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Aptamers: A Promising Tool for Cancer Imaging, Diagnosis, and Therapy

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ABSTRACT

Aptamers are a group of molecules, which can specifically bind, track, and inhibit target molecules, comprising DNA aptamers, RNA aptamers, and peptide aptamers. So far, there are much progress about developing novel aptamers and their expansile applications. This prospect systematically introduces the composition and technological evolution of aptamers, and then focuses on the application of aptamers in cancer diagnosis, imaging, and therapy. Following this, we discuss the potential to harness aptamers in discovering the biomarker of stem cells, which is favorable for us to study the normal developmental or abnormal pathological process of tissue and to deliver drugs into target cells or tissues in the future. J. Cell. Biochem. 114: 250–255, 2013. © 2012 Wiley Periodicals, Inc.

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Aptamers are composed of DNA aptamers, RNA aptamers, and peptide aptamers. They can specifically bind to target molecules, such as ions, DNA, RNA, proteins, glucides, even the whole bacteria and cells. They are rapidly generated through SELEX (Systematic Evolution of Ligands by EXponential enrichment) process and have high affinity and specificity to targets. Comparing to antibody, superiorities of aptamers are long half-life, nontoxic and they also can be produced with targets which have not immunogenicity. Meanwhile, they can also be easily produced through chemical synthesis or expressional system. So far, applications of aptamers growing rapidly and they have covered many aspects including development of methods to detect or monitor disease, to screen out a specific aptamer against key molecules involved in pathological or virus infectional process and to discover the biomarker of cells surface among membrane proteins.

In current state, popular studies focus on the application of aptamers in curing disease, especially in cancer therapy. They are not only used in detecting or imaging disease, but also in studying the mechanism of diseases.

Besides describing the composition and technological evolution of aptamers, this study will also focus on the recent progress of applying aptamers in cancer diagnosis and therapy. And then discuss the combination of high-throughput technology, namely nanotechnology, with aptamers to solve the scientific difficulties confronted with us.

COMPOSITION OF APTAMERS AND ITS TECHNOLOGICAL EVOLUTION

COMPOSITION OF APTAMERS

Initially, aptamers were modified DNA or RNA molecules that can specifically bind to targets. Subsequently, peptide aptamers emerged as an attractive member of aptamers for their roles of inhibiting many pivotal proteins, which were involved in many physiological processes. At present, method to screen out peptide aptamers mainly depends on yeast two-hybridization system and from a random peptide library. Through this classical method, many peptide aptamers have been identified. To stabilize the conformation of peptide aptamers derived from expressional library, we always inserted a series of variable open reading frames which encode the peptide aptamers into a scaffold protein (often the bacterial protein thioredoxin A) and co-express the fused proteins, thereby, selected peptide aptamers can generate a specific conformations that favors the interactions between aptamers and target molecules.

APPROACHES FOR APTAMERS DELIVERY

As promising therapeutic reagents, besides themselves, aptamers always are conjugated with drugs. Whatever the existence of aptamers are, the most challenge of applying aptamers is how they penetrate the cell membrane. In the past, traditional means of aptamers delivery is through transfection with liposomes. However,

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in order to obtain optimal effect, some modifications are indispensable and combination with nanoparticles will be the future trend. To exclude the non-specific toxicity in normal cells, Tan et al. [2011] realized drug delivery to MCF7 breast cancer cells by using PEGylated anti-MUC1 aptamer-doxorubicin complex. Farokhzad et al. [2004] designed nanoparticle-RNA aptamer conjugates to target prostate cancer cells, these nanoparticles have three significant characteristics such as negative surface charge, carboxylicacid groups and PEG on the particle surface, result of their study showed that these conjugates can efficiently deliver into prostate LNCaP epithelial cells. Aim to exclusively transfer cisplatin to prostate cancer and limit its dose toxicity, Dhar et al. [2008] constructed Pt(IV)-encapsulated PSMA (prostate-specific membrane antigen) targeted nanoparticles (NPs) of poly(D,L-lactic-co-glycolic acid) (PLGA)-poly(ethylene glycol)(PEG)-functionalized controlled release polymers, they demonstrated cisplatin was specifically delivered into prostate cancer cells and revealed a significant differences between nanopaticles with aptamers against PMSA or not. In a similar manner, Tong et al. [2010] utilized Ptxl-PLA NCs (Ptxl-PLA conjugate nanoparticles) as a vehicle to deliver aptamers and found these bioconjugates can effectively target prostate-specific membrane antigen in cell-specific manner. Besides approaches described above, there are many other applications of aptamer-nanoparticle conjugates to facilitate aptamers delivery [Kanwar et al., 2011; Yu et al., 2011]. It is noticeable that method of using nanotechnology in aptamers has evolved from nanoparticles to carbon nanotubes, which were wrapped with aptamers and stand for a more advanced assembly of aptamers to release drugs [Taghdisi et al., 2011]. For peptide aptamers, another frequent option for their delivery is using PTD (protein transduction domain), a positively charged sequence derived from HIV–TAT protein. However, the fusion of peptide aptamers with PTD may affect protein structure.

TECHNOLOGICAL EVOLUTION OF APTAMERS

On the occurrence of studying aptamers, they are short single DNA/RNA strands or peptides and they always play their roles without any modifications. To extend their applications, aptamers are required to be modified and should be formed as complex for better use. So far, technological evolution of aptamers mainly goes through four stages. The initial stage is using aptamers without any modification, the second stage is modifying aptamers with PEG [Takafuji et al., 2010; Tan et al., 2011], subsequent stage is combining aptamers with nanomaterial and many groups have published their successful studies related to nanoparticles [Farokhzad et al., 2004, 2006; Dhar et al., 2008; Chen et al., 2009; Liu et al., 2009; Tong et al., 2010; Chang et al., 2011; Medley et al., 2011; Yu et al., 2011; Kim et al., 2012]. Based on the development of nanotechnology, we speculate that the future trend of applying aptamers may be combining with nanotubes, which can be immobilized with aptamers [Taghdisi et al., 2011] and a more high-throughput method to deliver aptamers or capture targeted cells.

APTAMERS IN CANCER IMAGING AND DIAGNOSIS

APTAMERS IN CANCER IMAGING

Since concentration of cancer cells is extremely low at early stage of tumorgenesis, therefore, development of highly sensitive imaging and detecting methods is extremely urgent. Aptamers can be chemically synthesized and easily modified, thus they can be modified with fluorescent groups and used for imaging. Previous reports showed DNA or RNA aptamers have been utilized in imaging cancer cell and tracking cancer cells in vitro and in vivo, and these reports were summarized in Table I. From Table I, we know only DNA and RNA aptamers applied in imaging cancer cells and this field is emerging in recent years.

APTAMERS IN CANCER DIAGNOSIS

As reagents with property of sensitively and specifically binding to targets, aptamers are extensively applied in cancer diagnosis and their potential targets including whole cancer cells or proteins which were involved in tumorgenesis. Principal published studies regarding to diagnosis were summarized in Table II. From Table II, we know only six types of cancer are selected for diagnosis with aptamers.

APTAMERS IN STUDYING CANCER THERAPY

Besides monitoring cancer cells, important role of aptamers, scientists are more interested in, is their interfering RNA or protein and thereby achieve the aim of cancer therapy. Now, application of aptamers in cancer therapy can be divided into four aspects:

TABLE I. Aptamers Used in Imaging Cancer Cells

Types of aptamers	Aptamers	Target molecules	Cancer cells	References
DNA aptamers	AS1411	Nucleolin	Glioma cells	Hwang do et al. [2010]
	AS1411	Nucleolin	U-87MG, PC-12, C6, HepG-2, SK-Hep-1, Caco-2, CT-26, TPC-1, NPA, HeLa	Kim et al. [2012]
	Cy3-(5-BzdU)-modified-AS1411	Nucleolin	A549, PC-3, F9; C6, HeLa	Lee et al. [2010]
	Sgc8	Whole cells	CEM	Martin et al. [2011]
	KDED2a-3		DLD-1	
	KCHA10		HCT116	
	MUC1 aptamer	MUC1	A2780/AD	Savla et al. [2011]
	Sgc8	Whole cells	CCRF-CEM	Shi et al. [2011]
	TD05	Whole cells	Ramos cells	Shi et al. [2010]
RNA aptamers	A10	PSMA	Prostate cancer	Bagalkot et al. [2007]
	SE15-8	ErB2	MDA-MB-453, T47D, KPL-4	Kim and Jeong [2011]
	Ep-DT3-DY647	EpCAM	Kato III, MCF-7, SW480, T47D, HT29, MDA-MB-231	Shigdar et al. [2011]

TABLE II. Aptamers Applied in Cancer Diagnosis

Targets	Aptamers	Types of cancer	References
Protein	Unspecified	Lung cancer	Ostroff et al. [2010]
	A10/DUP-1	Prostate cancer	Min et al. [2010]
	Anti-VEGF RNA aptamer	Unspecified	Lee et al. [2009]
Cell	Unspecified	Acute lymphoblastic leukemia Burkitt's lymphoma	Herr et al. [2006]
	Unspecified	Acute lymphoblastic leukemia Burkitt's lymphoma Non-Hodgkin's B cell lymphoma	Smith et al. [2007]
	TD05	Burkitt's lymphoma	Liu et al. [2009]
	Unspecified	Acute lymphoblastic leukemia Burkitt's lymphoma	Medley et al. [2011]
	Sgc8	Acute lymphoblastic leukemia	Estevez et al. [2010]
	Sgc8	Acute lymphoblastic leukemia	Chen et al. [2009]
	TD05	Burkitt's lymphoma	
	Sgd5	Human diffuse large cell lymphoma	

regulating the gene transcription and mRNA splicing, generating chimeras with siRNA or cytotoxic agents, dissecting membrane proteins or biomarkers on cell surface, interfering the proteins which were involved in tumorgenesis or cancer process. Therefore, we will discuss these applications as follows.

APTAMERS INDIRECTLY REGULATES GENE TRANSCRIPTION AND MRNA SPLICING THROUGH ITS TARGETS

Similar to siRNA and miRNA, aptamers can also specifically bind to target molecules. However, they usually act as modulators indirectly through their target proteins. Kwak et al. [2009] selected and expressed some high-affinity RNA aptamers against PPAR-δ, a lipid-sensing nuclear receptor involved in inflammation and cancer, and found this RNA aptamers can efficiently suppress PPAR-δ-mediated transcription through repression of PPRE (PPAR responsive element) on the promoter, such as reduced transcription of VEGF-A, COX-2 and other genes mediated by β-catenin, all of these effects eventually lead to reduction of tumor-forming potential. To study the role of regulating transcription and splicing with β-catenin, Lee et al. [2006] obtained a high-affinity RNA aptamer targeting β-catenin and they found this aptamer inhibited β-catenin-dependent expression of cyclinD1 and c-myc, the inhibitive effect exhibited cell cycle arrest and reduced tumor forming potential, eventually, they established the direct role of β-catenin in transcripting and splicing of mRNA. Subsequently, they found β-catenin is involved in multiple steps of gene expression and plays a key role in coordinating RNA metabolism by using RNA aptamer [Lee et al., 2007]. Another example showed AS1411, a specific aptamer against nucleolin, can act as a competitor for its binding to nucleolin and thereby destabilize Bcl-2 mRNA in breast cancer cells [Soundararajan et al., 2008].

CHIMERAS WITH SIRNA OR CYTOTOXIC AGENTS

Worries from applying siRNA or cytotoxic agents are absence of an effective vehicle, which can exclusively access to disease cells, thus prevent them from clinical applications. However, as a small molecule, aptamers can be easily modified to link with siRNA or cytotoxic agents. Previous reports have shown aptamers were incorporated into siRNA expressing constructs or toxins, where they serve as therapeutic vehicles for target delivery. Shaw et al. [2008] proposed a model for synergistic downregulation of cancer receptors and modulators through boranophosphate siRNA-aptamers chimeras. To avoid the injury to noncancerous tissue or surrounding normal tissue derived from escalated doses of radiation, Ni et al. conjugated the PSMA aptamers A10-3 to DNAPK shRNA, combined with IR for human prostate cancer therapy. Their result indicated this strategy dramatically and specifically enhanced PSMA-positive tumor response to IR and has the potential for prostate cancer therapy [Ni et al., 2011]. On the other hand, aptamers can also be modified to serve as a component of complex which comprises cytotoxic agents, such as chemotherapy drugs (doxorubicin, docetaxel, daunorubicin, and cisplatin) and toxins (gelonin). Taghdisi et al. obtained targeted delivery and controlled release of daunorubicin to Molt-4 cells (a type of acute lymphoblastic leukemia T-cells) through Dau-sgc8c aptamer-SWNTs tertiary complex, including nanotubes which were wrapped with aptamers sgc8c, and this complex can selectively target Molt-4 cells. Furthermore, the release of daunorubicin is reversible and dependent on pH value [Taghdisi et al., 2011]. Another example related to this realm was published by Hu et al. [2012], in their study, they exploited a novel aptamer named MA3, which against MUC1, to deliver doxorubicin into MUC1-positive cells, they intercalated doxorubicin into MA3 aptamers and found this complex can selectively carry doxorubicin into MUC1-positive cells.

APTAMERS APPLIED IN DISSECTING MEMBRANE PROTEIN, DISCOVERING AND ISOLATING CELL BIOMARKER

Aptamers, which were screened with multiple cycles of cell-selex, can specifically bind to the target molecules on the cell surface and thereby have potential advantage in dissecting membrane. First of all, it is not requisite for us to know the differential proteins on the cell surface of comparative cells. In addition, it won't destroy the native conformations of target proteins throughout the selection process, thus keep their normal biological functions. Moreover, in the light of cell types, we can obtain the same number of aptamers for further study. Shuangguan et al. identified a biomarker, PTK7 (protein tyrosine kinase7), through cell-selex and mass spectrometry from T-ALL (T-cell acute lymphoblastic leukemia). Their method of discovering cell marker is classical and will be useful to image cancer cells and monitor tumorgenesis [Shangguan et al., 2008].

TABLE III. Aptamers Applied in Cancer Therapy

Types of aptamers	Aptamers	Target molecules	Types of cancer	References
DNA aptamers	5TR-1; S1.3/S2.2	Muc1	Breast cancer	Bruno [2010]
	AS-1411	Nucleolin	Acute myelogenous leukemia, renal cell carcinoma	Mongelard and Bouvet [2010]
	MUC1 aptamer	Mutated MUC1	Ovarian cancer	Savla et al. [2011]
	MUC1 aptamer	MUC1	Breast cancer	Chang et al. [2011]
RNA aptamers	NX1838	VEGF165	Wilms tumor	Huang et al. [2001]
	Modified A10	PSMA	Prostate cancer	Farokhzad et al. [2006]
	A10	PSMA	Prostate cancer	Bagalkot et al. [2007]
	A-p50	NF-kappaB	Non-small cell lung cancer	Mi et al. [2008]
	OPN-R3	Osteopontin	Breast cancer	Mi et al. [2009]
	A9	PSMA	Prostate cancer	Kim et al. [2010a]
	APT	PSMA	Prostate cancer	Kim et al. [2010b]
	P12FR2	PAUF	Pancreatic cancer	Kim et al. [2011]
	GSHapt 5.39; GSHapt class-I	Glutathione	Breast cancer	Bala et al. [2011]
	OPN-R3	Osteopontin	Breast cancer	Talbot et al. [2011]
	A10-3.2	PSMA	Prostate cancer	Wu et al. [2011]
Peptide aptamers	E61-1	HPV16 E6	Papillomaviruspositive cancer	Butz et al. [2000]
	KDI1	EGFR	SKBR3 breast carcinoma A431 vulval carcinoma	Buerger et al. [2003]
	DBD-1	Stat3	Melanoma Myeloma	Nagel-Wolfrum et al. [2004]
	AII-7	ErB2	Breast cancer	Kunz et al. [2006]
	Id1/3-PA7	Id1, Id3	Ovarian cancer	Mern et al. [2010a]
	Id1/3-PA7	Id1, Id3	Breast cancer	Mern et al. [2010b]
	Pep27-9R	Bfl-1	Lymphoma	Brien et al. [2011]
	Peptide524	Androgen receptor	Prostate cancer	Reeb et al. [2011]

APTAMERS APPLIED IN CANCER THERAPY

Traditional cancer therapy always results in severe adverse effect for the high toxicity of drugs in normal cells, however, because aptamers can differentiate normal cells and malignant cells based on their capability of specifically binding to target molecules or cells, therefore, they can exclusively kill malignant cells. In recent years, all three types of aptamers applied in studying cancer therapy are summarized in Table III. From Table III, we get the information that many types of cancer have been studied, including breast cancer, acute myelogenous leukemia, renal cell carcinoma, ovarian cancer, wilms tumor, prostate cancer, non-small cell lung cancer, pancreatic cancer, papillomaviruspositive cancer, A431 vulval carcinoma, melanoma, myeloma, lymphoma. Meanwhile, applications of aptamers are related to proliferation, metastasis, viability, migration and growth, apoptosis and other aspects of cancer cells.

FUTURE DIRECTIONS

Comparing to RNAi technology, aptamers has its unique superiority for their special binding to targets, even the domain of target molecules which will not result in inactivating whole molecules. All these superiorities are especially useful in studying the relationships between transcription factors. For example, there are interactions between transcription factor A and B, meanwhile, interacted A and B complex co-regulate the expression of target genes. It is difficult for us to dissect the expression patterns and roles of these genes through RNAi because it may also affect the cell behaviors derived from all of genes regulated by either of transcription factors, which are not only regulated by interacted A and B complex. However, screened apatmers from library, standing for a specific regulators of A and B complex-dependent transcription, can be easily utilized for analyzing these genes after determination of their interacted motifs and corresponding aptamers. Although our knowledge of aptamers involved in cancer has expanded in recent years and many successful reports have published, however, there are still many issues deserve to be improved. Future studies, we think, need to be performed in following aspects.

It is noticeable that application of aptamers is restricted to limited types of cancer. Previous studies focused on studying prostate cancer, lung cancer, acute lymphoblastic leukemia, lymphoma, colon cancer, and pancreatic cancer. And researchers in this realm mainly major in analytical chemistry and materials science. Therefore, as an interdiscipline, aptamers need to be popularized in biological research, most importantly, it requires to attract much more oncologists and cooperations among oncologists, chemists and materials scientist.

Currently, much advance has been achieved in nanotechnology. Whereas, only DNA and RNA aptamers were combined with nanoparticles and these complex are mainly used in cancer imaging or detection. Peptide aptamers, another powerful tool to inhibit proteins, are ignored in conjugating with nanoparticles. We make sure the peptide aptamers-nanoparticles complex will reform the therapeutic effect of cancer. Furthermore, we reason that future studies will focus on developing much more high-throughput nanomaterial such as nanotubes or nanorods to capture target cells.

As an effective tool of transferring gene into host cells without toxicity and injury, virus has been extensively manipulated in gene therapy, however, the blemish of applying virus is its non-specific infection as long as infected cells have corresponding receptors. To achieve more safer infection, we hope to modify the envelope of virus with peptide aptamers, and thus solve the controversy about safety of gene therapy or transgenesis mediated by virus.

Judging from described above, we know that application of aptamers in studying stem cells is too little. To study normal stem cells, developing much more novel aptamers against normal stem cells has important scientific value. As we have known, aptamers can really reflect the differential process in development and then

monitor the developmental process because of their high specificity and affinity to targets after cell-selex. Meanwhile, aptamers, which against differential proteins in developmental process, will also throw light on understanding the exact role of proteins in development. On the other hand, to study cancer stem cells, so far, only one case was published about cancer stem cells [Shigdar et al., 2011]. In their study, they developed a RNA aptamer against EpCAM (epithelial cell adhesion molecule), an overexpressed protein in most solid cancers and served as a cancer stem cell marker. Through selex, they demonstrated this RNA aptamer can specifically interacts with cancer cells which derived from breast, colorectal and gastric cancers and expressing EpCAM. According to this case, we deduce that the application of aptamers has much gap to be supplied, it is not only helpful for us to discover novel biomarkers on the surface of cancer stem cells, but also to monitor the process of tumorgenesis. In addition, aptamer-drug conjugates may exclude all cancer stem cells from cancer tissue through the directional role of aptamers in the future.

Additonally, there are another neckbottle limit the applications of aptamers. Although there are subtle conformational interactions between aptamers and targets, thereby it can specifically recognize targets from complicated compositions. However, the physical and chemical status has pivotal effect on screening aptamers, that means the acquired aptamers will play their roles in restricted and specific conditions. Therefore, aptamers, like a sword with two blades, are difficult to be applied in clinics for its inconsistent status to scientific research. At present, our group has developed some aptamers against many targets, including Pseudomonas aeruginosa [Wang et al., 2011], NB4 cells (unpublished). At the same time, we have identified several peptide aptamers against Sox2 protein from a peptide library, a constrained peptide expression cassettes inserted into the active site loop of thioredoxin and then fused to partial fragment of venus protein from bimolecular fluorescence complementation (BiFC). Following this, we have demonstrated their interactions through immunoprecipitaion and found these aptamers can reduce the proliferation of human esophageal cancer cells (unpublished).

Collectively, with the development of nanotechnology, we expect aptamers will not only play their roles in inhibiting gene function through directly binding to target molecules, but also can specifically target phenotypes of cancer cells after selection against whole cells or diseased tissues, thereby they can be adapted to serve as valuable diagnostic tools or vehicles that targeted delivery of siRNA into pathological sites. At the same time, applications of aptamers in clinical trials should be speeded up so as to pave the way for virtual target therapy into reality.

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