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REVIEW

Selection of aptamers against pathogenic bacteria and their diagnostics application

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Abstract
Aptamers are short nucleotide sequences which can specifically bind to a variety of targets with high affinity. They are identified and selected via systematic evolution of ligands by exponential enrichment (SELEX). Compared to antibodies, aptamers offer several advantages including easy labeling, high stability and lower cost. Those advantages make it possible to be a potential for use as a recognition probe to replace antibody in the diagnostic field. This article is intended to provide a comprehensive review, which is focused on systemizing recent advancements concerning SELEX procedures, with special emphasis on the key steps in SELEX procedures. The principles of various aptamer-based detections of pathogenic bacteria and their application are discussed in detail, including colorimetric detection, fluorescence detection, electrochemical detection, lateral flow strip test, mass sensitive detection and PCR-based aptasensor. By discussing recent research and future trends based on many excellent publications and reviews, we attempt to give the readers a comprehensive view in the field of aptamer selection against pathogenic bacteria and their diagnostics application. Authors hope that this review will promote lively and valuable discussions in order to generate new ideas and approaches towards the development of aptamer-based methods for application in pathogenic bacteria diagnosis.

Keywords Aptamer · Diagnostic detection · Pathogenic bacteria · Recognition elements · SELEX

Introduction

Pathogenic bacteria are one of the causative agents of various infectious diseases that are one of the leading causes of death all over the world. Conventional culture-based assay is time-consuming and laborious, and is insufficient to meet current market demands. Therefore, there is an urgent need for development of a rapid and sensitive diagnostic method to identify pathogenic bacteria.

Aptamers are short sequences of single-stranded DNA or RNA that can selectively bind to their target molecules. As new recognition elements, aptamers have great potential to be used as a diagnostic tool for rapid detection of pathogenic bacteria. The function of the aptamer is similar to that of the monoclonal antibody, but superior in many other aspects, such as, stability, easy chemical modification, small size, non-immunogenicity and variety of targets. Based on these advantages, more and more researchers have directed their attention to SELEX technology and aptasensors. A few excellent studies that have summarized the identification and application of aptamer against simple targets (thrombin, ATP, cocaine) were found (Kim et al. 2016; Song et al. 2008; Toh et al. 2015). These SELEX technologies and aptasensors designed for simple targets may not be suitable for bacteria. This may be due to the size and complex surface structures of bacteria, which complicate the selection process and the challenged aptasensor.

Recently, we found one review focusing on the identification and application of aptamers against foodborne pathogens (Teng et al. 2016). In Teng's review, aptamer SELEX including whole-cell SELEX and genomic SELEX were

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discussed. Meanwhile, aptamer-based biosensors including fluorescence detection, surface plasmon resonance, electrochemical biosensors and lateral chromatography test strips were briefly introduced. However, some notable strategies still need to be reviewed for improving the effectiveness of SELEX against pathogenic bacteria and generating new ideas and approaches towards the development of aptamer-based methods. Therefore, we intended to provide a comprehensive review, which is focused on systemizing recent advancements concerning SELEX procedures, with special emphasis on the key steps in SELEX procedures, and discussion on the principles of various aptasensors of pathogenic bacteria and their application in detail including colorimetric detection, fluorescence detection, electrochemical detection, lateral flow strip test, mass sensitive detection and PCR-based aptasensor.

Aptamer selection

Since the first aptamer was generated by SELEX in 1990s, SELEX has been widely used to select aptamers against a variety of targets. Figure 1 shows the general process of SELEX against pathogenic bacteria, including several steps: (a) defined target molecule, (b) creating a library of random oligonucleotide, (c) exposure of the oligonucleotide library to the target molecule, (d) separation of non-binding oligonucleotide, (e) amplification of bound sequences and (f) generation of ssDNA.

Defined target molecule

Unlike other targets, bacteria in its stable native conformation is very important for the success of SELEX. Therefore, incubation buffer parameters (osmotic pressure, pH, composition) in the selection process must be carefully considered.

Creating a library of random oligonucleotide

Before SELEX, single-stranded DNA (ssDNA) or RNA library and primers had to be designed and synthesized. The ssDNA or RNA contains a random sequence in a central region, and two fixed flanking regions for primer hybridization. It is worth noting that the primer design should follow the principle that primers should not hybridize to the target genome for avoiding cross-contamination of the library.

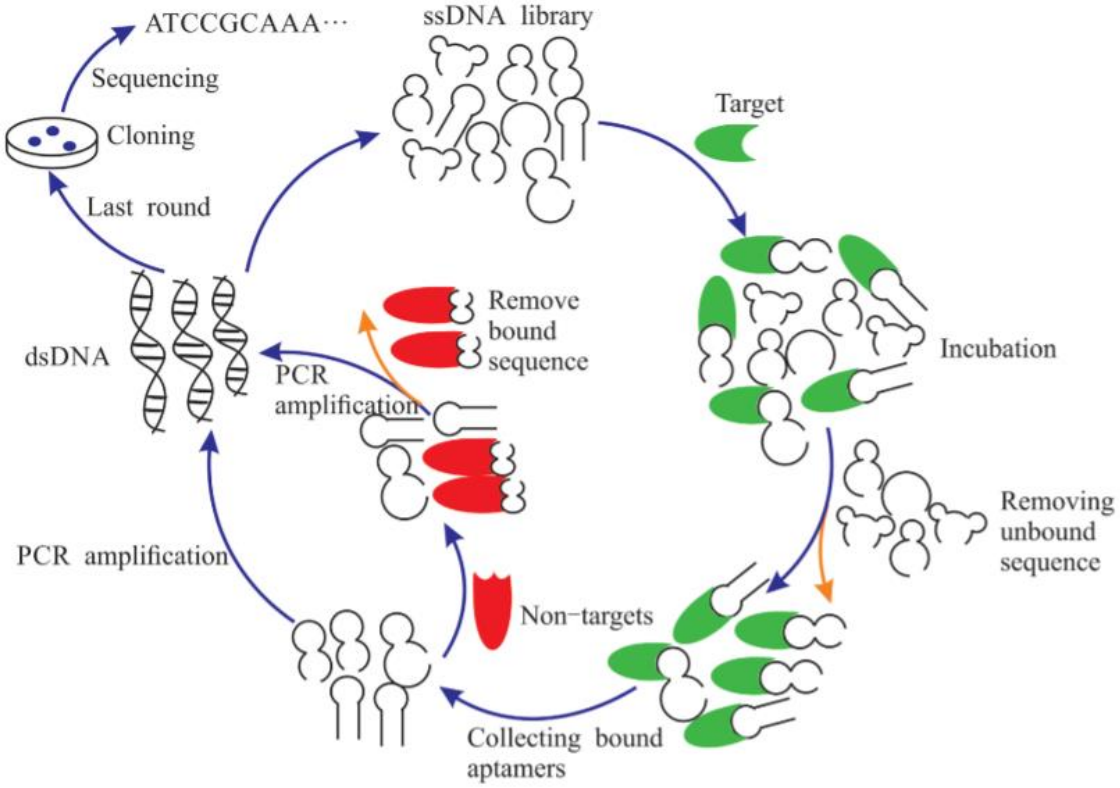

Fig. 1 The general process of SELEX against pathogenic bacteria

Exposure of the oligonucleotide library to the target molecule

To improve separation efficiency and reduce non-specific binding, tRNA and BSA as non-specific competitors were added into incubation buffer when library was exposed to targets molecules (Duan et al. 2013a, b). tRNA was added to compete with aptamer for target binding sites, and BSA was added to compete with desired targets for aptamer. With increasing amount of tRNA and BSA in each round, the selection stringency was increased, which resulted in the increase of sub-library affinity.

Separation of nonbinding oligonucleotide

This step determines the SELEX efficiency, which is often achieved by centrifugation or immobilization method.

The centrifugation method is the most common method for bacterial selection, which appears to be a simple, convenient and rapid approach to separate aptamer–target complexes from the unbound sequence. Centrifugation speed could range from 1500×*g* to 13,000×*g* depending on the size of bacteria.

To improve SELEX efficiency, the immobilization method is used as an alternative, to increase the stringency of separation in SELEX. The traditional immobilization substrates involved the use of ELISA plate or nitrocellulose membrane to immobilize target molecules and separate aptamer–target complexes from the unbound sequence (Li et al. 2011; Savory et al. 2013). Other new immobilization substrates such as magnetic beads, and electrodes were also used for SELEX (Wang et al. 2017a; Yu et al. 2017).

Amplification of bound sequences

Common PCR was used to amplify bound sequences. Prior to the selection, PCR conditions need to be optimized to avoid the generation of by-products which might result in the loss of potential high affinity and specificity aptamer (Tolle et al. 2014). In addition, PCR bias might lead to a partial loss of aptamer candidates (Cao et al. 2009). Therefore, numerous researchers tend to employ emulsion PCR to avoid the generation of by-products and loss of bound sequences during common PCR amplification stage (Luo et al. 2015; Shao et al. 2011).

Generation of ssDNA

Several approaches have been widely used to prepare ssDNA in DNA aptamer selection, including heating denaturation, lambda exonuclease digestion, streptavidin–biotin magnetic separation, streptavidin–biotin agarose beads separation, asymmetric PCR and size separation on denaturing urea polyacrylamide gel electrophoresis.

So far, whole-cell SELEX was widely used to generate aptamer binding to bacteria due to the particularity of target molecules. The enrichment of the sub-library was used through the centrifugation method as mentioned above. In addition, some advanced technologies in combination with SELEX were proposed to select aptamer against bacteria, for example, magnetic-bead SELEX (Yu et al. 2017), which is separation of nonbinding sequences by magnetic separation.

Diagnostic applications of aptamers

Once an aptamer sequence was known, a variety of aptasensors were developed to detect their target molecules, which could be developed into six categories: colorimetric detection, fluorescence detection, electrochemical detection, lateral flow strip test, mass sensitive detection and PCR-based detection.

Colorimetric detection

A colorimetric detection based on the color change of substrate solution upon target binding has recently gained considerable attention due to its simplicity, sensitivity, rapidity and low cost. Colorimetric detection was summarized into three fundamental formats (Fig. 2). Gold nanoparticles (AuNPs) as common nanomaterials have been widely used to develop colorimetric detection based on their unique properties (Verma et al. 2015). Without targets, aptamers can bind to AuNPs in salt solution and disperse AuNPs, which appear in red color. However, when targets are introduced into the system, aptamers release from AuNPs and bind to the targets, resulting in the aggregation of AuNPs and the color changes from red to purple (Fig. 2a). According to the color change, this aptasensor was applied to detect *Salmonella typhimurium, Escherichia coli* O157:H7 and *Staphylococcus aureus* (Chang et al. 2016; Lavu et al. 2016; Moon et al. 2014; Wu et al. 2012). To improve the sensitivity, aptamer 2 modified magnetic beads, as a concentration element, were coupled with aptamer 1 modified AuNPs to develop an aptasensor method for detection of *S. typhimurium* (Duan et al. 2016). With the help of magnetic beads, the limit of detection (LOD) was improved to 10 CFU/mL. However, there may be some difficulties for these label-free colorimetric detections in actual food samples, because complex food matrices may affect the color change of aptamer–AuNPs solution. To overcome these problems, Kim et al. (2017) developed two-stage label-free aptasensing platform for detection of *Cronobacter sakazakii* in powdered infant formula. In this system, aptamers were first bound

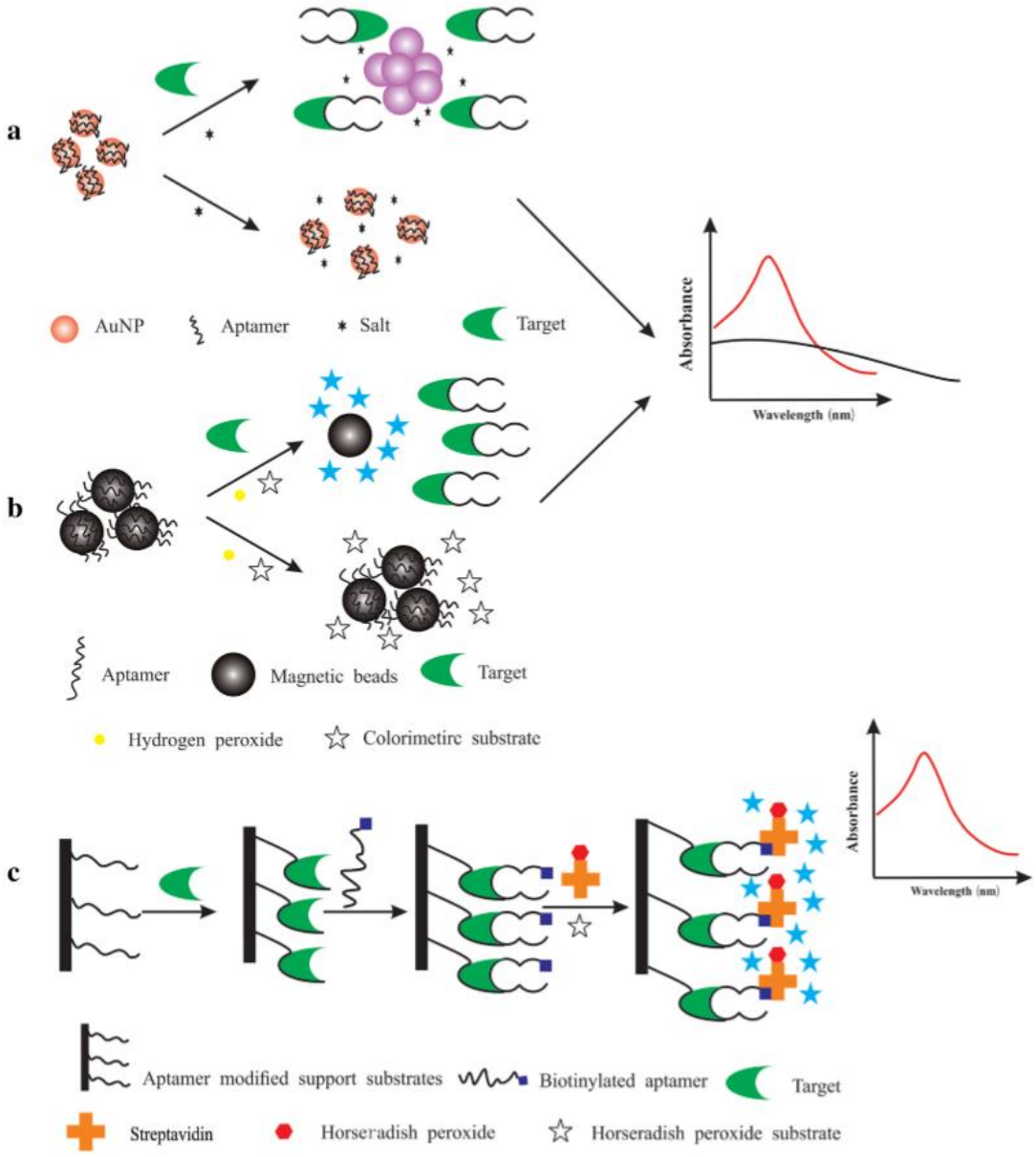

Fig. 2 The schematic illustrations of aptamer-based colorimetric detection: **a** based on label-free AuNPs; **b** based on peroxidase-like activity of magnetic beads; and **c** based on oxidation–reduction reaction

to *C. sakazakii* to form aptamer–*C. sakazakii* complexes, which can be removed from the solution via centrifugation method. Then the supernatant induced the aggregation of AuNPs with the presence of salt, resulting in a color change from red to purple.

Recently, it has been found that nanoparticles have an intrinsic peroxidase-like activity in presence of hydrogen peroxide. These features make it possible to develop a colorimetric method for detection of pathogenic bacteria. In this system, aptamers are adsorbed on the surface of nanoparticles via electrostatic interaction, which prevent the access of 3,3′,5,5′-tetramethylbenzidine (TMB, colorimetric substrate) to the surface of magnetic nanoparticles. When target bacteria is added into the solution, aptamers bind preferentially to targets, and nanoparticles are exposed to colorimetric substrates to recover peroxidase activity. With the presence of H_2O_2, the solution changes to a blue color (Fig. 2b). A colorimetric aptasensor based on the catalytic activity of magnetic nanoparticles was developed to detect *S. typhimurium* with a LOD of 7.5×10^5 CFU/mL

(Park et al. 2015). To improve the sensitivity of detection, $ZnFe_2O_4$-reduced graphene oxide ($ZnFe_2O_4$/rGO) nanocomposites (which exhibit enhanced catalytic activities superior to individual nanoparticles) were used to develop colorimetric aptasensor platform for *S. typhimurium* detection (Wu et al. 2017).

Aptamers have also been used as a replacement for antibodies in ELISA for pathogenic bacteria detection (Fig. 2c). Based on ELISA principles, an aptamer-based sandwich type capillary detection platform was proposed to detect *S. enteritidis* (Bayraç et al. 2017). Zhu et al. (2016) developed an aptamer-based colorimetric assay for detection of *S. typhimurium*. After biotin–aptamer–*S. typhimurium*–aptamer–biotin sandwich-type forms, avidin-catalase was added to catalyze gold ions to nanoparticles, resulting in change color of the solution. A similar method was employed by Yuan et al. (2014b) using aptamers coupled with tyramine signal amplification (TSA) to detect *S. aureus*. Wu et al. (2015) developed a colorimetric aptasensor to detect *V. parahemolyticus*, in which MNPs–aptamers were used as supporting substrates for capture targets, and AuNPs–aptamers were used as carriers of horseradish peroxidase. The LOD was 10^2 CFU/mL in spiked water. Yuan et al. (2014a) developed a specific and rapid method based on the recognition of aptamers–AuNPs coupled with silver signal amplification to detect *S. typhimurium*. After aptamer–bacteria–aptamer–AuNPs sandwich-type forms, AuNPs were subsequently coated with silver with the help of silver enhancer solution, and the color of solution became darker.

Fluorescence detection

Compared to colorimetric detection, fluorescence detection is a more promising technology to analyze biological samples due to its higher sensitivity. Fluorescence detection is based on the generation or quenching of fluorescence signals upon binding to targets. There are two common approaches, which are widely used to detect pathogenic bacteria (Fig. 3). A number of fluorescent groups such as quantum dots (QDs), FAM, upconversion nanoparticles (UCNPs), or carbon dots (CDs) conjugated with aptamer were designed to detect and identify pathogenic bacteria (Fig. 3a). QDs are common fluorescence molecules because of improved signal brightness and resistance against photobleaching. Ikanovic et al. (2007) used QD-aptamer to directly detect *Bacillus thuringiensis* spores with a LOD of 1000 CFU/mL, followed a similar approach using FAM (Li et al. 2011) and a multiple detection using multiple QDs (Duan et al. 2013d). A sandwich-type assay based on aptamer modified 96-well plate and QD-modified aptamer conjugates was developed for detection of *E. coli* O157:H7 (Demirkol and Timur 2016). Instead of QD,

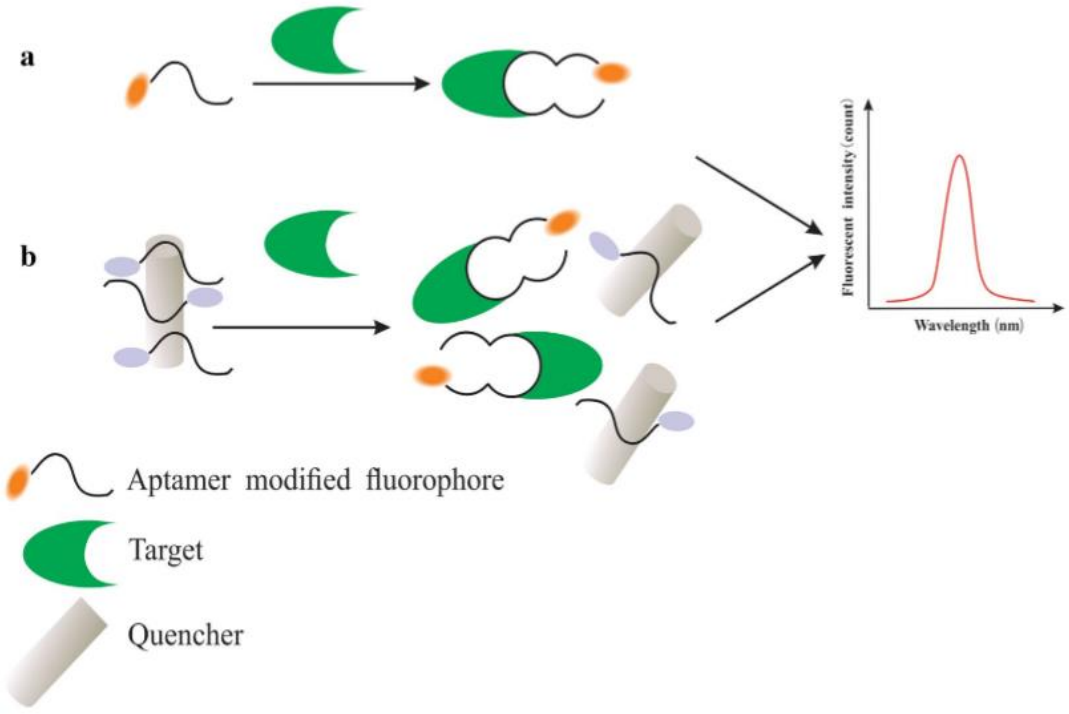

Fig. 3 The schematic illustrations of aptamer-based fluorescence detection: **a** fluorescence signaling format and **b** fluorescence resonance energy transfer format

FAM-aptamer was also used in sandwich-type assay with the same approach of the report above (Duan et al. 2013a, b). Next, to improve sensitivity, aptamers-magnetic nanoparticles were used to capture and concentrate the targets, and fluorescent group modified aptamers were used to amplify the fluorescence signal (Duan et al. 2012, 2013c). However, the same aptamer used in a sandwich-type assay has limitations due to the limited binding sites of target molecules. Therefore, many researchers tended to use two different molecular probes (a capture aptamer/antibody/complementary DNA and a reporter aptamer) in a sandwich-type assay (Gong et al. 2015; Kurt et al. 2016; Lee et al. 2015; Xu et al. 2015). However, it was found QD has rigorous preparation requirements and biotoxicity. Therefore, carbon dots (CDs) conjugated with aptamers were proposed to detect pathogenic bacteria (Wang et al. 2015).

More advanced strategy has been developed based on fluorescence resonance energy transfer (FRET) (Fig. 3b). Duan et al. (2015) developed a dual FRET based aptasensor using QD and carbon nanoparticles (CNPs) for simultaneous detection of *S. typhimurium* and *Vibrio parahaemolyticus*. In this study, both green-emitting QD-aptamer 1 and red-emitting QD-aptamer 2 were adsorbed on the surface of CNPs, resulting in the quenching of fluorescence. In presence of targets (*V. parahaemolyticus* and *S. typhimurium*), aptamer 1 and aptamer 2 were released from the CNPs and bound to *V. parahaemolyticus* and *S. typhimurium*, respectively, resulting in the recovery of fluorescence. The LODs were found to be 25 CFU/mL for *V. parahaemolyticus*, and 35 CFU/mL for *S. typhimurium*, respectively. Based on the same principle, FAM-aptamer combined with graphene oxide (GO) was used to detect *S. typhimurium* with a LOD of 10^2 CFU/mL (Duan et al. 2014). Recently, rapid and ultrasenstive detection for *E. coli* with a LOD of 3 CFU/mL was developed based on FRET by combining AuNPs–aptamer with corresponding complementary DNA modified UCNPs (Jin et al. 2017).

Electrochemical detection

An electrochemical detection is an attractive platform, which provides a simple, fast and sensitive method to detect pathogenic bacteria. Electrochemical detection is based on measuring changes in electrical properties of sensors when aptamers bind to its target bacteria (Fig. 4). Based on this principle, a label-free DNA aptamer-based impedance biosensor was developed by Queirós et al. (2013) by directly immobilizing aptamers on the electrode surface via S/Au bond to detect *E. coli* outer membrane proteins. To improve the sensitivity, aptamer cocktails (three different aptamers) were simultaneously immobilized the surface of electrode via S/Au bond to detect *E. coli* (Kim et al. 2014). This approach had a 18-fold lower LOD compared with the use of single aptamer. Considering the time-consuming process and stability of S/Au interaction, Bagheryan et al. (2016) developed a diazonium-based impedimetric aptasensor for detection of *S. typhimurium* by immobilizing NH_2-aptamer on diazonium-supporting layer electrode. Due to biocompatibility and high electron transfer properties of graphene oxide and AuNPs, another aptamer-based electrochemical biosensor was developed by Ma et al. (2014) using a glassy carbon electrode (GCE) modified with graphene oxide and AuNPs, followed by immobilizing the thiolated aptamer

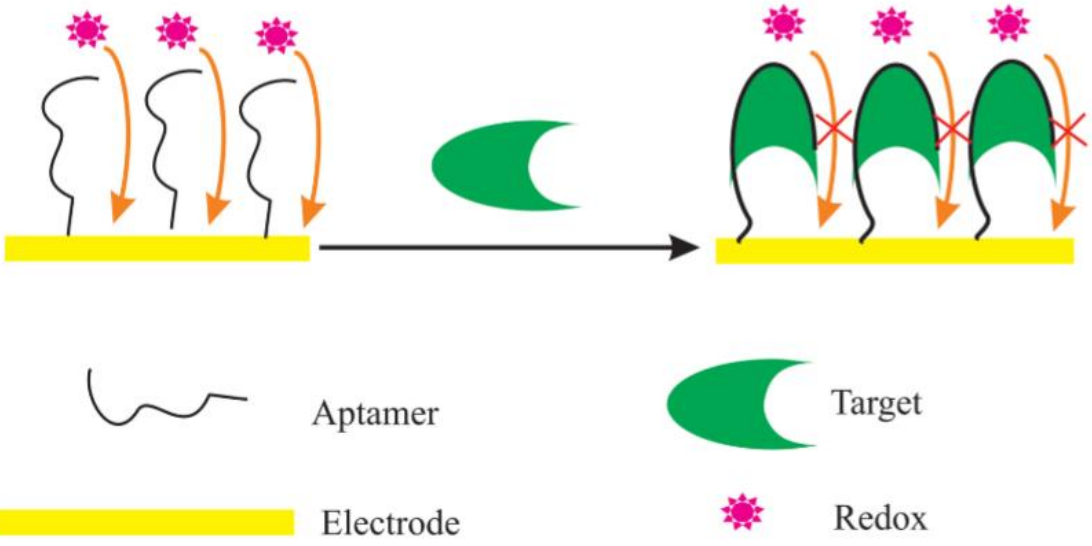

Fig. 4 The schematic illustrations of aptamer-based electrochemical detection

to detect *Salmonella* with a lower LOD of 3 CFU/mL. The method was successively applied in *S. aureus* detection (Jia et al. 2014). In addition, an electrochemical aptasensor was developed for detection of *S. typhimurium* by introducing a new conductive layer containing reduced graphene oxide-azophloxine (rGO-AP) on GCE (Muniandy et al. 2017). The change of peak current was measured after aptamer was doped on the rGO-AP/GCE platform for capturing *S. typhimurium*. As the results showed the LOD was 10 CFU/mL. Another functionalized Bridged Rebar Graphene (BRG) was also immobilized on screen printed electrodes and used for detection of *E. coli* O78:K80:H11 by incorporating aptamer (Kaur et al. 2017). This modification endowed good electrical properties and facile chemical functionality of electrode.

A novel aptamer/graphene interdigitated gold electrode piezoelectric was developed by Lian et al. (2015) to detect *S. aureus*. In this study, the graphene was immobilized on the surface of an interdigitated gold electrode via chemical reaction. In absence of *S. aureus*, the aptamers were adsorbed on the graphene. In presence of *S. aureus*, the aptamers preferentially bind to *S. aureus* and detach from the graphene, resulting in a marked change of frequency shift. This assay was able to detect 41 CFU/mL within 60 min. Luo et al. (2012) proposed an electrochemical biosensor based on target-induced aptamer displacement for *E. coli* O111 detection. In this study, the complementary DNA (capture probe) was immobilized on the electrode surface, and hybridized with the aptamer. In presence of *E. coli* O111, the aptamer preferred to bind to *E. coli* O111, and released from the aptamer–DNA duplex. Subsequently, the biotinylated detection probe hybridized with the capture probe, and conjugated with streptavidin–alkaline phosphatase to catalyze the hydrolysis of α-naphthyl phosphate substrate, resulting in the generation of electrochemical signal. After optimization of experimental conditions, this assay could detect 305 CFU/mL in milk within 3.5 h.

In addition, a dual-aptamer-based sandwich detection was proposed by Abbaspour et al. (2015) using aptamer-conjugated magnetic beads to capture *S. aureus* and the secondary aptamer-conjugated AgNPs to generate electrochemical signal though anodic stripping voltammetry. The assay demonstrated ultrahigh sensitivity towards *S. aureus* with a LOD of 1 CFU/mL. However, the dual-aptamer-based sandwich detection is only suitable for certain targets, due to the lack of available dual aptamer pairs. Therefore, other electrochemical aptasensors with the sandwich format were reported to use an antibody/aptamer pair (Guo et al. 2016). In this study, an antibody immobilized on the surface of Au electrode was used to capture *E. coli* and an aptamer-primer probe was used to amplify electrochemical signal through rolling circle amplification to form G-quadruplex/hemin complexes to catalyze H_2O_2.

Lateral flow strip test

The popularity of lateral flow strip especially for rapid tests such as pregnancy and food safety diagnostics is undeniable because of its low cost, ease of use and rapid results. As an alternative to antibody, aptamers conjugated to AuNPs have been recently used in lateral flow strip tests.

In sandwich format, the target molecules react with AuNPs–aptamer 1 conjugates loaded on the conjugated pad to form AuNPs–aptamer–target complexes. Then the complexes are captured in the test zone via interaction between aptamer 2 and their target molecules, which results in the accumulation of AuNPs on the test line. The excess AuNPs–aptamer 1 conjugates move to the control line and

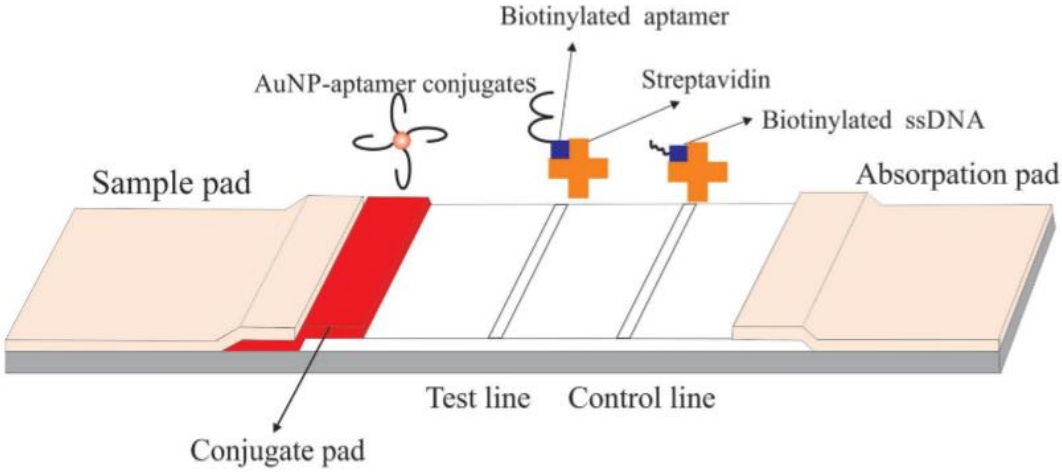

Fig. 5 The typical principle of lateral flow aptasensor (sandwich format)

are captured via nucleic acid hybridization between aptamer 1 and complementary ssDNA, and generate a signal (Fig. 5). Evolution from conventional sandwich format, a lateral flow biosensor based on aptamer mediated strand displacement amplification was developed for rapid detection of *S. enteritidis* and *E. coli* O157:H7 (Fang et al. 2014; Gong et al. 2015). However, the sample solution passed through the membrane quickly, resulting in the insufficient hybridization with the control probe, which affected the signal of the control line. Bruno (2014) sprayed anti-digoxigenin antibodies on control line to overcome this problem with a LOD of 6×10^3 cells/test for *E. coli* O157:H7.

Mass sensitive detection

A mass sensitive aptasensor is based on the change of a property that is proportional to mass upon the targets binding, including surface plasmon resonance (SPR), and quartz crystal microbalance (QCM).

SPR detection measures the change of refractive index caused by the mass change upon targets binding (Fig. 6a). An aptamer-functionalized localized SPR sensor was developed to detect *S. typhimurium* and *P. aeruginosa* (Yoo et al. 2015). In this study, a thin gold (Au) layer on silica nanoparticles (NPs) was modified on a glass slide to form a gold-capped nanoparticle array (MG-NPA) chip. After immobilization of thiol-aptamer on the MG-NPA chip, the sensor demonstrated a LOD of 10^4 CFU/mL.

QCM detection is based on the change of frequency caused by the mass on the surface of the crystal (Fig. 6b). Based on this principle, Ozalp et al. (2015) developed QCM aptasensor coupled with magnetic separation for detection of *Salmonella*, using magnetic beads to capture *Salmonella*, followed by aptamer-modified QCM detection.

PCR□based detection

Aptamers are made of nucleic acids, which offer an inherent advantage over antibodies in the field of diagnostics. Taking full advantage of aptamers as the recognition probe and nucleic acids, Lee et al. (2009) developed an immunomagnetic separation and aptamer real-time PCR method for detection of *E. coli*. As shown in Fig. 7, the aptamers were released from magnetic beads–antibodies–*E. coli*–aptamer sandwich-type format and amplified by real-time PCR for quantifying *E. coli*. This assay could detect 10 CFU/mL of *E. coli*. This aptamer-based PCR method was able to detect *S. typhimurium* in ground turkey (Wang et al. 2017b).

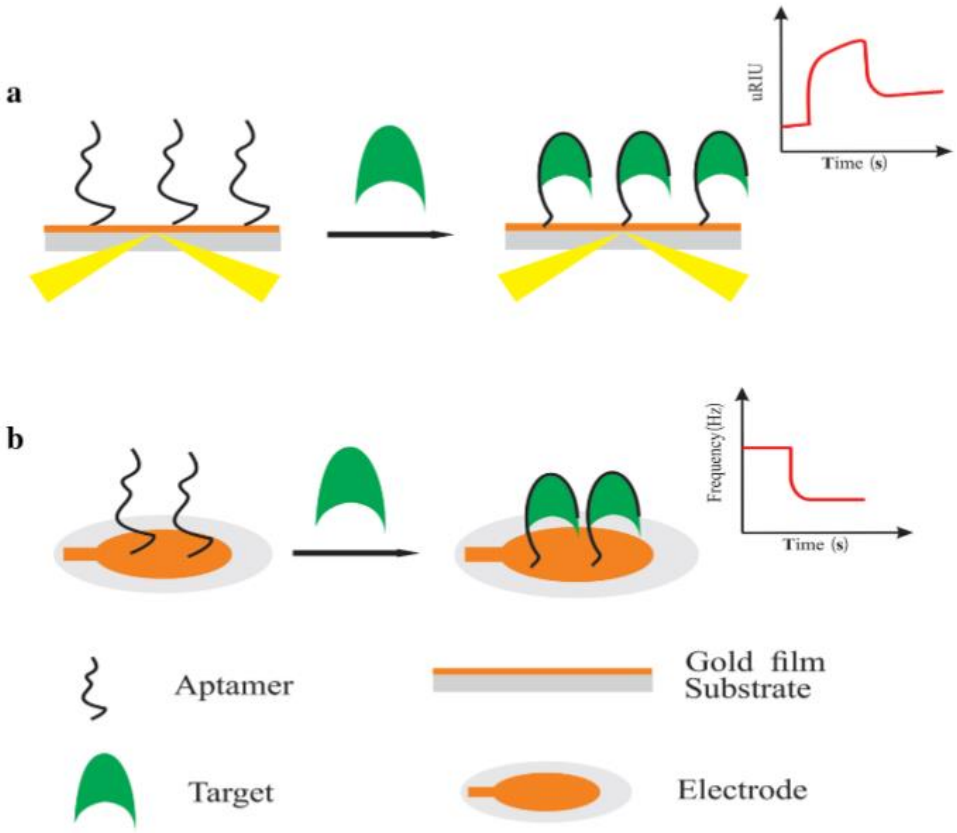

Fig. 6 The schematic illustrations of mass sensitive aptasensor detection: **a** SPR and **b** QCM

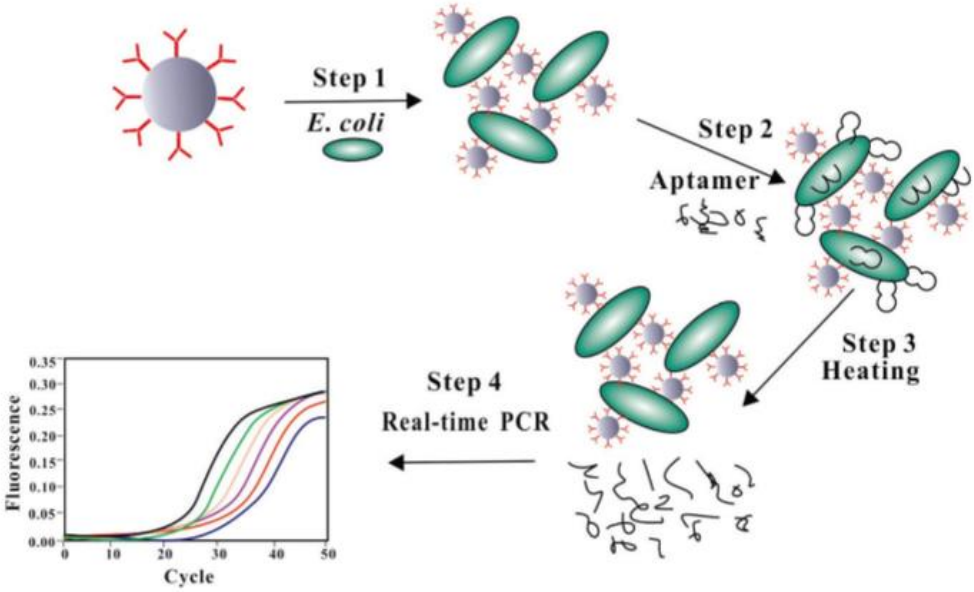

Fig. 7 The schematic illustration for aptamer-based PCR method coupled with immunomagnetic separation (Lee et al. 2009)

Conclusions

Although the remarkable progress has been made in diagnostics during the past 50 years, there are still numerous questions impeding the development of simple, rapid and cost-effective detection methods. Since the introduction of aptamers in the field of diagnostics, aptamers have been recognized to have a great potential to replace antibody due to their unique features. In recent years, aptamers have been proven to be versatile and effective as molecular probes in various types of detection. However, practical application of aptamer-based detection in clinical diagnostics is still rare. One reason is the difficulty in selection of high affinity and high specificity aptamer for widely different target molecules, especially bacteria. Another reason is that a majority of aptamer-based methods designed so far are sophisticated and complicated, requiring expensive equipment and professional laboratory-type operations, making the methods less useful in field. Further studies with aptamer selection technology and aptasensors need to be carried out in order to overcome limitations and facilitate their commercialization.

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