Applied Microbiology and Biotechnology
https://doi.org/10.1007/s00253-020-10940-1

MINI-REVIEW

The research of aptamer biosensor technologies for detection of microorganism

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Received: 21 May 2020 / Revised: 27 September 2020 / Accepted: 1 October 2020

Abstract

The activities and transmissions of microorganisms are closely related to human, and all kinds of diseases caused by pathogenic microorganisms have attracted attention in the world and brought many challenges to human health and public health. The traditional microbial detection technologies have characteristics of longer detection cycle and complicated processes, therefore, which can no longer meet the detection requirements in the field of public health. At present, it is the focus to develop and design a novel, rapid, and simple microbial detection method in the field of public health. Herein, this article summarized the development of aptamer biosensor technologies for detection of microorganism in the aspect of bacteria, viruses, and toxins in detail, including optical aptamer sensors such as fluorometry and colorimetry, electrochemical aptamer sensors, and other technologies combined with aptamer.

Key points

- *Aptamer biosensor is a good platform for microbial detection.*
- *Aptamer biosensors include optical sensors and electrochemical sensors.*
- *Aptamer sensors have been widely used in the detection of bacteria, viruses, and other microorganisms.*

Keywords Aptamer · Pathogenic bacteria · Optical sensors · Electrochemical sensors · Detection

Introduction

Microorganisms mainly include bacteria, viruses, fungi, and a small number of algae, which are widely distributed in the environment and closely related to human activities. Some microorganisms are beneficial to human health. For example, probiotics can promote intestinal absorption (Lu et al. 2019; He et al. 2019). While some microorganisms are harmful to human health like pathogenic bacteria can cause human diseases. For instance, *Staphylococcus aureus* (*S. aureus*) and its enterotoxin are a major cause of food poisoning (Wu et al. 2016). *Salmonella* can cause gastroenteritis and typhoid fever (Gasem et al. 1995; Mccormick et al., 1996). *Helicobacter pylori* (*H. pylori*) may induce peptic ulcer and gastric lymphoma (Cheng et al., 2017a). All kinds of influenza virus such as H5N1, H1N1, and H9N2 infect the human body, causing severe illnesses (Nguyen et al. 2016). Therefore, all sorts of diseases caused by pathogenic microorganisms are the main issues which people have concentrated on all the time. It is an important task of public health and clinical medicine to find out the cause of disease and diagnose it.

The traditional method of microbiological detection (Zhao et al. 2014) is to prepare culture medium for culturing microorganisms, then the suspected pathogenic bacteria are isolated and get the biochemical identification. Promoting bacteria step by step is the method of detecting *Salmonella* in food

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Published online: 13 October 2020

(GB 4789.4-2016), which generally can be divided into four procedures. The first step is sample handling. Microbial samples are incubated at 37 °C in a high nutrient and free selectivity medium for the growth of microorganisms in samples. The second step is selective enrichment. Target bacteria can grow up selectively while non-target bacteria are not able to grow up in the special culture medium. Finally, suspicious colonies on special culture medium were selected for biochemical identification (Rauch and Nauen, 2003; Alsina and Blanch, 1994) and serological typing (Takeuchi et al. 2018; Dümen et al. 2015). The results obtained by this method are accurate. However, it requires at least 4–7 days to get correct results. Other methods, such as ELISA test (Jiao et al., 2019) relying on antigen-antibody reactions, are susceptible to environmental effects such as pH and temperature. Meanwhile, the synthesis and preparation of antigen and antibody are expensive (Tang et al., 2015). Therefore, it is a hot issue to research a novel, rapid, and sensitive detection platform for pathogenic microorganisms which people pay close attention to (Pashazadeh et al. 2017).

Structure and characteristics of aptamer

In the 1990s, a new technique for systematic evolution of ligands by exponential enrichment, commonly known as SELEX technology (Moon et al. 2015), has been developed. Aptamer is a certain sequence of oligonucleotides which were multiple cycles screened from randomly generated DNA or RNA library by SELEX technology (Mondal et al. 2015; Hong and Sooter, 2015). Aptamer selected by SELEX technology have high specificity and high affinity for the target (Xiao et al. 2012). The methods of screening aptamer (Teng et al. 2016) by SELEX techniques include screening based on different fixed medium, fluorescent magnetic bead SELEX (Lin et al. 2015), capillary electrophoresis SELEX (Mosing et al. 2005), and cell SELEX (Ara et al. 2012). After SELEX screening and enrichment, the aptamer fragments needed are intercepted, and the base number of the intercepted aptamer is about 25–40 bp. As shown in Fig. 1, the common structures of aptamer (Lin and Pate, 1997) are spiral, hairpin, stem ring, convex ring, clover, and pseudo knot. It has been reported that aptamers have many advantages of easy synthesis, high stability, good repeatability, and low price through the research of aptamer for many years. Furthermore, aptamer can bind to many targets exclusively (Templier et al. 2016), such as cells, viruses, toxins (Ruscito et al. 2016), proteins (Tabarzad and Jafari, 2016), and vitamins (Ruscito and DeRosa 2016; Pfeiffer and Mayer, 2016; Fooladi et al. 2016).

The application of aptamer has come to be used for more and more field in recent years. In the field of clinical medicine, aptamer conjugated with drugs are delivered to the target organ (Chen et al. 2017; Chandola et al. 2016; Mokhtarzadeh et al. 2016), which can overcome the disadvantages of most drugs that they are not selective and may miss the target organs during treatment. In the field of medical biology (Zhang et al. 2016), aptamer plays a role as diagnostic tools in therapy (Sakyi et al. 2016; Mercier et al. 2017). As for some, clinical symptoms are not obvious or diseases are prone to misdiagnosis, identifying the pathogenic microorganism in human body can reduce the possibility of drug abuse (Chu et al. 2006). It is a very important and effective way of screening out specific aptamer by SELEX to directly diagnose the disease caused by pathogenic bacteria. In environmental protection, aptamer can be combined with many heavy metal ions (Yang et al. 2017; Wu et al. 2020), linked with fluorometry, colorimetry, electrochemistry, and other technologies to carry out quantitative detection of heavy metal ions (Nguyen et al.

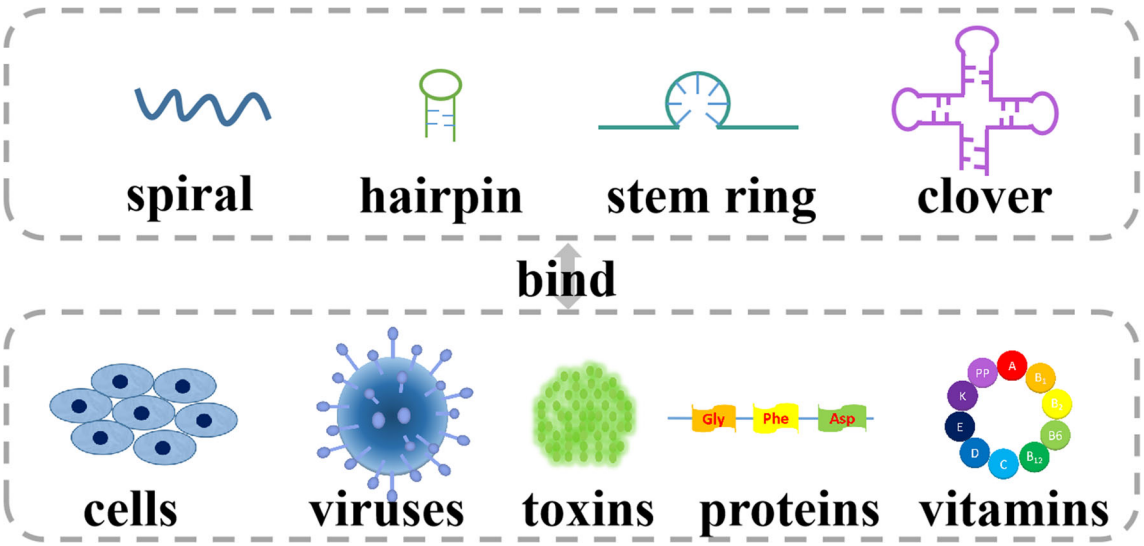

Fig. 1 Structure and application fields of aptamer

2018). In the aspect of microbiological detection, aptamer can be conjugated with a variety of bacteria and toxins, forming the complex so as to produce the measured signals (Sharma et al. 2017; Seok et al. 2016).

Combination of aptamer and biosensor

Aptamer can be combined with a variety of target specifically or non-specifically, so as to capture the target. These targets can be bacteria, viruses, or toxins. According to the different targets, different pretreatment methods are selected to extract the target sequence, so that the aptamer can specifically combine with the target sequence. So aptamers are usually used in biosensor technology to detect the target qualitatively or quantitatively. Biosensor (Wu et al. 2019; Chen et al. 2019) means that the compound can combine with the molecular recognition element specifically, then produce a complex which has special optical or electrical properties. It can be transformed into output electric signal or optical signal by signal converter, and then the substance to be tested can be detected qualitatively or quantitatively after amplification and display of electronic system. The simple principle is shown in Fig. 2. According to the converted signal, the biosensor can be roughly classified. The conversion of optical signal is derived from optical biosensor (Indyk et al. 2019), and electrochemical biosensor is to bring about the conversion of electrical signal (Idili et al. 2019). Optical biosensors can be divided into ordinary optical biosensors (Yetisen et al. 2019) and fluorescent biosensors (Prandi et al. 2019) according to the type of light.

Aptamer can be used as molecular recognition elements in biosensor technology. Due to the good characteristics of the aptamer, it can form a stable structure after capturing the target, and generate an easily detectable signal, which is convenient for measuring the target. Also based on the classification of biosensors, after aptamer is applied to biosensors, it can be divided into optical aptamer biosensors (Chen et al. 2018) and electrochemical aptamer biosensors (Wu et al. 2019). As for the method of promoting bacteria step by step, it takes at least 4–7 days from the incubation of the target bacteria to the final conclusion. Aptamer sensor can produce results in a very short time such as 30 min, if the aptamer material has been prepared in advance. So compared with the method of promoting bacteria step by step, the aptamer biosensor has a short detection cycle, a simple process, a stable output signal, a wide range of detection objects, and good sensitivity and selectivity. This article summarized the research and development of aptamer biosensor technology in the detection of microorganisms, and introduced the application of aptamer-based detection in three aspects including bacteria, virus, and toxin.

Detection of bacteria by optical aptamer biosensor

The light emitted by ordinary optical sensors is ultraviolet or visible light, with wavelengths in the range of 400–760 nm and 10–400 nm, respectively. Light signals can be generated by substances that can absorb or reflect visible light. Common substances include methyl orange, malachite green, nanoparticles, horseradish peroxide, and some metal ion solutions. These materials are easy to obtain and the principle of producing light effect is simple, so ordinary optical biosensors have been widely studied.

An optical colorimetric method for the detection of *Salmonella typhimurium* ATCC 14028 (*S. typimurium*) using aptamer technology was introduced by Yi et al. (Yi et al. 2019). The principle is shown in Fig. 3. Carboxymethyl chitosan (Wu et al. 2020), aptamer, and gold nanoparticles form a new material for capturing target. In the presence of target, it

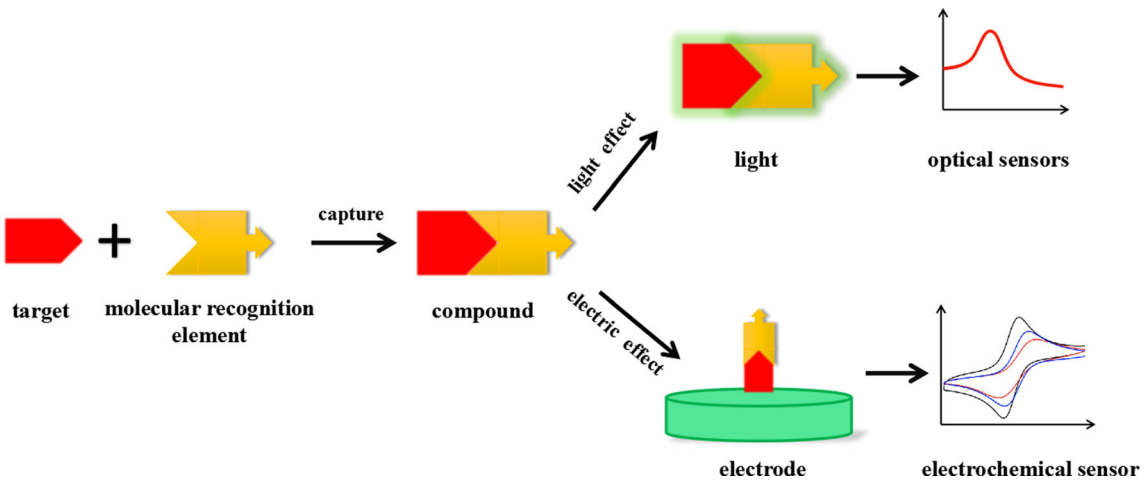

Fig. 2 Simple principle of optical biosensor and electrochemical biosensor

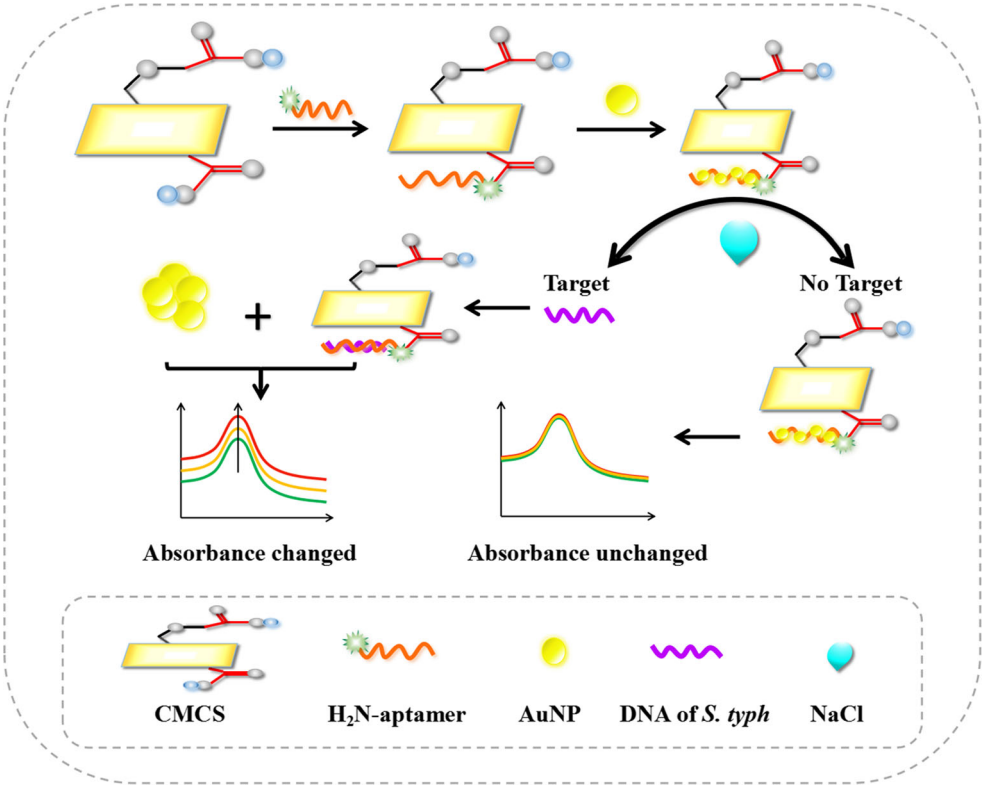

Fig. 3 The schematic diagram of optical aptamer biosensor for detecting *S. typimurium*. Reprinted with permission from Yi et al. (2019)

will be bound by the aptamer, and this changes the structure of the compound. After the configuration changes, gold nanoparticles fall off the compound. Free gold nanoparticles in solution can produce detectable optical signals. By studying the relationship between the optical signal and the concentration of the target bacteria, the target bacteria can be measured. The detection limit of this method is as low as 16 cfu/mL. It has good specificity and accuracy.

Equally, a colorimetric aptamer biosensor was also reported by Wu et al. (Wu et al. 2015) which is to detect *Vibrio parahaemolyticus* ATCC 17802 (*V. parahaemolyticus*) based on the catalysis principle of horseradish peroxidase. In this method, horseradish peroxidase combined with gold nanoparticles and aptamer complexes are signal probes, and the magnetic nanoparticles bound with specific aptamer are capture probes. When *V. parahaemolyticus* was present, the aptamer can bind to the target specifically, forming a sandwich composite with the structure of signal probes-target-capture probes. Horseradish peroxidase immobilized on the surface of the complex can catalyze the reaction of substrates, 3, 3′, 5, 5′-tetramethylbenzidine (TMB) and hydrogen peroxide, producing measurable optical signals. As carrier of horseradish peroxidase, gold nanoparticles can make the introduction of a large number of horseradish peroxidase in the system to play the effect of signal amplification, increasing the sensitivity of this method. There is a linear relationship between the optical signal and the logarithmic concentration of *V. parahaemolyticus* with a range of $10–10^6$ cfu/mL. This method can be used for simple detection of biological molecules in food samples.

Ma et al. developed a simple and rapid colorimetric aptamer sensor for the detection of *S. typhimurium* ATCC 14028 (Ma et al. 2017). The aptamer identifying *S. typhimurium* specifically was screened by SELEX technology, and then was modified on the surface of gold nanoparticles through the electrostatic interaction between the exposed base. After the addition of *S. typhimurium*, the aptamer was attached to the bacterium preferentially, resulting in the release of gold nanoparticles. As concentration of the *S. typhimurium* increased, more free gold nanoparticles were produced. The concentration of *S. typhimurium* can be determined quantitatively by measuring the absorbance of gold nanoparticles with UV visible spectrophotometer. The detection limit of this method is 56 cfu/mL, and it can be used for rapid detection of *S. typhimurium* without complicated instruments.

In addition to optical colorimetry, the fluorescent aptamer biosensor constructed by introducing fluorescent substances into aptamer sensor is also a common detection method. Fluorescent substances can be roughly divided into two types. One is the substances that can produce fluorescence by themselves, such as acid eosin, fluorescent yellow, red mercury, and other fluorescent dyes. After absorbing ultraviolet or visible light, these

fluorescent dyes can convert short-wavelength light into longer-wavelength visible light and reflect it, so as to produce fluorescence. The other is that the substance itself cannot produce fluorescence, but it can react with other substances in the system to make the substance whose fluorescence is inhibited to produce fluorescence again. Or it can quench the original fluorescence in the system, and reacts the content of the measured substance through the change of fluorescence intensity.

For example, Zhang and his colleagues designed a new type of capture probe. It is composed of aptamer and the target sequence of *Salmonella enteritidis* (*S. enteritidis*), which can directly identify target bacteria (Zhang et al. 2016). The target sequence can be hybridized with the aptamer by special design. In the presence of *S. enteritidis*, the bacterium bound to the aptamer specifically in the capture probe releases the single-stranded target sequence. The single-stranded target sequence is hybridized with the antisense sequence of the template-G-quadruplexes to form a double chain. The double chain can form a large number of complementary sequences through the action of endonuclease. This complementary sequence has G-quadruplexes sequence (G1) and 3-terminal connector, and then hybridizes with template two to produce a large number of complementary sequences. Unlike the above, the complementary sequence contains the sequence G2 of the G-quadruplexes. These G2 sequences can be hybridized to the template, initiating new reactions and providing raw materials for the circulation of the system. During the whole reaction process, G1 or G2 can form g-four-chain structure with the connector, respectively. A fluorescent dye combined with a G-quadruplexes can produce the fluorescent signal, consequently, it is convenient to detect *S. enteritidis* by testing the intensity of the fluorescent signal. This method has no need to label and modify the target bacteria and has high sensitivity. The limit of detection is proved to be 60 cfu/mL. Furthermore, it can also be applied in the detection of other pathogens by screening numerous aptamers with various sequences.

Liu and Su designed a novel fluorescent aptamer biosensor for the detection of *H. pylori* (Liu and Su, 2017). The aptamer was modified by amino groups, whereafter binding to carboxyl groups on CuInS2 quantum dots to form aptamer-quantum dots biosensor. In the absence of DNA of *H. pylori*, the graphene oxide was adsorbed to aptamer-quantum dots biosensor, inhibiting the fluorescence of quantum dots. While DNA of *H. pylori* was introduced to the system, DNA of *H. pylori* combined with the aptamer-quantum dots biosensor and the interaction between graphene oxide and aptamer-quantum dots biosensor was broke. Quantum dots emitted stronger fluorescent signals. In view of the above, a linear relationship between fluorescence intensity ratio and the concentration of *H. pylori* is established, and the bacterium can be detected quantitatively in the range from 1.25 to 875 pmol/L with the detection limit of 0.46 pmol/L. This method does not introduce additional dyes but directly uses fluorescent substance, so it has the advantages of low background noise, high sensitivity, and low toxicity.

In addition to the methods described above, Table 1 also introduces other methods for the detection of microorganisms by optical aptamer biosensor. It briefly summarizes the detection methods, objects, strategies, and detection limits of this method. It can be seen that the research on the detection of microorganisms by optical aptamer biosensor has made a lot of progress, and the detection limits have reached a lower level.

Generally speaking, the optical aptamer sensor is to establish the linear relationship between the intensity of light (fluorescence) and the concentration of the measured substance by detecting the change of light (fluorescence) signal, so as to realize the qualitative or quantitative detection of the measured substance. It has a simple construction method. The optical signal can be detected by ultraviolet visible spectrophotometer or fluorescence detector. The operation of the two kinds of instruments is simple and the detection time is short. In addition, the optical method can judge whether the target is detected by the naked eye according to the color change of the system, which provides a good basis for building fast and convenient detection equipment.

Detection of bacteria by electrochemical aptamer biosensor

The electrochemical sensor can detect the target by measuring the change of current signal in the system. Aptamer can be modified on the electrode surface to capture the target and change the electrical signal. Generally, after the aptamer is screened out, it is modified with sulfhydryl group, and then the sulfhydryl group interacts with the electrode to form chemical bond. So the aptamer can be fixed on the electrode. Besides sulfhydryl group, avidin and biotin can also fix the aptamer to the electrode. Not only the aptamer is modified on the electrode but also other materials that contribute to the change of the electrical signal, such as nanoparticles and graphene, can be modified. It can improve the sensitivity of the electrochemical aptamer sensor.

Abbaspour et al. prepared a dual aptamer sandwich sensor for the detection of *S. aureus* ATCC 25923 with high sensitivity and selectivity (Abbaspour et al. 2015). The method used two specific aptamers from *S. aureus*, a primary anti-*S. aureus* aptamer and a secondary anti-*S. aureus* aptamer. After the former is biotinylated, it binds to an avidin-coated magnetic bead. Primary anti-*S. aureus* aptamer was successfully immobilized on the magnetic bead. Magnetic beads play a role as a carrier. The secondary anti-*S. aureus* aptamer binds to silver nanometers. Once adding *S. aureus* to the solution, an aptamer-*S. aureus*-silver nanoparticle sandwich complex was formed, followed by detecting the change of the electric signal

Table 1 Method for detecting microorganisms by optical aptamer biosensor

Detection method	Detection objects (sample type)	Strategy	LOD	Ref
Colorimetry	*S. typimurium* (milk)	Gold nanoparticles modify aptamer	56 cfu/mL	Ma et al. (2017)
Colorimetry	*V. parahemolyticus* (water)	Horseradish peroxidase catalytic substrate	10 cfu/mL	Wu et al. (2015)
Colorimetry	*E. coli* (food extract)	Gold nanoparticles bind to target DNA fragments	< 1 logcfu/g	Quintela et al. (2015)
Colorimetry	*S. typimurium* (serum)	The binding affinity and specificity of aptamer are determined by fluorescence binding assays	10^2 cfu/mL	Lavu et al. (2016)
Colorimetry	H3N2 virus (pure virus)	Enzyme catalyze hydrogen peroxide to reduce gold ions	11.16 μg/mL	Chen et al. (2016)
Colorimetry	Patulin (food extract)	An enzyme-chromogenic substrate system	48 pg/mL	Wu et al. (2016)
Fluorescence	*S. enteritidis* (food and water)	Fluorescent dye bind with a G-quadruplexes	60 cfu/mL	Zhang et al. (2016)
Fluorescence	*H. pylori* (milk)	Aptamer-CuInS2 quantum dots sensor	0.46 pmol/L	Liu et al. (2017)
Fluorescence	*S. sonnei* (food extract)	A sandwich complex pair of SS-3 and SS-4	10^3 cells/mL	Song et al. (2017)
Fluorescence	*S. aureus* (whole blood)	Aptamer-functionalized silica magnetic nanoparticles	682 cfu/mL	Borsa et al. (2016)
Fluorescence	H1N1 virus (pure virus)	A sandwich-based aptamer assay is performed on an integrated microfluidic system automatically	0.032 HAU	Tseng et al. (2016)
Fluorescence	aflatoxin M1 (milk)	The quenching-dequenching mechanism	5.0 ng/kg	Sharma et al. (2016)
Absorbance	*L. monocytogens* (milk)	Vancomycin and aptamer recognize *L. monocytogenes* at different sites	5.4×10^3 cfu/mL	Zhang et al. (2016)
Chemilumine-scence	*E. coli* (milk)	*E. coli* O157:H7 bind with aptamer-conjugated 6-FAM	4.5×10^3 cfu/mL	Khang et al. (2016)

from silver nanoparticles by anodic stripping voltammetry. The addition of silver nanoparticles changes the electrical signal of the system. In this method, the electrical signals were detected by electrochemical stripping voltammetry, and the detection limit is as low as 1.0 cfu/mL. It is a practical method of high sensitivity, fast and low cost, which is suitable for detecting trace of bacteria in samples due to its ultra-low limit of detection.

Besides the common glassy carbon electrode, platinum electrode and gold electrode are also common electrochemical electrodes. Appropriate electrodes can be selected according to different targets or measurement methods. A gold interdigitated electrode is an electrode with a shape of a finger or comb, and a periodic pattern engraved on the electrode surface. It is one of the most common micro spacing electrode structure. Lian et al. developed a piezoelectric sensor based on gold interdigitated electrode using aptamer bound with graphene for the detection of *S. aureus* (Lian et al. 2015). The graphene was bound to gold interdigitated electrode under the action of cross-linking agent tetrafluoroborate. Then, the aptamer-targeted *S. aureus* was fixed to graphene as biological recognition elements. Finally the electrode was connected with a series of piezoelectric quartz crystals. In the presence of *S. aureus*, it is bound with aptamer specifically, then the aptamer was separated from the surface of graphene. The parameters of the electrode surface changed, and varying frequencies responded to the piezoelectric quartz crystal. The results show that the resonant frequency was linearly related to the concentration of *S. aureus* and the detection limit is 41 cfu/mL. This method is sensitive and fast, and has the characteristics of graphene and gold interdigitated electrode, increasing the rate of electron transfer. In addition, the electrode is low-cost, easy to regenerate, and recycling reuse, so that it can reduce environmental pollution.

In order to further improve the sensitivity of electrochemical aptamer biosensors, it is also a good method to combine the rolling circle amplification technology with biosensor. Rolling circle amplification is a new method for isothermal nucleic acid amplification, in which short DNA primers are complementary to cyclic DNA templates and convert a variety of nucleotides into single-stranded DNA by catalyzing enzyme (Hao et al. 2017). This method can amplify DNA and RNA directly, and enhance the signal of target nucleic acid. The technology of mimetic peroxidase based on rolling circle amplification was firstly used in the electrochemistry by Guo and his workmates (Guo et al. 2016). They have designed a non-labeled, high-sensitivity, and fast electrochemical sensor for the detection of *Escherichia coli* ATCC 25922 (*E. coli*). A primer probe of aptamer was synthesized. It consists of an aptamer-targeted *E. coli* and a primer sequence complemented with an annular probe which has two G-quadruplex. When target bacteria existed, the bacteria were specifically bound to aptamer, forming a free primer sequence complemented with an annular probe. Basing on the principle of rolling circle

amplification, the sequence can be transformed into single-stranded DNA under the action of the enzyme, resulting in the formation of G-quadruplex oligomers on the electrode. G-quadruplex oligomers interacted with hemoglobin under the effect of potassium ion, subsequently folded to form a complex of G-quadruplex and hemoglobin. The complexes have strong catalytic activity of hydrogen peroxide, which can set up an obvious electrochemical reaction. It requires no other complicated procedures and has high sensitivity and accuracy; moreover, this method has the advantages of convenience and cheap cost. The detection limit is proved as 8 cfu/mL.

Besides the electrochemical methods described above, numerous electrochemical methods are listed in Table 2. It can be seen from the table that there are more detection methods for electrochemical aptamer biosensors than optical aptamer sensors. Optical sensor can detect absorbance or fluorescence intensity. While electrochemistry can detect electrical signal, resonance frequency, piezoelectric signal, and so on. Electrochemical aptamer biosensors have low detection limits, high sensitivity, fast detection speed, and easy-to-carry equipment, and are the focus of convenient and rapid detection research in recent years.

Detection of bacteria by other aptamer sensor

In addition to common optical and electrochemical aptamer biosensors, aptamer can be used to detect microorganisms in combination with many other techniques such as the surface-enhanced Raman scattering and fluorescence resonance energy transfer. The development and utilization of these technologies make the application of aptamer not limited to optics or electrochemistry. In the field of detection, aptamer technology has a very wide range of applications.

The surface-enhanced Raman scattering, commonly known as SERS, refers to the determination of samples adsorbed on the surface of glial metal particles by Raman spectroscopy, based on the principle that the Raman scattering signal of the adsorbed molecule is greatly enhanced than the ordinary Raman scattering signal with the enhancement of electromagnetic field. The nanoscale rough metal surfaces is used as a substrate in the process of Raman enhancement, such as gold and silver. Molecules adsorbed on this surface can increase Raman intensity by several orders of magnitude. Duan et al. researched a SERS substrate for the detection of *V. parahemolyticus* ATCC 17802 (Duan et al. 2016), which was prepared by synthetic silica and gold core-shell nanoparticles (Hamidi-Asl et al. 2016). The researchers have screened two specific aptamers of *V. parahemolyticus*. On the one hand, aptamer 1 was fixed to the surface of the silica and gold core-shell nanoparticles, on the other hand aptamer 2 was bound to a cyanine dye 3. When *V. parahemolyticus* was present, aptamer 1-target–aptamer 2 sandwich complexes were formed. Based on the linear relationship between the SERS signal and the concentration of *V. parahemolyticus*, the intensity of the Raman signal from the dye was quantitatively detected, and the limit of detection is 10 cfu/mL. The method has wide linear range and low detection limit, and has been successfully applied to the detection of *V. parahemolyticus* in food. The method is also applied to the detection of *S. typhimurium* by designing different

Table 2 Method for detecting microorganisms by electrochemical aptamer sensor

Detection method	Detection objects (sample type)	Strategy	LOD	Ref
Electrochemistry	*S. aureus* (water)	The interaction between biotin and streptavidin	1.0 cfu/mL	Abbaspour et al. (2015)
Piezoelectricity	*S. aureus* (water)	Aptamer bound with graphene	41 cfu/mL	Lian et al. (2015)
Potentiometry	*V. alginolyticus* (water)	Solid-contact polycation-sensitive membrane electrode	10 cfu/mL	Zhao et al. (2016)
Electrochemistry	*E. coli* (milk)	Mimetic peroxidase based on rolling circle amplification	8 cfu/mL	Guo et al. (2016)
Electrochemistry	*S. typhimurium* (food)	Entropy-driven molecule witch signal amplification	13 cfu/mL	Zong et al. (2016)
Electrochemistry	Proteins (serum)	A surface formed aptamer-protein-antibody complex	100 fmol/L	Diba et al. (2015)
Impedance	*S. typhimurium* (apple juice samples)	A diazonium-supporting layer onto screen-printed carbon electrodes (SPEs)	6 cfu/mL	Bagheryan et al. (2016)
Impedance	*E. coli* (water and food)	EIS gap capacitance biosensor	2×10^4 cfu/mL	Dua et al. (2016)
Impedance	H3N2 viruses (pure virus)	Impedimetric glycan-based biosensor	13 vp/μL	Hushegyi et al. (2016)
Impedance	H5N1 viruses (pure virus)	Microfluidics flow cell and an interdigitated microelectrode	0.0128 HAU	Lum et al. (2015)
Impedance	Anatoxin-a (water)	A gold electrode using the isulfide modified aptamer	0.5 nmol/L	Elshafey et al. (2015)
Impedance	Norovirus (food and water)	A recognition affinity peptide-based electrochemical platform	7.8 copies/mL	Hwang et al. (2017)

aptamer and SERS substrates, and similarly, satisfactory results were obtained (Duan et al. 2016).

Fluorescence resonance energy transfer is also known as FRET. In short, FRET refers to the fluorescence group as a donor, whose emission spectrum overlaps the absorption spectrum of the group as a receptor. When the two groups have a certain distance, the phenomenon of fluorescence energy transfer from the donor to the receptor can be observed. The donor group is generally a substance that can produce fluorescence by itself. If the fluorescence quantum yield of the receptor group is zero, the fluorescence quenching will occur after energy transfer. If the receptor group can also emit fluorescence, it will transfer from the donor fluorescence to the receptor fluorescence. So FRET technology can be combined with an aptamer as a means of detecting bacteria. Jin et al. designed a specific aptamer sensor based on FRET to detect bacteria, which is together with the upconversion nanoparticles (Jin et al. 2017). The upconversion nanoparticles are composed of inorganic substrates and rare earth-doped ions embedded in them, which have the properties of upconversion luminescence, thus, it can be used as a means of detection (Cheng et al., 2017a). Gold nanoparticles conjugated with aptamer served as receptors, and upconversion nanoparticles were modified by complementary DNA as donors. In the absence of target bacteria, the fluorescence spectrum produced by the upconversion nanoparticles overlapped with the absorption spectrum of the gold nanoparticles owing to the combination of aptamer and its complementary DNA. Fluorescence resonance energy transfer occurred, resulting in upconversion fluorescence quenching. On the contrary, when target bacteria existed, aptamer preferentially conjugated with target bacteria, destroying the combination of the aptamer and complementary DNA, and restored upconversion fluorescence. The linear range of fluorescence intensity and concentration of target bacteria was established by detecting the fluorescence intensity, and the detection limit is 3 cfu/mL. The method used the characteristics of upconversion fluorescence to avoid the fluorescence of impurity molecules in real samples, which is highly specific to target bacteria.

In addition to the detection of single-target bacteria, the combination of these technologies and aptamer can also be used to detect a variety of bacteria at the same time. Hasan Kurt et al. introduced quantum dots together with upconversion nanoparticles to design an aptamer sensor that can detect multiple pathogens simultaneously (Kurt et al. 2016). The fluorescence spectra of quantum dots and the upconversion nanoparticles were obtained, respectively, under the UV excitation at 325 nm and near-infrared excitation at 980 nm, therefore, it can detect *S. aureus* ATCC 29,213 and *S. typhimurium* ATCC 14,028 at the same time. The method is applied to detect multiple substances simultaneously by using more quantum dots and non-overlapping fluorescence spectrum.

Except the optics and electrochemistry, other techniques combined with aptamer for the detection of microorganisms are listed in the Table 3. There are quartz crystal microbalances, magnetic particles, and quantum dots that can be combined with aptamer for the detection of bacteria. According to the contents of the three tables, the detection of optical and electrochemical sensors combined with aptamer technology is the current research focus and the joint application of other new technologies is also being studied.

Detection of virus by aptamer biosensor

In terms of detection objects, not only the detection of bacteria has received the attention of researchers but also the detection

Table 3 Method for detecting microorganisms by other aptamer sensor

Detection method	Detection objects (sample type)	Strategy	LOD	Ref
Raman signal	*V. parahemolyticus* (water)	A SERS substrate prepared by silica and gold core-shell NPs	10 cfu/ml	Duan et al. (2016)
Raman signal	*S. typhimurium* (food)	A SERS substrate bearing Au and Ag core/shell NPs	15 cfu/ml	Duan et al. (2016)
FRET	Bacteria (food and water)	Fluorescence resonance energy transfer together with the upconversion nanoparticles	3 cfu/ml	Jin et al. (2017)
Quantum dots	*S. aureus* *S. typhimurium* (food)	Quantum dots together with upconversion nanoparticles	16 cfu/ml 28 cfu/ml	Kurt et al. (2016)
Biosensor	*S. aureus* (water)	Aptamer-based magnetoelastic sensor	5 cfu/ml	Rahman et al. (2015)
Quartz crystal microbalance	*S. typhimurium* (food)	QCM-based aptasensor	10^3 cfu/ml	Wang et al. (2017)
Surface plasmon resonance	Ochratoxin A (food)	Anti-OTA aptamer immobilized sensor chip	0.005 ng/ml	Zhu et al. (2015)
Biosensor	Enterotoxin C1 (food)	Aptamer-based quantification of SEC1	6 ng/ml	Huang et al. (2015)
Atomic force microscopy	*S. typhimurium* (food)	The surface membrane model	3×10^4 cfu/ml	Wang et al. (2017)

of viruses is worthy of attention. Among them, the influenza virus has many subtypes and has a fast mutation speed, which causes harm to the social population almost every year. Influenza viruses are very common around the world, and they have a wide range of infection and a high speed of transmission. Influenza A virus is prone to mutate and produces many subtypes, such as H1N1, H5N1, H9N2, and so on, which endanger human health and public environment.

This part mainly introduced the method of detecting influenza virus with aptamer biosensor technology (Wang et al. 2016). Pang et al. designed a fluorescent aptamer sensor to detect recombinant hemagglutinin protein of H5N1 influenza virus in human serum (Pang et al. 2015). The schematic illustration is presented in Fig. 4. Firstly, silver and silica core-shell nanoparticles were prepared, and then aptamer screened by SELEX were immobilized on the surface of the nanoparticles. Thiazole orange was used as a fluorescent marker. When recombinant hemagglutinin protein did not exist in the reaction system, thiazole orange in free state did not emit fluorescence. Once adding recombinant hemagglutinin protein, an aptamer was combined with it specifically, and then binded with the thiazole orange. At this point, thiazole orange can emit fluorescence. Thiazole orange was immobilized on the surface of silver and silica nanoparticles, it can mediate the surface plasmon resonance to enlarge the fluorescence signal, improving sensitivity and accuracy of this method. The detection limit is 3.5 ng/mL. The advantages of this method is that it is not necessary to modify the dye on the aptamer beforehand, thereby reducing the background noise. Compared with the traditional detection of antigen-antibody reaction, this method greatly shortened the detection time, the whole process can be completed in 30 min.

As the same is true for the detection of H5N1 virus, Karash et al. prepared an impedance aptamer sensor to detect H5N1 virus directly (Karash et al. 2016). The schematic representation of this method is shown in Fig. 5. The H5N1 aptamer was labeled with biotin as capture elements, and bound with streptavidin fixed on the surface of gold interdigitated microelectrode, and polyethylene glycol–blocked microelectrode. In the presence of H5N1 virus, aptamer fixed on the surface of gold interdigitated microelectrode were combined with the virus specifically, causing the variation of impedance and the variable signal was measured by impedance analyzer. Thiocyanuric acid were added, forming a network structure of gold nanoparticles/H5N1 aptamer/thiocyanuric acid in order to expand the electrical signal and increase sensitivity. The detection limit of this method is 0.25 HAU, and it has high specificity and selectivity. Other subtypes of viruses, such as H5N2 and H5N3, can produce negligible impedance changes. The steps are simpler and faster, and can provide the basis for the development of portable sensors.

Besides, influenza virus can also be detected by fluorescent aptamer biosensor and impedance aptamer biosensor. Wang et al. designed a kind of electrochemical aptamer sensor combined with quartz crystal microbalance technology (Afzal et al. 2017) for the detection of influenza virus (Wang et al. 2017). Similar to the methods used by Sardar Karash, a specific aptamer-targeted virus is screened by SELEX, and the results are measured by the changes of the electric signal. However Wang et al. made a nanoporous gold film with a thickness of 120 nm and a pore size of 20 nm, and the gold film was immobilized on the surface of the gold electrode to form a nanowell-based electrode (Li et al. 2011). The aptamer functionalized by amino was linked to quartz crystal microbalance aptamer sensor by covalent binding, thereby reducing the resonance frequency of the sensor, and greatly shortened the reaction time, making the reaction complete within 10 min. The nanoporous gold film is used to form nanowell-

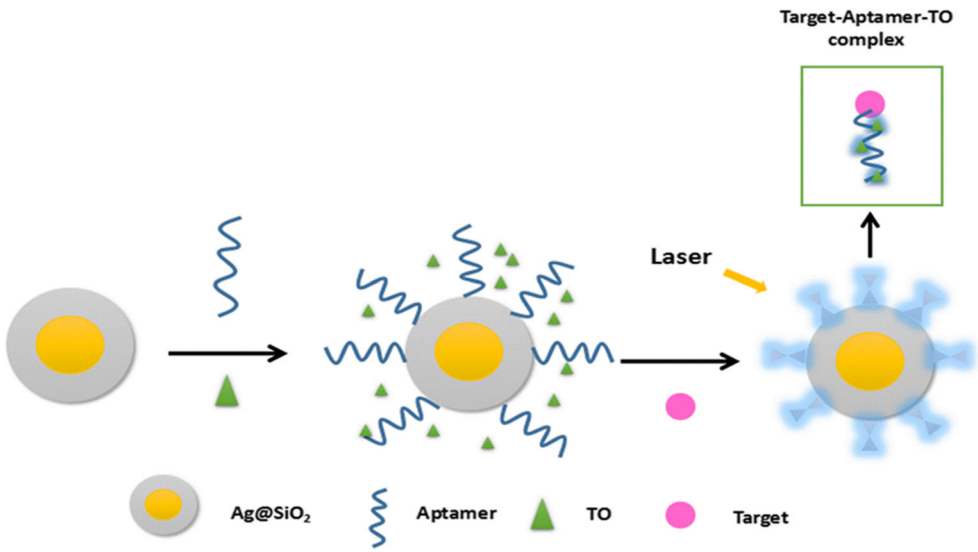

Fig. 4 Illustrative diagram of a fluorescent aptamer sensor to detect recombinant hemagglutinin protein of H5N1 influenza virus in human serum Pang et al. (2015)

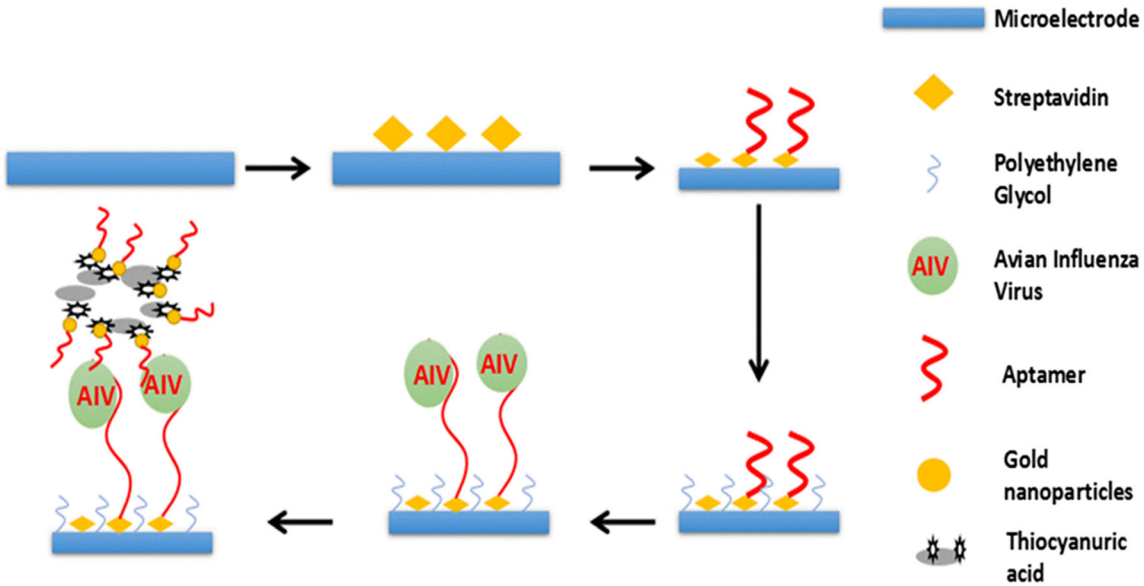

Fig. 5 Illustrative diagram of an impedance aptamer sensor to detect H5N1 virus directly Karash et al. (2016)

based electrodes, which can immobilize more aptamer on the electrodes, and the immobilized aptamer are five times higher than that without the nanowell structure.

Detection of toxins by aptamer biosensor

Besides bacteria and viruses, some toxins produced by bacteria or fungi can also be detected by aptamer technology (Bazin et al. 2017; Rhouati et al. 2016). Lv et al. researched a new fluorescence sensor for the detection of ochratoxin A (Lv et al. 2016; Lv et al. 2017). The schematic illustration is shown in Fig. 6. The specific aptamer of ochratoxin A (OTA) (Schax et al. 2015) is modified by carboxyfluorescein (FAM). When the target is not present, DNA-FAM is adsorbed to the surface of single-walled carbon nanohorns (SWCNHs). In this case, the fluorophore and the quencher (SWCNHs) are close to each other, resulting in fluorescence quenching. When the target is present, the aptamer binds to the target and is far away from SWCNHs, and the fluorophore is separated from the quencher to generate fluorescence. Concentration of ochratoxin A can be measured according to fluorescence intensity quantitatively. The limit of detection is 17.2 nmol/L. The method has the advantages of carbon nanomaterials with high sensitivity and selectivity, and the detection is rapid and simple.

Li et al. synthesized an aptamer sensor for the detection of aflatoxin AFB1, combined with the technology of surface-enhanced Raman scattering (Li et al. 2017). The schematic representation is illustrated in Fig. 7. A variety of complex reactions occur on the surface of the gold membrane, such as the hybridization of aptamer and complementary DNA, and the hydrolysis of double-stranded DNA by exonuclease to produce single-stranded DNA, which will be used as raw materials for the next cycle. These DNA can be combined

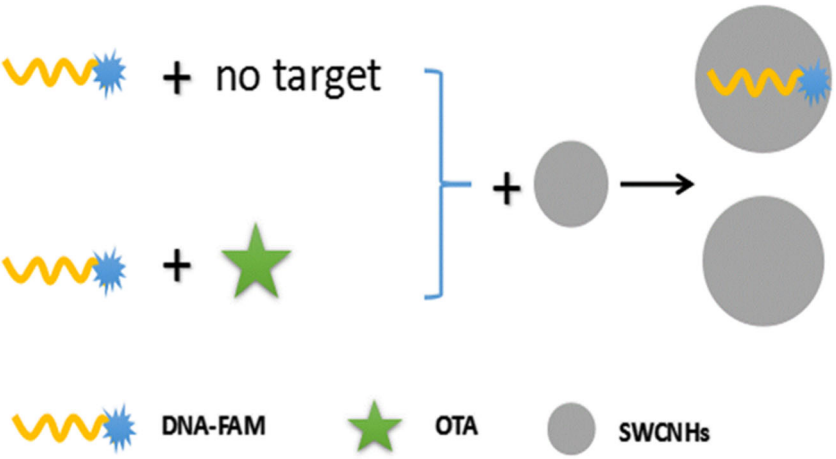

Fig. 6 Illustrative diagram of a new fluorescence biosensor for the detection of ochratoxin A. Reprinted with permission from Lv et al. (2016)

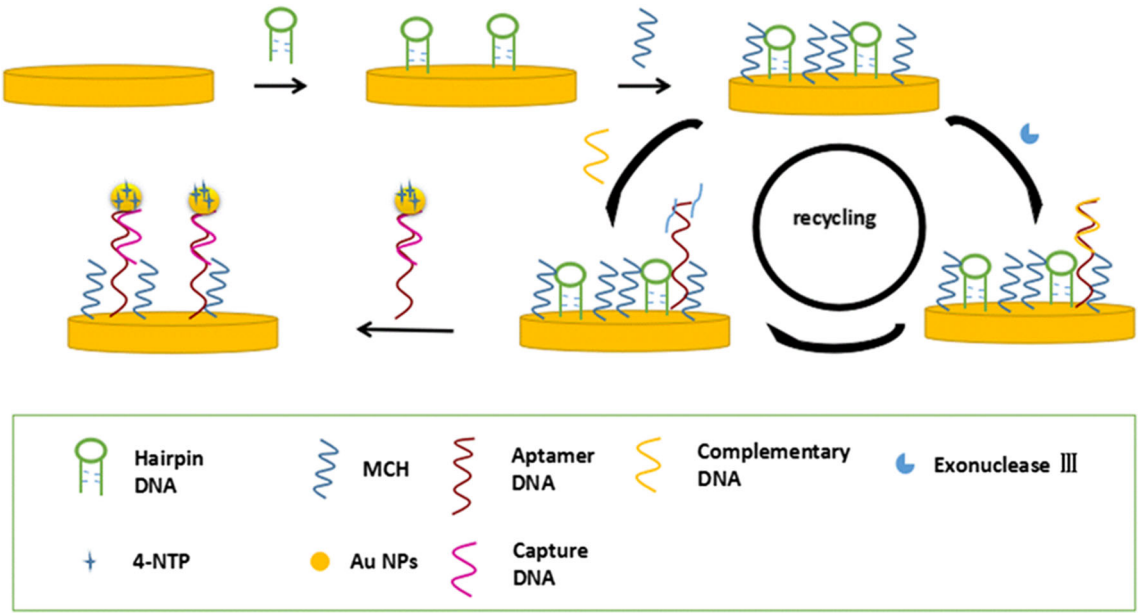

Fig. 7 Illustrative diagram of an aptamer sensor for the detection of aflatoxin AFB1, combined with the technology of surface-enhanced Raman scattering. Reprinted with permission from Li et al. (2017)

with a large number of aptamer, improving the number of immobilized aptamer. According to the electrochemical impedance spectroscopy and the spectrum of surface enhanced Raman scattering, the concentration of AFB1 were detected, and the detection limit is 0.4 fg/mL.

By combining the advantages of exonuclease-assisted circulation amplification and enhanced signals of surface-enhanced Raman scattering, the sensitivity and specificity of this method are improved. Moreover, some complex pretreatment steps can be completed ahead of time. So, the rapid detection will be carried out at the point of care, providing a train of thought for portable sensor research.

Conclusion

In conclusion, this article reviewed the research and application of aptamer technology in microbiological detection including bacteria, viruses, and toxins in recent years. Ordinary optical aptamer sensors and electrochemical aptamer sensors, as the most common detection methods, have been widely used in the field of clinical medicine, drug targeting, and microbial detection. Aptamers have a wider range of applications than antibodies or traditional detection methods because they can be combined with a variety of techniques. For example, aptamer can be combined with roll ring amplification technology, Raman scattering technology, quantum dots, surface plasmon resonance technology, etc. to improve the sensitivity of the detection method. Various aptamer sensors have their own unique advantages, such as the optical aptamer sensor, which can judge the positive result quickly by naked eye depending on the change of absorbance. Fluorescence aptamer sensor have low background interference and high signal intensity. According to the detection limits in the three tables, the electrochemical aptamer sensor has a very low detection limit, so its sensitivity is high. However, aptamer technology still has shortcomings. Some kinds of aptamers are not very selective. In the process of material preparation, the configuration and properties of aptamers may be changed due to temperature, pH, and other experimental factors, so the target objects cannot be well captured during detection. Another problem is that although some aptamer can get good results in the buffer, they cannot be applied well in real samples. This may be because most of the factors were optimized during the experiment, and the buffer composition was simple, so that the aptamer had a good performance in the buffer. However, due to the complex composition of actual samples, the detection results are often not as good as the experimental results. How to better apply laboratory methods to practice has always been a problem to be broken through. These problems need to be solved in the future research.

Author contributions DP conceived the ideas and concepts of the manuscript. All authors wrote, reviewed, and approved the manuscript.

Funding This work was supported by the National Science Foundation of China under Grant [21676305] and Food and Drug Safety Science and Technology projects of Hunan Food and Drug Administration [R201704].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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