Aptamer Sensors

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Contributor: samy shaban

Recently, aptamers have attracted attention in the biosensing field as signal recognition elements because of their high binding affinity toward specific targets such as proteins, cells, small molecules, and even metal ions. Aptamers have intrinsic advantages, such as their availability for both chemical modifications and conjugation with different labels, facilitating their ability to be used to construct a sensitive and highly selective platform sensor. Aptamers can be easily functionalized and engineered, providing several signaling modes such as colorimetric, fluorometric, and electrochemical, in what is known as aptasensors.

Keywords: aptamer ; colorimetric aptasensor

1. Introduction

Owing to the advances in various areas of life, the population has become more exposed to pollutants, whether from industry, agriculture, or medical waste, resulting in an increase in the pollution associated with humans' daily lives, leading to an increase in the rate of diseases. In this context, the development of fast, simple, low-cost, high-sensitivity, and specific sensors for detecting pollutants or early stages of diseases is important.

Because of the great advances in molecular biology and genetic engineering, the use of RNA and DNA has expanded not only in biology, for storing and transmitting genetic information, but also in the identification of antibiotics, proteins, peptides, amino acids, and even small molecules. Gold et al. and Szostak et al. reported the first studies involving a specific targeting affinity toward proteins.

Aptamers consist of 3D-folded structures of single-stranded oligonucleotides with lengths of usually 20–60 bases of nucleotides selected in vitro via the systematic evolution of ligand exponential enrichment (SELEX) process. The SELEX process is applicable for single targets, complex target structures, or even mixtures without proper knowledge of their composition. SELEX can be used to select aptamers with high affinities and specificities for their targets and low dissociation-constant values, across the low nanomolar to picomolar range. Aptamers can be selected through the in vitro process independent of animals or cell lines. The selection of aptamers for toxic target molecules or molecules with no or low immunogenicity is possible. Different modifications can be introduced in the basic SELEX process for the selection of the desired aptamer specifications for a specific application. The aptamers can be functional for native conformations of target molecules on live cells, so cell surface transmembrane proteins can be considered as targets.

This systematic review is focused on recent approaches to aptamer engineering for biorecognition for several objectives. Herein, previous and current advances related to aptamer-based sensing protocols are provided, highlighting the possible detected signals, with a focus on the use of different nanomaterials with distinct configurations. The most significant studies on aptasensor development have been collected, providing the possible strategies available for using aptasensors. Moreover, a deep discussion on colorimetric, fluorescence and electrochemical detection strategies is provided

2. Colorimetric Aptasensor

Among the available assay recognition signals, colorimetric methods are considered simple and efficient with a great potential for point-of-care diagnostics, as the detection responses are simply visually discerned by the naked eye using simple, low-cost, and effective instrumental techniques. The basic colorimetric strategies involve the detection of the target by a color change through the naked eye and simple instrumentation. Colorimetric biosensors based on aptamers have demonstrated their sensitivity and selectivity, in addition to their effective potential for rapid onsite diagnosis without complicated instrumentation. However, the colorimetric aptasensor has some limitations such as the influence of color from samples; the time-consuming nature of the fabrication process, which is highly demanded in clinical diagnosis; and the small range of optimized pH solutions.

3. Fluorescence Aptasensor

Fluorescence-based aptasensors are characterized by high sensitivity, large-detection ranges, multiplexing capabilities, rapid assaying, and the highly selective recognition of aptamers for several targets, which can be distinguished under UV light, in comparison with the colorimetric sensor's. The integration of both fluorescent materials (fluorophore dyes and fluorescent nanoparticles such as upconversion nanoparticles (UCNPs), GO, and CQDs) and aptamers can produce high sensitivity and selectivity, and a rapid analysis strategy, making them useful candidates for fluorescence-aptasensor

bioassays [1][2][3]. The recognition affinity between aptamers and analytes induces conformational changes in the aptamer. This process can trigger changes in the fluorescent emission properties of the fluorophore dye or fluorescent nanomaterials, owing to changes in the original environments of these materials.

The design of fluorescent aptasensors requires the use of hairpin aptamers (aptabeacons), which are labeled with either a fluorophore or a quencher. Forster resonance energy transfer (FRET) typically uses a donor fluorophore and an acceptor quencher material. Different strategies are often employed via FRET operations, which are performed through either “signal-on” or “signal-off” assaying protocols. These operations are based on the disparity in the fluorescence responses of the fluorophores as a function of the potential and unique aptamer–target binding and the conformational-change degree [4][5][6]. Owing to the conformational change of the aptamer induced via target interactions, the probe was successfully switched on/off via the FRET mechanism.

4. Electrochemical Aptasensor

An electrochemical aptasensor was fabricated using an aptamer as a bioreceptor and an electrochemical transducer, which translated the target–aptamer affinity into a measurable electrochemical signal through potentiometry, voltammetry, amperometry, impedimetric, or electrochemiluminescence. The potentiometric approach involves the measurement of the potential between the probe and the reference electrode without any net charge transfer. The amperometric approach is based on applying a potential and allowing a redox reaction to occur. The signal is defined as the current between the electrode and the counter-electrode. The voltammetric strategy includes the sweeping potential over time and recording the corresponding current; this strategy is based on a three-electrode system, with working, reference, and counter electrodes. The impedimetric technique involves measuring the charge transfer rate on the surface of the electrode for a kinetic study.

The electrochemical aptasensors were modified with various nanomaterials such as carbon-based nanomaterials, metal-organic frameworks (MOFs), AuNPs, and polymers for signal amplification [7][8][9][10]. The aptamers were immobilized on the electrode surface via π–π interactions, hydrogel grafts, biotin-avidin interactions, thiol–gold self-assembly, and carboxyl–amine covalent reactions.

The electrochemical aptasensor mainly depends on the interactions occurring on the surface of the transducer as a result of the induced reaction between the target and its specific aptamer, providing amperometric or potentiometric electrochemical signals. Another technique is based on the increase in charge transfer resistance via the impedance technique. Therefore, an electrochemical aptasensor was provided for the detection of several targets, such as ampicillin (AMP), avian influenza virus (H5N1), carbohydrate antigen 125, Pb^{2+}, lysozymes, insulin, thrombin, CD44, vanillin, circulating human MDA-MB-231 breast cancer cells, bisphenol A, furaneol, and Hg^{2+}, among others.

5. Conclusions and Future Outlook

The distinctive and impressive advantages of aptamers compared with antibodies permit them to be preferred in molecular diagnostics for a wide range of biomarkers. Aptamers have intrinsic advantages, such as their availability for both chemical modifications and conjugation with different labels, facilitating their ability to be used to construct a sensitive and highly selective platform sensor. The simplicity and small sizes of the aptamers combined with the versatile optical properties and large surface areas of nanomaterials leads to a platform with great potential for highly sensitive and selective biological recognition and signal transduction for various analytes such as metals, small molecules, toxins, proteins, cells, and bacteria with lower LODs and high sensitivity and selectivity.

Each detection method with its own different strategies was emphasized briefly with schematic designs and all the aptamer information, including the detection ranges of the discussed aptasensors, summarized in Table 1. Each aptasensor method has advantages, but the limitations of each method have to be considered before assaying the biomarkers. The optical strategies are considered promising assay methods, as a sensitive response could be achieved; however, some limitations should be considered before assigning a suitable strategy. The colorimetric aptasensor sensors are considered more promising for point of case testing (POCT) owing to naked-eye readout; however, their sensitivity fails to meet the required criteria owing to the higher LODs compared to other methods. Moreover, some limitations were demonstrated in the AuNP–salt-induced aggregation, in which the surface of the AuNP was easily accessible by several targets and aptamers, affecting the reliability of the sensor. This hurdle was overcome by using a strong capping agent [11][12][13]. Despite the fact that the fluorescent aptasensor achieved a high sensitivity for the assay of different targets compared to colorimetric, it requires laboratories and clinical centers with infrastructure for achieving POCT diagnosis, and the limitations of the photobleaching of the fluorescent molecules over time, compromising their stability, is considered an obstacle regarding fluorescent aptasensor development. Generally, electrochemical aptasensors are rapid, easy, and higher in sensitivity compared to optical sensors, making them the best candidates for the on-site rapid assay of biomarkers.

Table 1. Examples of application of aptasensors for quantitative detection.

Sensor Type	Target	Aptamer Sequence
Colorimetric	*E. coli*	Fp: TAGGGAAGAGAAGGACATATGAT, Rp: TTGACTAGTACATGACCACTTGA)
	Malathion	5′-TAT ACA CAA TTG TTT TTC TCT TAA CTT CTT GAC TGC-3′
	Cd^{2+}	5′-CTCAGGACGACGGGTTCACAGTCCGTTGTC-3′
	Salmonella typhimurium	Apt1: 5′-biotin-GAGGAAAGTCTATAGCAGAGGAGATGTGTGAACCGAGTAA-3′
		Apt2: 5′-CTCCTCTGACTGTAACCACGGAGTTAATCAATACAAGGCGGGAACATCCTTGGCGGTGCCGCATAG
	Salmonella typhimurium	NH_2-GCGCTCGGCCTCCTCTGCCATCTCATTCGCGAGCGC
	AFM1	5-Biotin-ACTGCTAGAGATTTTCCACAT-3′
	AFB1	5′-GTTGGGCACGTGTTGTCTCTCTGTGTCTCGTGCCCTTCGCTAGGCCCACA-3′
	Salmonella typhimurium	Apt1 5′-AGT AAT GCC CGG TAG TTA TTC AAA GAT GAG TAG GAA AAG A-C_6-SH-3′
		Apt2 5′-TAT GGC GGC GTC ACC CGA CGG GGA CTT GAC ATT ATG ACA G-C_6-SH-3′
	ABA	AAAATGGGTTAGGTGGAGGTGGTTATTCCGGGAATTCGCCCTAAATACGAGCAAC
	Cortisol	5′-GGA ATG GAT CCA CAT CCA TGG ATG GGC AAT GCG GGG TGG AGA ATG GTT GCC GCA CTT CGG CTT GAA GCT T-3′
	Thrombin	TBA1 (5′-thiolated-TTT TTT TTT TTT TTT GGT TGG TGT GGT TGG-3′)
		TBA2 (5′-thiolated-TTT TTA GTC CGT GGT AGG GCA GGT TGG GGT GAC T-3′)
	Cd^{2+}	5′-biotin-ACC GAC CGT GCT GGA CTC TGG ACT GTT GTG GTA TTA TTT TTG GTT GTG CAG TAT GAG C
	PDGF-BB	5′-CAGGCTACGGCACGTAGAGCATCACCATGATCCTG-3′
	ATP	5′-ACC TGG GGG AGT ATT GCG GAG GAA GGT-3′
	Pb^{2+}	5′-biotin-GGGTGGGTGGGTGGGT-3′
	E. coli	Apt1: 5′-biotin-TGAGCCCAAGCCCTGGTATGCGGATAACGAGGTATTCACGACTGGTCGTCAGGTATGGTTGGC 3′
		Apt1: 5′-biotin-TGAGCCCAAGCCCTGGTATGAGCCCACGGAACACTGGTCGCGCCCACTGGTTTCTATATTGGC 3′
	17β-E2	5′-GCTTCCAGCTTATTGAATTACACGCAGAGGGTAGCGGCTCTGCGCATTCAATTGCTGCGCGCTGAAG
	AFB1	5′-biotin-GTT GGG CAC GTG TTG TCT CTC TGT GTC TCG TGC CCT TCG CTA GGC CCA
	PSA	5′-Biotin-ATTAAAGCTCGCCATCAAATAGC-3′
	E.coli O157: H7	5′-ATCCGTCACACCTGCTCTGTCTGCGAGCGGGGCG
		CGGGCCCGGCGGGGGATGCGTGGTGTTGGCTCCCGTAT-3′

Sensor Type	Target	Aptamer Sequence
Fluorometric	T-2	5′-CAGCTCAGAAGCTTGATCCTGTATATCAAGCATCGCGTGTTTACACATGCGAGAGGTGAAGACTCGAA(
	DGX	5′-AGCGAGGGCGGTGTCCAACAGCGGTTTTTTCACGAGGAGGTTGGCGGTGG-3′
	ZEN	5′-NH_2-AGCAGCACAGAGGTCAGATGTCATCTATCTATGGTACATTACTATCTGTAATGTGATATGCCTATGCG
	PAT	5′-GGC CCG CCA ACC CGC ATC ATC TAC ACT GAT ATT TTA CCT T-3′CFL
	AFB1	TARMA-5′-GTT GGG CAC GTG TTG TCT CTC TGT GTC TCG TGC CCT TCG CTA GGC CCA
	AMP	5′-CACGGCATGGTGGGCGTCGTG-Thiol-3′
	IFN-γ	Apt1: 5′-H_2N-C_6-CCGCCCAAATCCCTAAGAGAAGACTGTAATGAC ATCAAACCAGACACACACTAC
		Apt2: 5′-TGGGGTTGGTTGTGTTGGGTGTTGTG-Azide(N_3)-3′
	MUC1	5′-Cy3-GCAGTTGATCCTTTGGATACCCTGG-NH_2-3′
	Isocarbophos	5′-AGCT_2GCTGCAGCGAT_2CT_2GATCGC$_2$ACAGAGCT-3’
	Hg^{2+}	5′-FAM-TTC TTT CTT CCC CTT GTT TGT T-3′
	E. coli	5′-CCG GAC GCT TAT GCC TTG CCA TCT ACA GAG CAG GTG TGA CGG-C_6 NH_2-3′
	E. coli ATCC8739	5′-ATCCGTCACACCTGCTCTGTCTGCGAGCGGGGCGCGGGCCCGGCGGGGGATGCGTGGTGTTGG(
	Malathion	5′-ATCCGTCACACCTGCTCTTATACACAATTGTTTTTCTCTTAACT TCTTGACTGCTGGTGTTGGCT
	Pb^{2+}	Apt1: 5′-Biotin-CGA TCA CTA ACT ATr AGG AAG AGA TG-HS-3′
		Apt2: 5′-NH_2-TGA GTG ATA AAG CTG GCC GAG CCT CTT CTC TAC-3′
	Chlorpyrifos	5′-CCTGCCACGCTCCGCAAGCTTAGGGTTACGCCTGCAGCGATTCTTGATCGCGCTGCTGGTAATCCTTCTTTAAG(3′
	ATP	5′-CCCCAACTCCTTCCCGAAACCTACCTGGGGGAGTATTGCGGAGGAAGGTTTCGGG-
	ATP	5′-CCCCCCCCCCCCCACCTGGGGGAGTATTGCGGAGGAAGGT-3′
	AFB1	5′-GTT GGG CAC GTG TTG TCT CTC TGT GTC TCG TGC CCT TCG CTA GGC CCA CA-
	Acetamiprid	5′-TGT AAT TTG TCT GCA GCG GTT CTT GAT CGC TGA CAC CAT ATT ATG AAG A-3
	Exosomes	5′-CATCCATGGGAATTCGTCGACCCTGCAGGCATGCAAGCTTTCCCTATAGTGAGTCGTATTACTGCCTAG
	ATP	5′-FAM-AATTCTGGGGGAGCCTTTTGT GGG TAGGGC GGG TTG GTT TTG CCC CGG AGG AGG A
	Cd^{2+}	5′-AGTGACGTGCTGGACTCCGGACTATTGTGGTATGATCTGGTTGTGACTATGCAGTGCGTGCA-(
	MC-LR	5′-GGC GCC AAA CAG GAC CAC CAT GAC AAT TAC CCA TAC CAC CTC ATT ATG CCC CAT C
	Chloramphenicol	5′-AGCAGCACAGAGGTCAGATGACTTCAGTGAGTTGTCCCACGGTCGGCGAGTCGGTGGTAGCCTATGCG

Sensor Type	Target	Aptamer Sequence
Electrochemical	OTA	5′-triple SH-GAT CGG GTG TGG GTG GCG TAA AGG GAG CAT CGG ACA-3′
	Amoxicillin	5′-(SH)-TTA GTT GGG GTT CAG TTG G-3′
	Thrombin	Apt1: 5′-COOH-$(CH_2)_{10}$-GGTTGGTGTGGTTGG-3′.
		Apt2: 5′-NH_2-$(CH_2)_6$-AGTCCGTGGTAGGGCAGGTTGGGGTGACT-3′
	PSA	5′-NH_2-TTT TTA ATT AAA GCT CGC CAT CAA ATA GCT TT-3′
	OTC	5′-SH-GGA ATT CGC TAG CAC GTT GAC GCT GGT GCC CGG TTG TGG TGC GAG TGT TGT GTG GAT CCC
	PAT	5′-NH_2-GGCCCGCCAACCCGCATCATCTACACTGATATTTTACCTT-3′
	Thrombin	5′-AGTCCGTGGTAGGGCAGGTTGGGGTGACT-3′
	Pb^{2+}	5′-GGGTGGGTGGGTGGGT-3′ and its complementary strand 5′-CCACCCACCC–$(CH_2)_6$–S
	H5N1	5′-biotin-GTGTGCATGGATAGCACGTAACGGTGTAGTAGTAACGTGCGGGTAGGAAGAAAGGGAAATAG
	Sulfadimethoxine	5′-GAG GGC AAC GAG TGT TTA TAG A-3′, DNA probe, 5′–SH–TCT ATA AAC ACT CGT TGC C
	Malathion	5′-COOH-ATCCGTCACACCTGCTCTTATACACAATTGTTTTTCTCTT AACTTCTTGACTGCTGGTG
	ATZ	5′-TGT-ACC-GTC-TGA-GCG-ATT-CGT-ACG-AAC-GGC-TTT-GTA-CTG-TTT-GCA-CTG-GCG-GAT-TTA-GCC-AG GTG-C-3′
	OTA	5′-AAAGATCGGGTGTGGGTGGCGTAA AGGGAGCATCGGACA-3′

Biomarker detection based on aptamer functionalization still needs to overcome these limitations in order to be available for the multi-detection of metal ions, DNA, and proteins. Furthermore, the development of more specific aptamers is still needed, as is also integration into sensor platforms. Aptasensor platforms need more attention regarding (1) simultaneous multiple marker detection; (2) the long-term stability of biosensor assays; (3) direct assays in real sample matrixes; (4) understanding the nature of the binding competition between an aptamer and target on the surface of a nanomaterial, which could affect the sensor reliability; (5) more focus on the future development of in vivo aptamer sensing technology, the possible problems, and their solutions; and (6) more intensive research regarding the improvement of the POCT of biomarkers using aptasensors. The aforementioned hurdles need to be overcome quickly for the achievement of a reliable and selective detection of markers with ultrasensitivity, with affordable and portable on-site analytical devices. We are sure that the scientific community has the talent to offer solutions to these hurdles in order to design an affordable, easy-to-use nanomaterial-based electro-optical aptasensor integrated with rolling-cycle amplification technology.

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