstract Targeting nanoparticles equipped with diagnosis “tools” to malignant cells or tissues for optimal therapy is a popular concept of theranostics. As one of the most reliable and sensitive diagnosis “tools,” nucleic acid detection is of growing practical interest with respect to molecular diagnostics of cancer and other genetic diseases. Particularly, PCR-based and other nucleic acid amplification strategies are most widely used in theranostics. This chapter aims at systematization and critical summarization of the applications of DNA- or RNA-targeted nucleic acid amplification strategies in theranostics.

14.1 Introduction

Cancer is the first leading cause of disease-associated death in China (Chen et al. 2016) and the second leading cause of death in the USA (Olaku, Taylor 2017) in decades. Current treatment modalities for tumors or cancers mainly focus on surgery, radiotherapy, chemotherapy, and immunotherapy, among which medicine treatment is still the most widely used therapeutic way for various types of tumors or cancers (Xiao et al. 2017). Nevertheless, typical anticancer therapies, such as radiotherapy and chemotherapy, cannot always work for the patients, even they helpful, they may not cure the patients completely (Weeks et al. 2012). Besides, radiotherapy and chemotherapy are also well known as their adverse side effects due to the treatment cannot distinguish the similarity between cancerous cells and healthy human cells (Emmenegger and Kerbel 2010; Karimi et al. 2016; Abou-Elkacem et al. 2016; Fan et al. 2016; Park et al. 2016). What’s more, drug resistance, insufficient curative effect, and tumor relapse during therapeutic process are still the huge challenges when patients treated by conventional cytotoxic drugs or molecularly targeted therapeutics (Al-Lazikani et al. 2012; Yano et al. 2012), and the efficacy of typical anticancer therapies is usually limited in clinic.

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The ability to kill diseased cancerous cells while causing less harm to the normal cells is of great significance to reduce adverse side effects during therapeutic process especially in radiotherapy and chemotherapy. How to distinguish healthy cells and cancerous cells, how to achieve tumor cells specific targeting, are the vital factors in a cancer cure process. Particularly, a typical adopted strategy is to design a cancerous cells target-specific drug delivery system (DDS) that can transport an effective dosage of anticancer drugs to targeted cells, cancerous tissues or diseased area of the body (Nicolas et al. 2013; Ge and Liu 2013; Chen et al. 2014; Frandsen and Ghandehari 2012), and sustained release drug over a period of time in a controlled manner to increase survival of drugs (Bertrand and Leroux 2012).

Generally speaking, theranostics is a process combined diagnosis and therapy, popularly in cancer. Cancerous cells target-specific DDS accelerates the advancement of therapy; at the same time, more effective and reliable early tumor detection and diagnosing methods have also been put forward result from the clinical needs, which are also significant for cancer therapy in theranostics. The technology of nucleic acid amplification strategy opens up avenues for meeting this clinical diagnosis requirement in theranostics. Hybridization chain reaction (HCR), rolling-circle amplification (RCA), the strand displacement reaction (SDR), loop-mediated amplification (LAMP), and target-recycling amplification with endonuclease, exonuclease, and polymerase, and these nucleic acid amplification strategies have already become powerful tools for early diagnosis of cancer, due to their high sensitivity, excellent stability, and subtly designability, which demonstrate good prospects to meet clinical requirements, and assist DDS employed in theranostics.

14.2 Theranostics

“Theranostics,” generally, points out emphatically the inseparability of diagnosis and therapy, the pillars of medicine (Baum and Kulkarni 2012). It means that “we know which sites require treatment and confirm that those sites have been treated.” The term “theranostics” was first used by John Funkhouser at the beginning of the 1990s, while the concept of personalized medicine appeared at the same time (Choudhury and Gupta 2018). Theranostics provides a clinical transition from conventional disease trial and wrong medicine treatment to much more personalized and precision medicine time. Theranostics should have the ability to cure patients with more accurate diagnosis and more specific therapy plan.

Diagnostic and therapeutic agents can be formulated as a single theranostic platform and then can be attached to a biological ligand for cancerous cells or area targeting (Muthu et al. 2014). The use of aptamers as targeting ligands which conjugated to DDS nanoparticles as nanotheranostic system has been substantially studied (Vandghanooni et al. 2018). For example, Mosafer et al. (2017) loaded SPIONs and doxorubicin simultaneously into poly (lactic-co-glycolic acid) (PLGA) nanoparticles and then modified PLGA nanoparticles with AS1411 aptamer for tumor cell-targeted theranostic purposes. It turned out that the AS1411 aptamer-conjugated

PLGA nanoparticles enhanced its cellular uptake and cytotoxicity effect of doxorubicin in murine C26 cells.

Nanotechnology has been proved to be a promising platform for theranostic in recent advances. Nanoparticle-based contrast drug agents in theranostic offer improved capabilities for specific cancer targeting, high-resolution imaging, and prolonged circulation times in comparison with the custom used methods (Hahn et al. 2011). Even though theranostic has drawn world widely particular interest in cancer therapy since it shows significantly more advantages compared to typical radiotherapy and chemotherapy, its application also raises critical questions simultaneously. For example, is the optimal nanoparticles used in DDS for patients' therapy also the optimal nanoparticles used for cancer diagnostics (Dreifuss et al. 2015)?

14.3 DDS Applied in Theranostics

Nanotechnology has already involved in all fields of biochemical and chemical science and technology, according to its high financial investment and rapid development (Heath 2015). Simultaneously, nanotechnology breaks a new ground for drug delivery, especially for tumor-targeted drug delivery system (DDS). In 2004, National Cancer Institute (NCI) launched the NCI Alliance for Nanotechnology in Cancer to exploit the nanotechnology to fight cancer (Hull et al. 2014; Farrell et al. 2010).

Targeted DDS, as its name means, is to deliver the loaded cargos or treatment drugs to the interested site while reducing or avoiding the cargos or treatment drugs distribution to normal tissue or cells (Bae and Park 2011). For decades, several series of nanocarriers applied in DDS have been used for anticancer drugs delivery, including liposomes (Felfoul et al. 2016; Sharma and Sharma 1997; Gregoriadis and Florence 1993; Drummond et al. 2000), organic nanoparticles (Horcajada et al. 2010a, b), inorganic nanoparticles (Rotello 2008; Liong et al. 2008; Vivero-Escoto et al. 2010; Zhi et al. 2006), hybrid nanoparticles (Hrkach et al. 2012), polymeric micelles (Matsumura and Kataoka 2009; Norased et al. 2006, Bae et al. 2003), polymer-drug conjugates (Zhu et al. 2013), nanogels (Du et al. 2010; Jung-Kwon et al. 2008), as shown in Fig. 14.1.

In addition to solubilizing poorly soluble drugs and protecting drugs from cellular degradation, the drug-loaded nanocarriers in DDS could prolong the circulation time of released drugs and selectively deliver them to the targeted tumor tissue, tumor cells, or subcellular organelle (Shi et al. 2017). Besides, the released drugs from the nanocarriers can be controlled in a spatiotemporal manner, sustained release drug over a period of time, achieving their pharmacological activities only at the targeted site (Dai et al. 2012). FDA has already approved several nanotechnology-based anti-tumor preparations for decades, such as Doxil® (PEGylated liposomal doxorubicin (DOX)) and Abraxane® (paclitaxel (PTX) loaded albumin nanoparticles) (Hare et al. 2017).

Even though targeting nanocarriers to malignant tissues, tumor cells, or subcellular organelle to improve diagnosis and therapy is a popular concept, the literature

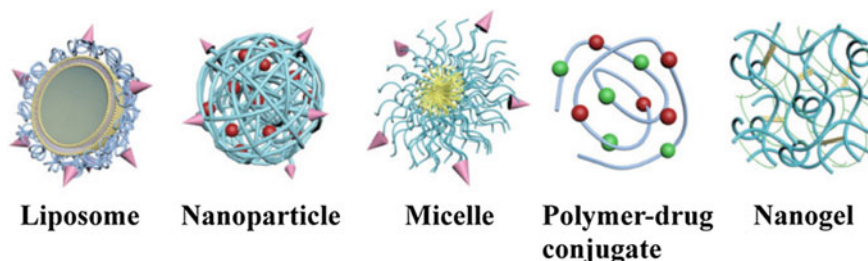


Fig. 14.1 Illustration of several representative nanomedicines for cancer therapy, including liposome, nanoparticle, polymer micelle, polymer–drug conjugate, and nanogel. Reprinted from Dai et al. (2017). Copyright 2017, with permission from Elsevier

survey during the past 10 years turned out that only 0.7% (median) of the administered nanocarriers is delivered to the targeted solid tumor. This has a negative effect on nanotechnology for human clinic use with respect to manufacturing, financial investment, toxicity, and imaging and therapeutic efficacy (Table 14.1) (Wilhelm et al. 2016).

14.4 Nucleic Acid Amplification Strategies Applied in Theranostics

For a particular disease, such as cancer, there is a growing significant interest in theranostic approaches that permit concurrent diagnosis and treatment with therapeutic development. With the increased insights into delivery kinetics and biological response, the theranostic may help open the field of medicine toward to an era of more effective and precise treatment (Peer et al. 2007; Conway et al. 2014). Unfortunately, probing and detection low-abundance cancer biomarker and transporting a high-load drug nanocarrier to specifically targeted tumor cells and, particularly, their combination still are a major challenge nowadays. Currently, theranostic approaches for probing and detection in cancer typically rely on targeting tumor-associated biomarkers with aptamer, antibodies or other ligands, which allows an accumulation of signal reporters or drug payloads in tumors and thus renders contrast imaging and selective treatment (Andersen et al. 2009). However, the lack of intelligent designs for probing and detection in diagnosis step in theranostic leads to limited imaging sensitivity and increased background interference (Bhuniya et al. 2014). The pursuit of activatable probe and detection designs represents a vital effort in cancer theranostics.

Table 14.1 Delivery efficiency and the number of data sets. Reprinted from Wilhelm et al. (2016), with kind permission from Springer Science + Business Media

Category	Delivery efficiency [%ID]*	Number of data sets
All data sets	0.7	232
<i>Year</i>		
2005	1.4	8
2006	0.7	8
2007	1.0	24
2008	0.3	8
2009	0.9	11
2010	0.8	14
2011	0.7	27
2012	0.7	14
2013	0.5	35
2014	0.8	38
2015	0.5	45
<i>Material</i>		
Inorganic	0.8	86
Organic	0.6	137
<i>Inorganic material</i>		
Gold	1.0	45
Iron oxide	0.6	8
Silica	0.4	13
Quantum dots	0.9	5
Other	0.6	14
<i>Organic material</i>		
Dendrimers	1.4	7
Liposomes	0.5	27
Polymeric	0.6	62
Hydrogels	0.5	18
Other	0.9	23
<i>Targeting strategy</i>		
Passive	0.6	175
Active	0.9	57

14.4.1 Theranostics Based on DNA Rolling-Circle Amplification

Rolling-circle amplification (RCA) is an isothermal nucleic acid amplification technique, and a variety of biomarkers such as genes, microRNAs, proteins with ultra-low cellular abundance have been successfully detected using developed RCA-based probes. In recent decades, various approaches have been achieved to improve the RCA technique, and it has become an attractive detection tool for biomedical applications. In this section, I will summarize the RCA-DDS combined cancer clinical applications, making an outlook on the trends of the related research fields in the future (Wang et al. 2015a; Chen et al. 2015).

In most assays based on RCA, the quantification of the target is achieved through the RCA product quantification. The RCA products not only can turn into nanostructures by self-assembly, but also can form solubilized threads. Zhang's group synthesized MNP/DNA-SP as nanocarrier and doxorubicin embedded in MNP/DNA-SP as therapy drug to constructed a DDS (Guo et al. 2017b). By modification of different functional elements in the surface of MNP/DNA-SP, such as aptamers and disulfide linkages, the synthesized MNP/DNA-SP-DOX can be used for targeted GSH or CEM cells detection and doxorubicin delivery, resulting in the relief of cell apoptosis in target GSH or CEM cells, as shown in Fig. 14.2. For those that have not yet been screened by their aptamers specifically, functional element (e.g., FA) modified poly T tailed sequences were taken to MNP/DNA-SP by terminal transferase-mediated chain elongation. Different functional elements as ligands for different targets can be incorporated into MNP/DNA-SP, which can achieve versatile targeted and detection applications. The advantages of MNP/DNA-SP-DOX cargo displayed high selectivity, superior biocompatibility, and convenient drug delivery. The potent antitumor efficacy of DOX delivered by the biocompatible MNP/DNA-SP nanocarrier was also tested in a model of xenografted tumors of mice. Consequently, the result is a combination of traceable targeted detection and drug delivery that serves as a multi-functional MNP/DNA-SP, which will provide a novel theranostic platform for cancer targets detection and may also approve other clinical applications.

Considering the requirement for combination of cancer clinical diagnosis and therapy, Guo and her co-workers developed a magnetic nanoparticle (MNP)-based cellular DDS for DOX cellular load and release to kill cancerous cells (Guo et al. 2017a). As shown in Fig. 14.3, MNPs surface was modified with RNA nanoflowers (RNA NF) through biotin-avidin conjugation (MNP/RNA NF), and RNA NF was produced based on rolling-circle transcription (RCT). To realize the specific targeting cancerous cell delivery, they employed folic acid (FA) as active targeting ligands to functionalize MNP/RNA NF and constructed FA/MNP/RNA NF nanostructure. While for specific binding, folate receptors (FRs) is a wise choice for specific binding of FA, which is overexpressed on the cancer cell membrane, while low expressed in the normal cell. The anticancer drug DOX as well as the photosensitizer TMPyP4, which could generate reactive oxygen species (ROS) with 650 nm light, was both loaded into this FA/MNP/RNA NF nanocarrier. The result showed that

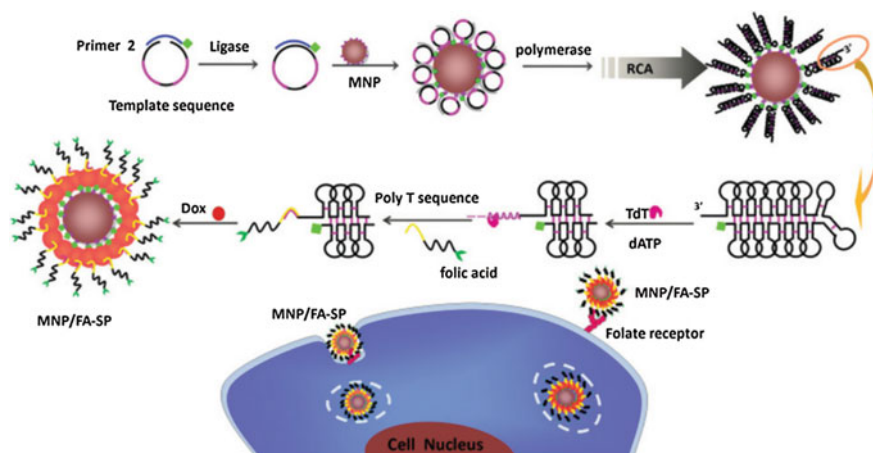


Fig. 14.2 Schematic diagram of folic acid decorated MNP/DNA-SP for cellular targeted drug delivery Reproduced from Guo et al. (2017a, b) by permission of the Royal Society of Chemistry

FA/MNP/RNA NF nanocarrier has better treatment efficacy than DOX traditional delivery way. Additionally, FA/MNP/RNA NF could also be used as a probe for HeLa cells' detection, and it can detect as low as 50 cells (Guo et al. 2017b). Thus, the nucleic acid amplification technique assisted by MNPs holds great promise for potential applications in cancer diagnostics and therapeutics.

14.4.2 *Theranostics Based on Hybridization Chain Reaction*

Hybridization chain reaction (HCR), in which stable DNA monomers assemble only upon exposure to a target DNA fragment (Dirks and Pierce 2004). Generally speaking, two stable DNA hairpins' species coexist in reaction solution and then introduce initiator strands to trigger a cascade of hybridization processes that yields nicked double helices analogous to alternating copolymers. By coupling HCR to aptamer triggers, amplification of more diverse recognition reactions can be achieved. In HCR, this functionality allows DNA to act as an amplifying transducer for biosensing applications.

Based on the feature and function of the telomerase primer and its extension products (Qian et al. 2013, 2014), Zhang and her co-workers proposed a new strategy for synthesis a novel nuclear-shell biopolymers initiated by telomere elongation and can be used for telomerase activity detection and drug delivery to cancer cells (Zhang et al. 2017). As shown in Fig. 14.4, telomerase can elongate the telomere primers, which resulting in inner chain substitution followed by the release of RCA primers and loaded drug. A core nanoball, an outer shell of RCA, biopolymers labeled with fluorescence probes constituted the nuclear-shell self-assembly body. After equipped

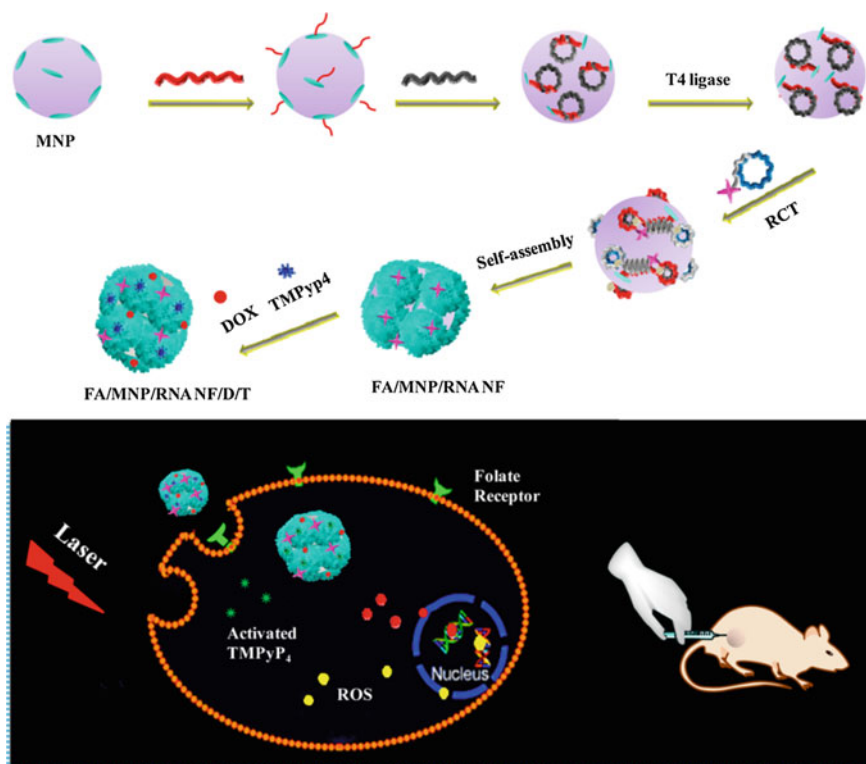


Fig. 14.3 Schematic diagram of magnetic nanoparticle-based co-delivery system Reprinted with the permission from Guo et al. (2017a, b). Copyright 2017 American Chemical Society

this platform with functionalized silica-nanoflowers (FSNFs), it was supported to detect and monitor telomerase activity and to achieve drug delivery to cancer cells. The results showed that the nuclear-shell self-assembly body, which was the product of RCA, displayed high sensitivity and activity for monitoring cellular telomerase, and efficient signal amplification effect. Consequently, as RCA product, the nuclear-shell biopolymer can efficiently deliver drugs to targeted cancer cells, which reduce the undesired death of healthy cells, might prove a new way for diagnosis–treatment processes in theranostics.

By applying a structure-switching aptamer-triggered HCR on cell surface, Chu's group developed a novel activatable theranostic approach. It is the first time that achieves real-time activation and amplification for fluorescence imaging and targeting therapy use an aptamer platform (Wang et al. 2015b). The aptamer probe (AP) used in this system is designed to trigger HCR on binding to the target cell via structure switching, instead of initiating HCR in its free state, skillfully. The HCR not only amplifies fluorescence signals from a fluorescence-quenched probe (H1) for activatable tumor imaging but also accumulates high-load prodrugs from a drug-labeled

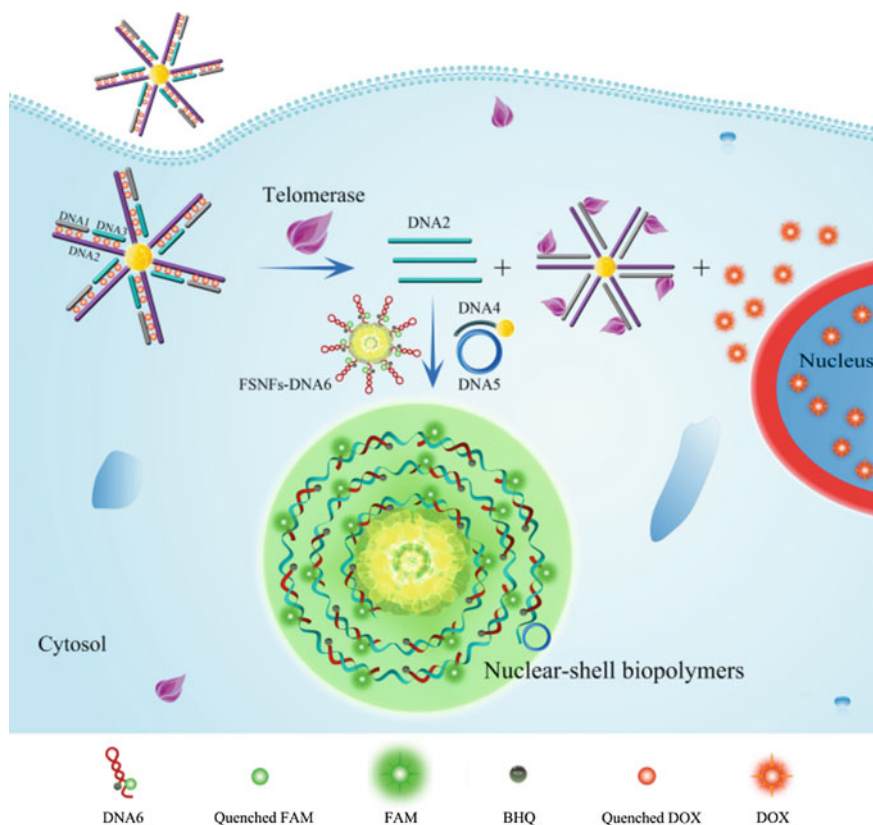


Fig. 14.4 Illustration of telomerase activity monitoring and drug delivery based on novel nuclear-shell biopolymers in individual cancer cells. Reprinted with the permission from Zhang et al. (2017). Copyright 2017 American Chemical Society

probe (H2) and induces its uptake and conversion into cisplatin in cells for selective tumor therapy. The *in vitro* result showed that this approach affords efficient signal amplification for fluorescence detection of target protein tyrosine kinase-7 (PTK7) with a detection limit of 1 pM. Live cell studies also reveal that this approach provides high-contrast fluorescence imaging and highly sensitive detection of tumor cells, while renders high-efficiency drug delivery into tumor cells via an endocytosis pathway. The results imply the potential of the HCR approach as a promising platform for early-stage disease diagnosis and precise cancer therapy (Fig. 14.5).

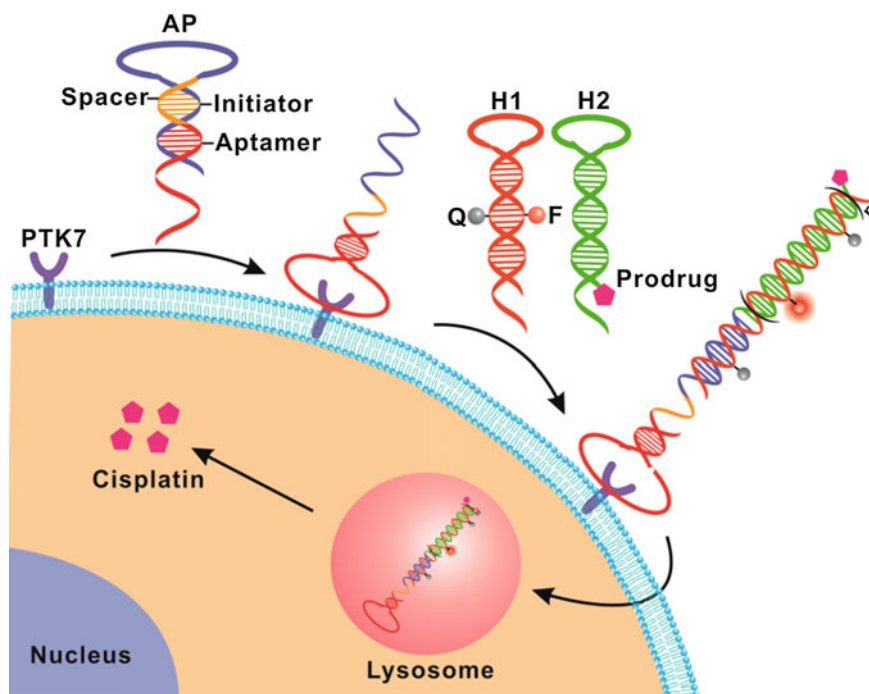


Fig. 14.5 Illustration of SATHCR for activatable theranostics. Reprinted with the permission from Wang et al. (2015a, b). Copyright 2015 American Chemical Society

14.4.3 Theranostics Based on Aptamer-Incorporated Nucleic Acid Amplification

Definitely, in theranostics, it is essential to monitor the expression of low-abundance biomarkers and transport a high-load drug to target cancer cells (Srinivasarao et al. 2015). Aptamers are single RNA or DNA strand with unique intramolecular conformations for selective binding to various targets. Aptamer-ligand recognition depends on the precise stacking of flat moieties, specific hydrogen bonding, and molecular shape complementarity (Bock et al. 1992; Jayasena 1999; Hermann and Patel 2000). Aptamer possesses dominant advantages over antibodies in terms of size, synthetic accessibility, and chemical modification. Therefore, aptamers are under worldwide development as a potential diagnostic or therapeutic tool in theranostics (Table 14.2) (Keefe et al. 2010).

In theranostics, the applied aptamers are functionalized with therapeutic agents or imaging probes (Wang et al. 2014; Kruspe and Hahn 2014). How to discriminate different types of cancer cells still remains challenging in the detection step due to the subtle differences in cancer cell expression of membrane receptors. Zhang's group developed a multicolor cell imaging method for distinguishing different types

Table 14.2 Aptamers to targets of therapeutic interest. Reprinted from Keefe et al. (2010), with kind permission from Springer Science + Business Media

Target (alternative name)	K_d (nM)	Therapeutic applications	Refs
α -thrombin	25	Prevent thrombosis	9
HIV-1 reverse transcriptase	1	Inhibit viral replication	134
HIV-1 Rev	<1	Inhibit viral replication	135
Fibroblast growth factor 2, basic	0.35	Prevent angiogenesis	136
Respiratory syncytial virus	40	Prevent infection	137
HIV-1 integrase	10	Inhibit viral replication	138
Vascular endothelial growth factor	0.1	Prevent neovascularization	139
Platelet-derived growth factor	0.1	Prevent tumor development	83
Immunoglobulin E	10	Prevent allergies	140
L-Selectin	3	Modulate inflammation	141
D.Adenosine	1100	Unknown	39
Acetylcholine-specific auto-antibodies	60	Treat myasthenia gravis	142
Interferon- γ	68	Modulate inflammation and immune response	143
Keratinocyte growth factor	0.0002	Treat epithelial hyperproliferative disease	144
Neutrophil elastase	n/o	Modulate inflammation	145
P-selectin	0.04	Inhibit viral adhesion	146
Acetylcholine receptor	2	Control neurotransmission	147
Phospholipase A ₂	118	Treat ARDS, septic shock	148
Protein tyrosine phosphatase	18	Inhibit oncogenesis, viral regulation	149
Activated protein C	110	Prevent thrombosis	150
CD4	0.5	Modulate immune response	151
Nuclear factor- κ B	1	Treat chronic inflammatory disease	152
Lymphocyte function-associated antigen 1	500	Prevent tumor development, modulate inflammation	153
Cytohesin 1	5	Modulate cytoskeletal reorganization	154
α v β 3 integrin	2	Prevent tumor development	155, 156

of cancer cells with fluorophore-tagged aptamers (Fig. 14.6) (Wang et al. 2014). Aptamer sequence and aptamer-labeled dyes affect the recognition process between aptamers and cancer cells. For different cancer cell lines, even though they own the same biomarkers, when interact the fluorophore-tagged aptamers with different cancer cell lines in different degree, the result turned out that there is a distinct color to discriminate different types of cancer cells at single cell level. Based on cross-reactive ability of the fluorophore-tagged aptamers, distinguish the cancer cells from

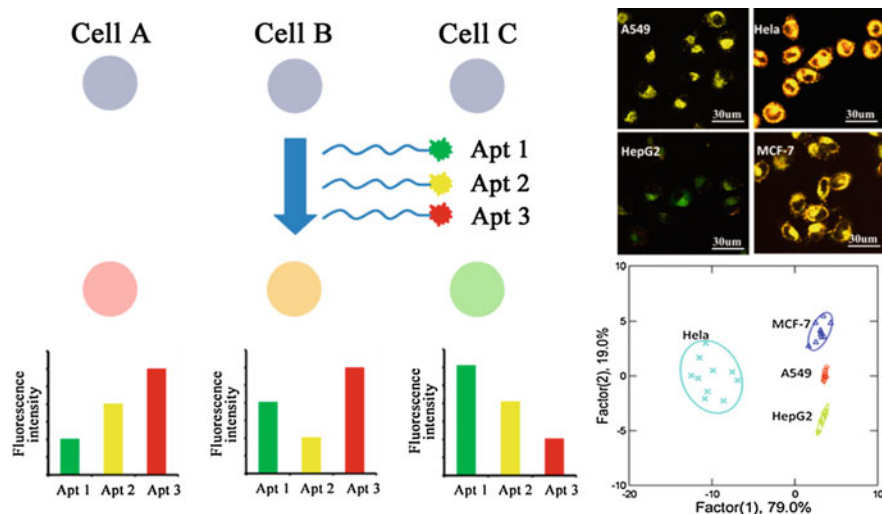


Fig. 14.6 Schematic presentation of the multicolor imaging for single cell typing with fluorophore-tagged aptamers. Reprinted with the permission from Wang et al. (2014). Copyright 2014 American Chemical Society

large quantities of normal cells quickly, and identify different types of the cancer cells are achieved, simultaneously. These fluorophore-tagged aptamers have a promising application for cancer diagnostic and therapy in the future.

As one of the class of therapeutic nucleoside and nucleobase analogues drugs, 5-fluorouracil (5-FU) has been used in cancer therapy and in the treatment of various diseases for decades (Longley et al. 2003). Therefore, in DDS, nanoparticles, nanogels, and nanopolymers are mainly focus on 5-FU cellular delivery for cancer therapy (Burke et al. 2014). By applying a cell-specific cytotoxic aptamer, Sven's group found that it can be prepared in a one-step enzymatic reaction by incorporating multiple units of a nucleoside analogue directly into an aptamer that targets a cytokine receptor. In targeted cancer cells, the controlled cellular release of 5-FU is initiated by intracellular nucleolytic hydrolysis of the cell-specific cytotoxic aptamer (Kruspe and Hahn 2014). Cytotoxic nucleoside and nucleobase analogues, such as 5-fluoro-2'-deoxyuridine (5-FUdR), are advantageous drugs for receptor-mediated active targeting as they benefit from this intracellular turnover. As showed in Fig. 14.7, 5-FUdR becomes part of the aptamer molecule itself, replacing all the uridines in the original aptamer. The controlled release of the drug inside the target cells is mediated through naturally occurred degradation by lysosomal nucleases. The hydrolysis of the aptamer would yield 5-FUdR, which could escape the lysosome by active nucleoside transporters, which normally serve as recycling gateways for lysosomal degraded nucleic acids (Fig. 14.7).

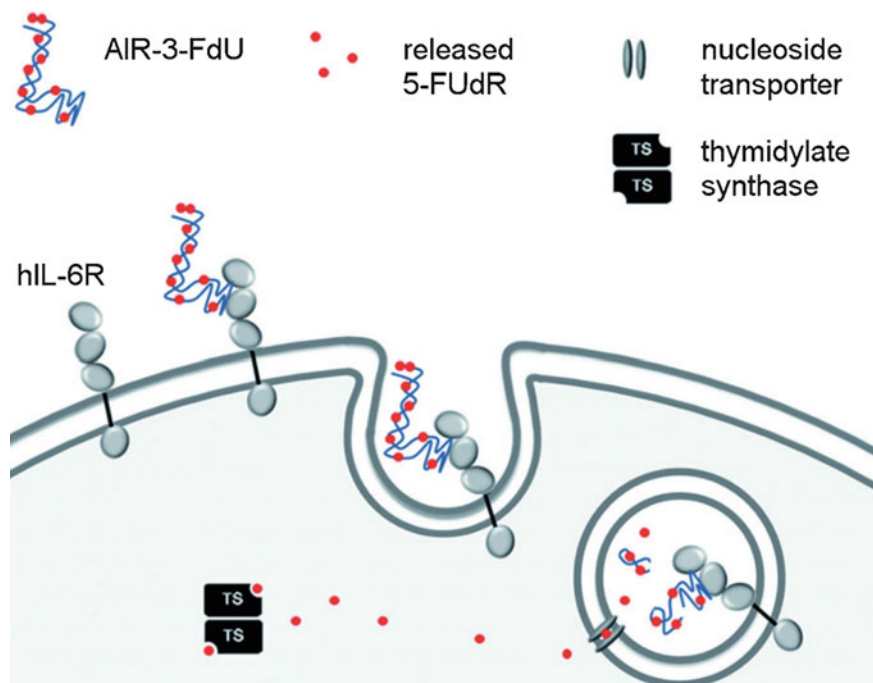


Fig. 14.7 Principle of drug delivery by AIR-3-FdU. The 5-FUdR-modified aptamer (AIR-3-FdU) binds to the human interleukin-6 receptor on the cell surface and is internalized. Reproduced from Kruspe and Hahn (2014) by permission of John Wiley & Sons Ltd.

14.5 Conclusion

Theranostics is a prosperous field of cancer which combines specific targeted cancer therapy with specific cancer biomarkers-targeted diagnosis. Theranostics uses specifically diagnostic ways in the human body, to acquire diagnostic images and also to deliver a therapeutic dose of medicine to the patient. It applies nanoscience to unite diagnostic and therapeutic applications to form a single agent, allowing for diagnosis, drug delivery, and treatment response monitoring. Besides, theranostics provides a transition from conventional medicine therapy to a contemporary personalized and precision medicine approach.

In theranostics, the nucleic acid amplification strategy-based diagnostic method recognize the particular biomarkers on a tumor, amplify the signal, and allow loaded therapy drug released to specifically targets on the tumor, rather than more broadly the disease and location it presents. This contemporary form of treatment moves away from the one-medicine-fits-all and trial-and-error medicine approach, to offering the right treatment, for the right patient, at the right time, with the right dose, providing a more targeted, accurate and efficient pharmacotherapy in the form of theranostics.

This chapter covers part of the reported applications, and many efforts have been made to develop diagnostic and therapeutic assays using nucleic acid amplification combined DDS in theranostics. In the past decade, DNA- or RNA-targeted nucleic acid amplification has been well developed to help in the detection and quantification of cancer biomarkers and cells in patient-derived blood and tissue samples as well as the patient's body. While tumor is a heterogeneous tissue consisting of different types of cancer or cancer-associated cells, it may vary between different patients or even between different cancer stages in an individual patient. Therefore, currently, the discovery of new and effective diagnostic and prognostic DDS cargoes seems necessary in theranostics.

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