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Review

Electrochemical and optical aptamer-based sensors for detection of tetracyclines

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ABSTRACT

Background: Aptasensors are promising biosensors with prominent recognition capabilities. They have fascinated a lot of attention among scholars, due to the excellent characteristics of aptamers in combination with the use of nanostructures and new interface materials. The high sensitivity and selectivity of such platforms provide a promising view in food analysis.

Scope and approach: The uncontrolled usage of antibiotics, such as tetracyclines (TCs), results in the accumulation of antibiotics in food products. The traditional analytical method for detection of antimicrobial residues in food products is liquid chromatography coupled to mass spectrometric detection. Today, simple, sensitive and rapid schemes are needed for an on-site screening analysis. However, the routine techniques for TCs detection are not designed for this purpose. This review summarizes electrochemical and optical tetracycline aptasensors in food and buffer samples with focusing on modern methods and recent advances on aptamer-based tetracycline detection methods.

Key findings and conclusions: Here, we discussed several optical and electrochemical transduction systems and their principles in aptasensor-based tetracycline detection for the first time and we focused on modern methods and recent advances. Although an optical biosensor will always have the advantage of being easier to operate with inexpensive instrument, but electrochemical aptasensors offer higher sensitivity, repeatability and accuracy. Finally, we address current challenges and future directions.

1. Introduction

Antibiotic resistance has become an important public health threat around the globe. According to the Centers for Disease Control and Prevention (CDC), about 23,000 deaths which happens in the united states every year are related to infections caused by antibiotic resistant bacteria (Frieden, 2013). The uncontrolled usage of antibiotics such as tetracyclines (TCs) in farms, results in their accumulation in food products. For the European Union as well as New Zealand, Australia and Japan, the amount of residue tolerance for TCs is 100 ng/g for milk and muscle (Andersen et al., 2005; Naik et al., 2017). This value is set as a higher amount of 300 ng/g by the United States food and drug administration (Aalipour, Mirlohi, Jalali, & Azadbakht, 2015).

Although current TCs detection and quantification methods like immunoassays (Jeon & Rhee Paeng, 2008), hollow fiber liquid phase micro extraction technique (Shariati, Yamini, & Esrafili, 2009), High-performance liquid chromatography (HPLC) (H. Xu et al., 2017) and capillary electrophoresis (Tong, Rao, Zhu, Jiang, & Ding, 2009) are among the most popular and sensitive methods in antibiotic detection, but they are hard to handle and require instruments as well as trained operators (Y.-J. Kim, Kim, Niazi, & Gu, 2009). Other methods are mostly based on liquid chromatography coupled to mass spectrometry (Santos & Ramos, 2016). These methods are rapid and their combination provides excellent and albeit structure-dependent sensitivity.

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However, these techniques are rather confirmatory methods than high-throughput on-line and on-site screening tests. Hence, it would be extremely desirable to produce rapid, accurate, uncomplicated, and sensitive methods for TCs detection (Syedmoradi et al., 2017). Aptamer-based biosensors, aptasensors, have been inaugurated as new alternative methods to fulfill these means (McCauley, Hamaguchi, & Stanton, 2003).

Aptamers are short nucleic acid-based sequences capable of binding to a wide range of targets, namely, ions, toxins, antibiotics, proteins and viruses, due to their three dimensional structures (Mayer, 2009; Na, Liu, Wang, & Su, 2015; Prabhakar, Thakur, Bharti, & Kaur, 2016; Seok Kim, Ahmad Raston, & Bock Gu, 2016). They are prepared through an *in vitro* process called SELEX (systematic evolution of ligands by exponential enrichment) (Tuerk & Gold, 1990). Advantages such as better target versatility, stronger affinity, higher specificity, low immunogenicity and convenient synthesis over antibodies make aptamers proper choices for therapeutic and diagnostic applications (Jalalian et al., 2013; Ranjan, Esimbekova, & Kratasyuk, 2017). Moreover, their dissociation constants, K_d, are ranging from nano-molar to pico-molar levels (Iliuk, Hu, & Tao, 2011). The three dimensional structure of aptamers can provide a quick and accurate recognition platform, leading to their application in many fields of scientific researches including environmental monitoring, food safety (Fischer, Tarasow, & Tok, 2007; Tombelli, Minunni, & Mascini, 2005) and drug delivery (Danesh, Lavaee, Ramezani, Abnous, & Taghdisi, 2015). Both DNA and RNA aptamers have been reported for detection of TCs (Berens, Thain, & Schroeder, 2001; Niazi, Lee, Kim, & Gu, 2008). Table 1 lists several aptamers that have been developed to detect TCs, including both single stranded DNA and RNA sequences.

There has been a huge progress in biological detection methods since 1970s. Alternative bio-synthetic components such as aptamers, nano-enzymes and nano-bodies have been emerged as a promising substitute to conventional bio-recognition elements including enzymes and antibodies (Bazin, Tria, Hayat, & Marty, 2017; Pokrzywnicka et al., 2011). Simply, a biosensor is a chemical sensor which consists of two major parts, a sensing biological component such as antibodies, enzymes or aptamers, and a transducer that convert the sensing signal to measurable physicochemical, optical and electrochemical signals (Turner, 2000). The fact that the signal is generated in real time, make biosensors fast analytical devices. Moreover, the advances offered by micro- and nano-technology leads to the flexibility in design and configuration of biosensors which can also be applied to analyte capture, signal amplification and sensor fabrication (Pérez-López & Merkoçi, 2011).

Aptasensors are promising biosensors with notable recognition capabilities. While aptasensors use single stranded DNA (ssDNA) or RNA aptamer as sensing probes, they can fold into distinct secondary and tertiary structures in order to bind to their target with high affinity (Y.-J. Kim et al., 2009). Generally, developed aptasensors for TCs can be classified into optical and electrochemical based sensors. The optical transduction scheme, which generally uses labels, can be achieved by methods such as fluorescence (Sarreshtehdar Emrani et al., 2015; H.; Zhang et al., 2017), chemiluminescence (X. Wang et al., 2007), and surface plasmon resonance (SPR) (Jalit et al., 2013; Park et al., 2014). Electrochemical aptasensors provide an electrode surface for current variation detection, due to an aptamer-target binding. Amperometric, potentiometric, conductometric and impedimetric are mostly used methods in electrochemistry. Herein, various strategies have been developed for signal transduction and amplification as well as utilizing label-free and label required systems (D. Chen, Yao, Xie, & Liu, 2014; Y.-J. Kim et al., 2009). In recent years, Quartz Crystal Microbalance (QCM) aptasensor has been introduced as a new technology which could measure very small mass changes on its sensing interface. Being untagged is the main advantage of this type of biosensors, which provides great simplicity for its construction (L. Wang et al., 2017). A number of drawbacks are associated with QCM aptasensors, including

Table 1
Tetracyclines aptamer Sequences obtained by SELEX.

Aptamer Sequences obtained by SELEX	Size (mer)	Type	K_D (nM)	References
5′-CGTACGGAATTCGCTAGCCCCCCGGCAGGCCACGGCTTGGGTTGGTCCCACTGCGCGTGGATCCGAGCTCCACGTG-3′	76	DNA	63.6	(Niazi, Lee, & Gu, 2008)
5′-GTTTGTGTATTACAGTTATGTTACGCTCATTTTTCTGAAC-3′	40	DNA	2.94	(Sai Wang, Liu, Dong, et al., 2015)
5′-CGTACGGAATTCGCTAGCCGAGTTGAGCCGGCGCGGTACTGGGTATGTGTGGGATCCGAGCTCCACGTG-3′	76	DNA	56.84	(Niazi, Lee, & Gu, 2008)
5′-CGACGCACAGTGCTGGTGCGTACCTGGTTGCCGTTGTGT-3′	40	DNA	4.7	(C.-H. Kim et al., 2014)
5′-GAGCUCAGCCUGUACUGCUGCUUAAAGCCUAAAACAUACCAGAUCGCCACGCGGCUUUAAUCUGGAGAGGUGAAGAAUUCGACCACCUAGGCUGCACCACGG-3′	103	RNA	1000	(Berens et al., 2001)
5′-GGGCCUAAAACAUACCAGAUCGCCACCGCGCUUUAAUCUGGAGAGGUGAAGAAUACGACCACCUAGGCUC-3′	71	RNA	0.77	(Müller, Weigand, Weichenrieder, & Suess, 2006)