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Aptamer based electrochemical sensors for emerging environmental pollutants

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Environmental contaminants monitoring is one of the key issues in understanding and managing hazards to human health and ecosystems. In this context, aptamer based electrochemical sensors have achieved intense significance because of their capability to resolve a potentially large number of problems and challenges in environmental contamination. An aptasensor is a compact analytical device incorporating an aptamer (oligonucleotide) as the sensing element either integrated within or intimately associated with a physiochemical transducer surface. Nucleic acid is well known for the function of carrying and passing genetic information, however, it has found a key role in analytical monitoring during recent years. Aptamer based sensors represent a novelty in environmental analytical science and there are great expectations for their promising performance as alternative to conventional analytical tools. This review paper focuses on the recent advances in the development of aptamer based electrochemical sensors for environmental applications with special emphasis on emerging pollutants.

Keywords: electrochemical sensor, aptamer, emerging pollutants, environmental applications, analytical monitoring

INTRODUCTION

Nucleic acid, as the biological polymer for the storage and propagation of genetic information, possess remarkable structural and functional characteristics (Tang et al., 2014). Highly specific base pairing properties of nucleic acid permit for replication and transcription processes (Seeman, 2003). Recently, nucleic acid has emerged as a powerful and versatile building block in the construction of biosensors (Seeman, 2010). A variety of nucleic acid (DNA or RNA) based biosensors have been designed and reported in the literature. Among them, aptamers are nucleic acid (DNA or RNA) that selectively bind to low molecular weight organic or inorganic substrate or to relatively big macromolecules. The affinity constant of aptamers toward their specific targets is reported in the micromolar to pico molar ranges, comparable to the binding constant of antibody and antigen affinity interaction (Jenison et al., 1994; Willner and Zayats, 2007). They are engineered through an in vitro selection procedure, also called SELEX (Systematic Evolution of Ligands by EXponential enrichment), which was first reported in 1990 (Hayat et al., 2012b, 2013c; Paniel et al., 2013).

Recently, aptamers have found tremendous interest as an active separation material in chromatography and electrophoresis, therapeutic and diagnostic agent, and as acting recognition element for diverse analytical applications, particularly environmental analysis.

Recent years have witnessed increasing need to monitor the environmental contaminations. Food, air and water are the main victims of the contaminants that may have impact on human and animal life. The environmental contaminants have mild to severe short-term or long term effect and some of them even have deadly effects and lead to widespread havoc. The contaminants that need monitoring in the environment can be broadly classified as small organic and inorganic pollutants, pharmaceutical and personal care products, toxins of microbial origin and pathogens. Although there has been lot of interest in developing techniques for monitoring of environmental pollutants, there is
transduction is simple, rapid, cost effective, highly sensitive and over optical, piezoelectric or thermal detection. Electrochemical tion of current or potential changes resulting from interactions biomolecular reaction monitoring is mainly based on the detec-
of electrochemical aptasensors. Electrochemical aptasensor for plenty of research work has been devoted to the development favored for some electrochemical detection techniques. Till now, sensitivity. The use of aptamer as bio-recognition element is strongly advantages including simplicity, rapidity, low cost and high sen-
tivity. The use of aptamer as bio-recognition element is strongly favored for some electrochemical detection techniques. Till now, plenty of research work has been devoted to the development of electrochemical aptasensors. Electrochemical aptasensor for biomolecular reaction monitoring is mainly based on the detection of current or potential changes resulting from interactions occurring at the transducer surface. It presents several advantages over optical, piezoelectric or thermal detection. Electrochemical transduction is simple, rapid, cost effective, highly sensitive and selective, compatible with novel micro-fabrication techniques, disposable, easy to miniaturize, robust, and independent of sample turbidity, in view of high-throughput. Electrochemical reactions usually provide an electronic signal directly, avoiding the requirement of expensive signal transduction equipment (Castillo et al., 2012; Rhouati et al., 2013a,b).

As aptamer are nucleic acid strand and can be very easily immobilized on the transducer electrode surface, chip-based, portable, and miniaturized electrochemical systems can be designed accordingly. For electrochemical aptasensor, most of the commonly used electrode materials are gold and carbon surfaces on which aptasensor construct can be built via different immo-
obilization strategies and detection formats (Figure 1) (Lai et al., 2006; White et al., 2008).

CONVENTIONAL METHODS FOR ELECTROCHEMICAL APTASENSING

There is a great variety of different labels which have been applied in electrochemical aptasensors. These reporters can be covalently conjugated to the aptamer itself, conjugated to a complementary oligonucleotide, or indirectly attached with aptamers. Following the incorporation of an electrochemical reporter, detection can be either signal-on (Figure 2) or signal-off (Figure 3), depending on the format of the assay. Among the most valuable labels are enzymes such as horse radish peroxidase (HRP), glucose oxidase (GOD), alkaline phosphatase (ALP). Other reporters can also be used to overcome problems typically associated with enzymes. In particular, electroactive compounds such as ferrocene, ferrocyanide, methylene blue (MB), Pt and Cds quantum dots (QDs), and other nanoparticles (NPs) offer a number of advantages over standard enzymes for monitoring biological systems (Ikebukuro et al., 2005; Mir et al., 2006; Centi et al., 2007; Park et al., 2011).

REDOX LABELING METHODS FOR APTASensors

Sensitive electrochemical signaling is usually based on the redox properties of the reported molecules confined to the transducer surface. Different redox labels for electrochemical aptasensor have been developed in the past two decade. Various reporter

Figure 1 (A) Aptamer conformational changes after target analyte incubation; (B) various possible formats of aptasensing.
molecules including ferrocene and methylene blue have been covalently tethered to the distal terminus of aptamer through flexible alkyle linkages. Based on the restriction of redox reporter mobility, the position of the aptamer can be controlled by varying their orientation or surface density. When the length of alkyle linkages is limited, the reaction is only a surface controlled process, without involvement of diffusion processes resulting in simplified electrochemical output data (Ihara et al., 1996; Pheeney and Barton, 2012). Intercalation is another procedure to insert a ligand between the base pair of DNA through non covalent interactions. The ligands called intercalators mostly include polycyclic, aromatic, and planar molecule (Kelley et al., 1997, 1999). Similarly, negatively charged reports which are freely diffusing in solution, cannot get into close proximity with the aptamer modified transducer surface due to electrostatic interactions. For example ferri/ferrocynide ions in the solution are repelled by the negatively charged species, increasing the electron transfer resistance. This increase in electron transfer resistance can be measured as a function of analyte concentration by using electrochemical impedance spectroscopy (Yu et al., 2003; Cheng et al., 2007).

**RATIONAL DESIGN OF ELECTROCHEMICAL APTASENSORS**

In functional aptamer based electrochemical sensors, aptamer undergoes various structural or conformational changes in the presence of external stimuli, resulting in an alteration in the electrochemical signal. The most commonly explored pattern in this context is aptamer-ligand binding phenomena. When aptamers are immobilized on the electrode surface, the binding of the target analyte may induce structural and conformational changes. In the presence of redox reported, electrochemical signals can be obtained by employing conventional electrochemical techniques. Aptmaer constructs are mainly single or double stranded in which the target binding induces the dissociation of duplexes or the folding of single strands. Aptamers may bind to their target analytes by two different recognition events; (a) binding to their ligands and (b) binding to their Watson-Crick complementary strand. This competition can be employed to design novel types of electrochemical aptasensors. These types of formats form a fully or partially double stranded DNA sensor with one strand incorporating aptamer sequence. Upon incubation with target analyte, the aptamer selectively binds to the analyte with the dissociation of the DNA duplex, which is further employed to get the electrochemical signal (Zuo et al., 2007; Lu et al., 2008; Chakraborty et al., 2009). Alternatively, folding of single strand aptmaer is used to construct the electrochemical sensors. This type of aptasensor design offer advantages such as; (a) the aptamer conformational changes upon target analyte bindings are simple and does not involve the dissociation of the duplex, (b) surface can be very easily regenerated, without requirement of re-hybridization of the dissociated strand. The later type of format is mostly commonly used to fabricate simple and robust electrochemical aptasensors (Xiao et al., 2005; Baker et al., 2006; Radi et al., 2006).

**DIFFERENT METHODS OF APTAMER IMMOBILIZATION**

Immobilization of aptamer on the transducer surface is one of the fundamental and critical steps in the design of electrochemical aptasensors. Aptamer can be immobilized on electrode surface via 5’-end or the 3’-end. However, the 3’-end is more suitable because it simultaneously confers resistance to nuclease after its binding to electrode surface. Physical adsorption method by means of electrostatic forces is the simplest strategy to immobilize the aptamer on the transducer surface. Aptamer immobilization methods generally operate through chemisorption of thiol onto gold, followed by formation of self assembled monolayer (SAMs) by the attachment of amine-terminated aptamer to a thiol end group. Similarly, thiol-tethered aptamers have been reported for planar gold (Baker et al., 2006; Li et al., 2008). This method, however, has the disadvantage of low stability caused by desorption from the surface. The use of gold nanoparticles (NPs) as immobilization support for aptamer to fabricate aptasensors has also been very well established. The immobilization of aptamer on gold NPs has been performed through direct attachment on gold using a symmetric mixed disulfide (Liu and Lu, 2004). The other used format is a complex dipstick in which two different types of gold NPs are used. Metal NPs have also been used for the immobilization of DNA and could be a useful alternative to gold NPs in future (Wu et al., 2007).

To perform covalent attachment to chemically modified surface, aptamers labeled with chemical functional groups interact with the corresponding chemical groups to form a layer of ordered film of aptamer on the sensor surface (Lee et al., 2009; Actis et al., 2011). The most commonly used groups for surface attachment are hydroxyl, amine, and carboxylic acid surface functional groups. Silicates and silicones have also been used as immobilization support for the fabrication of aptasensors (Zhu et al., 2006). The interaction between avidin (or streptavidin) and biotin has been exploited for surface immobilization of number of biorecognition elements, including aptamer (Becker and Wilchek, 1972). Avidin or streptavidin can easily be immobilized on the
Electrochemical aptasensors for environmental pollutants

...the challenges associated with the traditional methods with similar or improved specificity and affinity characteristics in comparison to antibody based assays/sensors. Based on the nature of the target analyte, electrochemical aptasensor designed for environmental monitoring are classified into two major groups, for simplicity and better understanding of the scientific community.

1. Electrochemical aptasensor for small molecules detection.
2. Electrochemical aptasensor for pathogen detection.

**ELECTROCHEMICAL APASSENSORS AGAINST SMALL MOLECULES**

Small target analytes including antibiotics, toxins, pesticides and heavy metals can be present in a variety of environmental samples. One such example is theophylle, commonly used bronchodilator used for asthma patients, however, its overdose lead to severe toxicity like seizure.. etc. For this molecule, RNA based electrochemical aptasensors have been reported in the literature to monitor its level in human serum (Ferapontova et al., 2008). Similarly, aptamers against drugs such as cocaine have been developed and successfully implemented for their detection (Chen et al., 2008).

**Electrochemical aptasensors against antibiotics**

Antibiotics are used to farm animal along with their feed for prophylactic and therapeutic purpose. However, a certain amount of these antibiotics remains un metabolized and accumulate in the tissue or excrete in the surroundings (Chen et al., 2008). The presence of antibiotics in the environment may results in antibiotic resistance with the subsequent possibility of transmission to the human being through food chain. Chloramphenicol, antimicrobial drug, has lost its favor due to resistance and serious side effects like aplastic anemia. Burka et al. were the first one who designed and reported an aptamer against chloramphenicol (Burke et al., 1997). However, RNA aptamers are suspected to nuclease attack and needs transcription and reverse transcription, making it difficult to screen. Recently, Metha et al. developed DNA aptamers, and the designed aptamers were used for the electrochemical detection of chloramphenicol. The aptamers were immobilized onto gold electrode surface via self-assembly approach. The developed aptasensors were very sensitive and selective toward detection of chloramphenicol (Mehta et al., 2011). Tetracyclines are another group of broad spectrum antibiotics which inhibits prokaryotic translation (Spahn and Prescott, 1996). They are often used as veterinary drug to promote growth in animals. Their residues have been detected in meat, milk, honey, eggs etc. (Pena et al., 1999; Muriuki et al., 2001). On the other hand, this antibiotic has also been reported as hepatotoxic to pregnant women (Gwee, 1982). Traditional detection methods such as HPLC have been failed for their detection due to lack of specificity. Recently, aptamer have been selected for the detection of tetracyclines (Berens et al., 2001). In this context, Kim et al. recently designed an electrochemical aptasensor over glassy carbon electrodes (Kim et al., 2010). After this work, many electrochemical aptasensors were designed and reported in the literature for the detection of tetracyclines (Kim et al., 2010; Zhang et al., 2010; Jeong and Rhee Paeng, 2012). Xiao et al. improved the structure of the aptamer to obtain a very high affinity constant against tetracyclines (Kd ∼ 0.8 nM) (Xiao et al., 2008). Zhang...
et al. reported a rapid electrochemical aptasensor using aptamers immobilized over glassy carbon electrodes. The aptasensor was able to rapidly detect tetracycline in milk with very high sensitivity (Zhang et al., 2010). Similarly, a competitive enzyme linked aptamers assay (ELIAA) for tetracycline was developed by Jeong et al. using both DNA and RNA aptamers (Jeong and Rhee Paeng, 2012). Zhou et al. fabricated a simple electrochemical tetracycline aptasensor with multi-walled carbon nanotubes modification. The electrochemical aptasensor exhibited a good sensitivity and was successfully applied to the determination of tetracyclines in real samples (Zhou et al., 2012).

**Electrochemical aptasensors for toxins**

Mycotoxins are the major group of toxins that are present in our food. They are group of naturally occurring chemicals produced by molds growing on different types of crops. They have several adverse impacts on human health such as gastrointestinal diseases to kidney damage and immune suppression. Among the mycotoxins, Ochratoxin A (OTA) is the most commonly occurring toxins, and a DNA aptamer was selected against it in 2008 (Cruz-Aguado and Penner, 2008). Afterwards, numerous number of electrochemical aptasensors were developed to detect this toxins (Rhouati et al., 2013b). Bacterial endotoxins are also one of the major contaminants present in pharmaceutical products, causing severe septic shock in humans and animals (Magalhaes et al., 2007). Kim et al. fabricated an electrochemical aptasensor for the detection of endotoxins from crude biological liquor (Kim et al., 2012). Seeds of the leguminous herb lupin are the widely used source of low cost protein. However, there have been an increasing number of cases reporting severe allergic reactions to these seeds. To meet this challenge and detect Lupin allergen levels in food, a DNA aptamer based assay was developed by Nadal et al. (2012). Many toxins are excreted by human sand animals and subsequently entering into water effluents. Endocrine disrupting compounds form a major class of pollutants with several health hazards (Chang et al., 2009). Estradiol is one such compound which has adverse effects on the male reproductive system. Recently, Yildrim et al. designed a DNA sensor based on fluorescence detection method for environmental water samples (Yildirim et al., 2012). However, this method can be adapted to the electrochemical methods for better analytical performance in future. Bisphenol A is used as a monomer constituent in plastic poly hydrocarbonate products. However, it has potential harmful effect for humans and animals as it interact with endocrine system by blocking of estrogen with its receptors. Jo et al. developed a sol gel biochip aptasensor to detect Bisphenol A in water samples. Further, electrochemical aptasensors can be designed to measure Bisphenol A based on the aptamer platform (Jo et al., 2011). Zhou et al. developed a simple and label-free electrochemical aptasensor for bisphenol A (BPA) determination. The method was based on the gold nanoparticles doted graphene nanocomposite film modified glassy carbon electrode. The proposed aptasensor was rapid, convenient and low-cost for effective sensing of BPA (Zhou et al., 2014).

**Electrochemical aptasensors against heavy metals**

Heavy metals including mercury, arsenic.. etc. cause severe toxicity to nervous and endocrine system, and also heart problems, skin lesions, and cancer. According to official sources, arsenic level in water is exceeded than the allowable limit leading to serve arsenic toxicity among inhabitants. As a result, an aptansensor has been proposed by Kim et al. group to detect arsenic, with potential tool to be used as alarming method (Kim et al., 2009). Mercury has also been detected by the combination of gold nanoparticles and aptamer with optical output (Li et al., 2009; Helwa et al., 2012). However, the mercury specific aptamer can be very easily extended to electrochemical sensing platform in future. Li et al. developed an electrochemical DNazyme sensor for sensitive and selective detection of lead ion (Pb2+), taking advantage of catalytic reactions of a DNazyme upon its binding to Pb2+ and the use of DNA-Au bio-bar codes to achieve signal enhancement. Although this DNazyme sensor was demonstrated for the

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**Table 1 | Electrochemical aptasensors designed for the detection of different target analytes.**

<table>
<thead>
<tr>
<th>Sr no</th>
<th>Analyte</th>
<th>Transduction methodology</th>
<th>Year</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Theophylline</td>
<td>RNA aptamer-based biosensor</td>
<td>2008</td>
<td>Feraportova et al., 2008</td>
</tr>
<tr>
<td>2</td>
<td>Cocaine</td>
<td>Aptamer biosensor</td>
<td>2008</td>
<td>Chen et al., 2008</td>
</tr>
<tr>
<td>3</td>
<td>Chloramphenicol</td>
<td>RNA aptamers</td>
<td>1997</td>
<td>Burke et al., 1997</td>
</tr>
<tr>
<td>4</td>
<td>Chloramphenicol</td>
<td>DNA aptamers</td>
<td>2011</td>
<td>Mehta et al., 2011</td>
</tr>
<tr>
<td>5</td>
<td>Tetracycline</td>
<td>RNA aptamer</td>
<td>2001</td>
<td>Berens et al., 2001</td>
</tr>
<tr>
<td>6</td>
<td>Tetracycline</td>
<td>Electrochemical aptasensor</td>
<td>2010</td>
<td>Kim et al., 2010</td>
</tr>
<tr>
<td>7</td>
<td>Tetracycline</td>
<td>Aptamer biosensor</td>
<td>2010</td>
<td>Zhang et al., 2010</td>
</tr>
<tr>
<td>8</td>
<td>Tetracycline</td>
<td>Aptamer-based assay</td>
<td>2012</td>
<td>Jeong and Rhee Paeng, 2012</td>
</tr>
<tr>
<td>9</td>
<td>Mycotoxins</td>
<td>DNA aptamer</td>
<td>2008</td>
<td>Cruz-Aguado and Penner, 2008</td>
</tr>
<tr>
<td>10</td>
<td>Endotoxin</td>
<td>Electrochemical aptasensor</td>
<td>2012</td>
<td>Kim et al., 2012</td>
</tr>
<tr>
<td>11</td>
<td>Bisphenol a</td>
<td>DNA aptamers</td>
<td>2011</td>
<td>Jo et al., 2011</td>
</tr>
<tr>
<td>12</td>
<td>Acetamiprid</td>
<td>DNA aptamer</td>
<td>2011</td>
<td>He et al., 2011</td>
</tr>
<tr>
<td>13</td>
<td>Pesticides</td>
<td>DNA aptamers</td>
<td>2012</td>
<td>Wang et al., 2012</td>
</tr>
<tr>
<td>14</td>
<td>Virus-infected cells</td>
<td>Aptamers</td>
<td>2009</td>
<td>Tang et al., 2009</td>
</tr>
<tr>
<td>15</td>
<td>Escherichia coli</td>
<td>Aptamer-functionalized carbon-nanotube</td>
<td>2008</td>
<td>So et al., 2008</td>
</tr>
<tr>
<td>16</td>
<td>Anthrax</td>
<td>Nano aptasensor</td>
<td>2010</td>
<td>Cella et al., 2010</td>
</tr>
</tbody>
</table>
detection of Pb2+, it has the potential to serve as a general platform for design sensors for other small molecules and heavy metal ions (Shen et al., 2008). Chen et al. reported a highly sensitive and specific electrochemical aptasensor for Cu2+ detection based on gold nanoparticles. Rapidity, simplicity, and excellent selectivity made it suitable for practical use in determination of Cu2+ from heavy metals. But still there are many toxic heavy metals for which aptamer have not been designed, so future work may focus to synthesize aptamer against the rest of toxin metal target analytes.

**Electrochemical aptasensor for pesticides**

Atrazine is one of the most intensively used pesticides to inhibit the growth of weeds. However, its presence may cause reproductive damage in humans. Sinha et al. screened a series of aptamers against atrazine and then cloned them into E. coli cells (Sinha et al., 2010). The screened aptamers may find potential applications in developing electrochemical aptasensors to detect atrazine in future. Similarly, insecticides are also applied to crops to protect them from insect attack. One example is acetamiprid, which when leached into the environment can cause toxicity in humans and animals. A series of aptamers which bind to acetamiprid with high dissociation constant have been synthesized recently (He et al., 2011; Wang et al., 2012). Wang et al. designed a DNA aptamer which was able to detect up to four highly poisonous organo-phosphorous pesticides including phorate, profenofos, isocarbophos, and omethoateas (Shen et al., 2008). Fan et al. developed an aptasensor for sensitive and selective detection of acetamiprid based on electrochemical impedance spectroscopy (Fan et al., 2013). To improve sensitivity of the aptasensor, gold nanoparticles were electrodeposited on the bare gold electrode surface by cycle voltammetry. The applicability of the developed aptasensor was successfully evaluated by determining acetamiprid in the real samples, wastewater and tomatoes. Although aptamers have been selected against various types of pesticides, however, their potential as ligand molecules in a biosensor is mainly unexplored.

**ELECTROCHEMICAL APTASSENSORS AGAINST PATHOGENS**

Detection, identification, and quantification of microbial pathogens are crucial for public health protection. Areas where detection of microbial pathogens is critical include water and environmental analysis. Aptasensors capable of rapidly detecting pathogens with improved analytical performance are highly desired to meet the increasing environmental problems. The aptamer based assays are able to identify and detect different types of pathogens without prior information of their membrane molecules and structural genes. Among the pathogens, aptamers assays against virus are in their infancy and some of the reported aptamers against specific viruses could get potential in the fabrication of biosensors. Various aptasensor platform have been reported in the literature for various types of viruses (Minunni et al., 2004; Tombelli et al., 2005; Lee et al., 2007; Tang et al., 2009). Similarly, detection of bacteria is also a relatively emerging and new area. Aptasensors based on different types of nanomaterials in combination with electrochemical transduction output are described for the measurement of bacteria (So et al., 2008; Cella et al., 2010). Aptamer-functionalized single walled carbon nanotube field-effect transistor (SWNTFET) arrays aptasensor was developed to detect E. coli DH5 α (Fan et al., 2013). The binding between E. coli cells and the aptamer-functionalized FET resulted in a change in conductance of the samples which was subsequently related to detection mechanism. Recently, bioterrorism has been considered as a major threat to national security. One of the leading examples is Anthrax that is associated with the spores of gram positive bacteria Bacillus anthracis. Cella et al. reported an aptasensor for detection of protective antigen of anthrax (Tang et al., 2009). The aptasensor consisted of single stranded DNA aptamer functionalized to single walled carbon nanotubes having sensitivity in the nanomolar range.

**CONCLUSION AND PERSPECTIVES**

Despite of the attractive advantages, aptamer based assays are still under phase of development as compared to immunoassays for environmental monitoring. The primary hurdles are the limited number of available aptamers and relatively poor knowledge of aptamer immobilization strategies. However, recent years have witnessed important and rapid advances in the sequences of new aptamers, along with integration of new nanomaterials in aptamer based assays, rapidly improving the existing procedures. Electrochemical aptasensors reveal certain advantages when compared to the optical sensors, For example, the possibility of integrating signal amplifying catalytic or biocatalytic labels to the aptamer-target complex enables the highly sensitive detection of the target substrate. Recent advances have also witnessed the electrochemical label free detection, thus overcoming the requirement of labels. Even though substantial progress has been accomplished in the design of electrochemical aptasensors, several exciting, and improving opportunities still exist in the field of aptasensors. For example, the use of synthetically modified nucleotide as co-component and integration of the binding properties of aptamer with DNAzyme may yield the hybrid structures with superior sensing functions by combining selected binding and catalytic properties of aptamer. Overall, the potential of electrochemical aptasensors is immense in the environmental monitoring, and this exciting and challenging area is on the brink of exponential growth. The future development in aptasensors with respect to environmental monitoring may focus on the design of aptamers against unexplored target analyte, and then their subsequent integration in the electrochemical platform to monitor those target analytes.

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