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Split aptamers and their applications in sandwich aptasensors

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A B S T R A C T

Most aptasensors are designed based on aptamers' conformational change or structural transformation upon interaction with their targets. A limitation of these strategies is the unpredictability of such structural alterations that may yield false-positive or nonspecific signals. In bioanalysis, a dominant strategy for protein determination is the sandwich assay because of its high specificity and sensitivity resulting from the dual recognition mechanism. However, the approach is poorly suited to detection of low molecular weight targets, which unlikely bind to two aptamers simultaneously due to steric hindrance. To circumvent this drawback, a split aptamer strategy was recently developed, in which nucleic acid aptamers were split into two fragments that could specifically form a ternary assembly in the presence of ligand. This elegant approach has been extensively adopted for detection of various targets, especially small molecular weight targets, with different transduction methods including colorimetric, fluorescence, and electrochemical techniques. This review first introduced split aptamers and how to obtain split aptamers, and then summarized recent advances in the development of sandwich-format biosensing assays based on split aptamer fragments, aiming at providing a general guide for the design of split-aptamer-based sandwich assays. Furthermore, we discussed possible challenges in the development of split-aptamer-based sandwich assay regarding stability, sensitivity and multiplicity, so as to offer future opportunities of this assay.

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Abbreviations: AD, adenosine; ADA, adenosine deaminase; ATP, adenosine triphosphate; AuNPs, gold nanoparticles; AVP, arginine vasopressin; BHQ1, black hole quencher-1; CD, cyclodextrin; CNTs, carbon nanotubes; DNA, deoxyribonucleic acid; ECL, electrochemiluminescence; EDTA, ethylenediaminetetraacetic acid; EIS, electrochemical impedance spectroscopy; FAM, fluorescein amidite; Fc-PEI, ferrocene-appended poly(ethyleneimine) (Fc, redox probe); FITC, fluorescein isothiocyanate (separation of the fluorophore); FRET, fluorescence resonance energy transfer; GNR, gold nanorod; GO, graphene oxide; GQDs, graphene quantum dots; GSGHs, graphene–mesoporous silica–gold nanoparticle hybrids; HRP, horseradish peroxidase; KF, Klenow fragment; LFIA, lateral flow immunoassay; LOD, limitation of detection; LSPR, localized surface plasmon resonance; NMR, nuclear magnetic resonance spectroscopy; QDs, quantum dots; RNA, ribonucleic acid; Ru-SiNP, 2,2′-bipyridyl)-ruthenium(II)-doped silica nanoparticle; SAM, self-assembled monolayer; SELEX, systematic evolution of ligands by exponential enrichment; Si@UCNPs, silica coated photon upconverting nanoparticles; SiNPs, silica nanoparticles; SNP, silver nanoparticles; SPR, surface plasmon resonance; ssDNA, single-stranded deoxyribonucleic acid; StAPL, split aptamer proximity ligation; TAMRA, 6-carboxy-tetramethyl-rhodamine; γ-CD, γ-cyclodextrin.

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1. Introduction

1.1. Aptamers and aptasensors

Aptamers are artificial functional DNA/RNA oligonucleotides selected in vitro from random-sequence nucleic acid libraries by an in vitro evolution process called systematic evolution of ligands by exponential enrichment (SELEX) [1,2]. They can bind to various given targets with high selectivity and affinity, which range from small inorganic and organic molecules to macromolecules and even cells [3,4]. As biosensing elements become increasingly important, aptamers show competitive advantages over other naturally occurring or artificial receptors including antibodies or molecularly imprinted polymers (MIPs) [5]. The advantages include low cost, synthetic convenience, thermostability, modification flexibility, wide applicability, and easy regeneration capabilities [6,7]. These features hold great promise in therapeutic, diagnostic, and analytical applications, especially for their great potential in detecting various targets with approaches including electrochemistry [8–11], fluorescence [12–14], colorimetry [15–18], surface plasmon resonance (SPR) [19–21], and chemiluminescence [22–24]. Upon binding to targets, aptamers generally have their conformations significantly changed into hairpins, stem-loops, G-quadruplexes, pseudoknots or bulge structures [25]. Most aptasensors are designed on the basis of conformational changes or structural modification of aptamers after their interaction with targets [26–28]. The structural switching properties of aptamers allow homogeneous biosensor development in order to mediate target-responsive signal transduction. However, structural alterations are susceptible to some interfering factors in complex matrixes, which may yield false-positive or nonspecific signals, thus hampering aptamers' further applications in detection of significant molecules [29–31].

1.2. Split aptamers and sandwich aptasensors

In general, biosensors can be generically classified into two groups (competitive and sandwich assays) depending on the number of recognition elements used against targets. A sandwich assay is always preferred for protein detection because of its high specificity and sensitivity resulting from the dual recognition mechanism, especially in clinical diagnostics. In such an assay, two probes such as antibodies or aptamers are simultaneously used for both signal capture and signal generation, so as to recognize two spatially distant regions of a macromolecule target. However, low molecular weight analytes with a small size cannot be typically measured by sandwich assays, but rather by less sensitive and specific competitive methods [32–34]. The main reason lies in that a small molecule presents only one epitope or even a part of an epitope and that steric hindrance prevents it from binding to two probes simultaneously.

To address this issue, Stojanovic et al. notably developed a split-aptamer-based strategy, in which nucleic acid aptamers were split into two fragments to specifically form a ternary complex in the presence of ligand [31]. The two separate oligonucleotides lack secondary structures, thus not yielding false-positive or nonspecific signals. To obtain positive signals, the two split aptamer fragments must be drawn close to each other, which appears only when the probes bind to a target. This elegant approach has been extensively adopted for detection of various targets, especial small molecular targets, using different transduction methods including colorimetric, fluorescence and electrochemical techniques [35–42].

Up to now, there are totally six aptamers that have been split into two fragments against different molecules (Table 1). Among them, the adenosine triphosphate (ATP) aptamer and its split aptamer fragments were extensively studied and were widely used to develop various methods for ATP detection [24,33,43–53].

2. Split aptamer acquisition methods

Split aptamers have significant potential in the development of sandwich aptasensors. However, effective methods for splitting aptamers into fragments are still scarce. In principle, split aptamers can be generated by dividing an aptamer sequence. To date, more than 100 types of small-molecule-binding aptamers have been reported, but only six of them have been successfully constructed into split aptamers. The difficulty of engineering aptamers into split aptamers results in lack of understanding of the aptamer-target complex structures and roles of nucleobases.

Table 1
Reported targets and their split aptamer fragments

Targets	Aptamer fragment 1	Aptamer fragment 2	Reference
Adenosine/ATP	ACCTGGGGGAGTAT	TGCGGAGGAAGGT	[23,29,31–33,38,40–59]
Cocaine	GTTCTTCAATGAAGT GGG ACGACA	GGGAGTCAAGAAC	[37,38,52,60]
Cocaine*	ACAGCAGGGTGAAGTAACTTCTTGCTT	GGGAGTCAAGAACGAA	[31]
Cocaine*	AGACAAGGAAAA	TCCTTCAATGAAGTGGGTCG	[32,61]
Thrombin	GGTTGGTG	TGGTTGG	[41,42,54,62–64]
17β-Estradiol	GCTTCCAGCTTATTGAATTACACGCAGAGGGTA	GCGGCTCTGCGCATTCAATTGCTGCGCGCTGAAGCGCGGAAGC	[65]
D-vasopressin	TCACGTGCATGATAGACGGCG	AAGCCGTCGAGTTGCTGTGTGCCGATGCACGTGA	[34]
Theophylline	rGrGrCrGrArUrArCrCrArGrCrCrGrArArA	rGrGrCrCrCrUrUrGrGrCrArGrCrGrUrC	[66]

* For cocaine, different split aptamer fragments were used in different studies and all were listed in this table.

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