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Novel biosensing methodologies for improving the detection of single nucleotide polymorphism

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ABSTRACT

The growing volume of sequence data confirm more and more candidate single nucleotide polymorphisms (SNPs), which are believed to reveal the genetic basis of individual susceptibility to disease and the diverse responses to treatment. There is therefore an urgent demand for developing the sensitive, rapid, easy-to-use, and cost-effective method to identify SNPs. During the last two decades, biosensing techniques have been developed by integrating the unique specificity of biological reactions and the high sensitivity of physical sensors, which provided significant advantages for the detection of SNPs. In this feature article, we focused attention on the strategies of SNP genotyping based on biosensors, including nucleic acid analogs, surface ligation reaction, single base extension, mismatch binding protein, molecular beacon, rolling circle amplification, and strand-displacement amplification. In addition, the perspectives on their advantages, current limitations, and future trends were also discussed. The biosensing technique would provide a promising alternative for the detection of SNPs, and pave the way for the diagnosis of genetic diseases and the design of appropriate treatments.

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1. Introduction

With the completion of human genome sequencing, the analysis of variations among individual genomes has become a focus in recent research. One of the most common forms of genetic variation is the single nucleotide polymorphism (SNP), which is the single nucleotide variation in a given and defined genetic location and occurs in human genome at a frequency of approximately 1 in every 1000 bases (Collins et al., 1998). Currently, about 1.42 million SNPs have been identified by the SNP consortium

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(Sachidanandam et al., 2001). SNPs are highly conserved and widely distributed in the genome, so the map of SNPs proves to be a high-resolution genetic marker (Hood et al., 2004; Jorde, 2000). In addition, these benign sequence variations in gene coding regions may alter the amino acid sequence and in turn influence the function of the corresponding protein (Collins et al., 1997; Kim and Misra, 2007). All these properties collectively suggest that SNPs could be used as a new generation of genetic markers and valuable indicators for clinical diagnosis and prognosis.

Various techniques for SNP genotyping have been reported in recent years. Classic methods such as DNA sequencing could be used for the detection of new and unknown SNPs (Syvanen, 2001), but the complex procedures and lengthy operation times make direct sequencing sub-optimal. The alternative approaches include conformation changes (Salimullah et al., 2005; Tahira et al., 2009), mass spectroscopy (Millis, 2011), polymerase chain reaction (PCR) (Beaudet et al., 2001; Fujii et al., 2000), and DNA hybridization (Barreiro et al., 2009; Russom et al., 2006). These approaches could specifically detect SNP-containing regions to avoid complicated DNA sequencing, but the intrinsic shortcomings, such as low throughput and specificity, limit their applications. Recently, DNA microarray and denaturing high performance liquid chromatography have been proposed for fast, efficient, and large-scale analysis of SNPs (Deulvot et al., 2010; Ding and Jin, 2009). However, these methods require expensive facilities and radioactive/fluorescent tags. In this context, the rapid, simple, and specific technology is urgently needed for high throughput SNP analysis in both basic research and clinical diagnosis.

At present, biosensing techniques have been developed and adopted to SNP detection for their advantages of high sensitivity, good reproducibility, and short detection time. Moreover, in the use of biosensing techniques, it is possible to detect multiple SNPs in the same biosensor by constructing a microarray, which will increase the fluxes of detection and decrease the cost. This review focuses only on the latest trends in biosensor-based SNP genotyping. Firstly, the basic knowledge on the properties of biosensors is presented. Subsequently, the evolution of biosensor research is introduced. Then, the strategies for SNP genotyping based on biosensors are covered. The following conclusions provide the future trends for development of novel, cost-effective, and high-throughput approaches for SNP genotyping with biosensors.

2. Biosensors

Biosensors are the devices that use biochemical reactions mediated by isolated enzymes, organelles, or whole cells to detect the effects of chemical compounds by electrical, thermal or optical signals, as defined by the International Union of Pure and Applied Chemistry (Thevenot et al., 2001). The biosensor has received considerable attentions due to its sensitivity, selection, and specificity with detection of the concentration of a specific substance (Murugaiyan et al., 2014; Turner, 2013). In general, the biosensor essentially consists of a biological sensing element and a physicochemical transducer (Fracchiolla et al., 2013). The biological sensing element contributes to transforming the analyte of interest into chemical signal or physical signal. And then, the physicochemical transducer, as the key component of biosensors, could effectively convert the chemical or physical signal into a thermal, electrical or optical signal (Bohunicky and Mousa, 2010). Biosensors could be divided into four classes based on the biological sensing elements: enzyme-based biosensors, antigen/antibody-based biosensors, cell/virus-based biosensors, and nucleic acid-based biosensors. Alternatively, biosensors are also classified based on the type of transducers: optical biosensors, electrochemical biosensors, mass sensitive biosensors, and calorimetric biosensors (Chang et al., 2014; Chen et al., 2005; Mehrvar and Abdi, 2004; Monošík and Šturdík, 2012; Zhang et al., 2013b). The classification of biosensors is shown in Table 1.

Table 1
The classification of biosensors.

Transducers	Biological sensing elements
Optical	Enzyme-based biosensors
SPR biosensors	Antigen/antibody-based biosensors
Colorimetric biosensors	Cell/virus-based biosensors
BRET	Nucleic acid-based biosensors
FRET	
Electrochemical	
Amperometric biosensors	
Impedimetric biosensors	
Conductometric biosensors	
Mass sensitive	
QCM	
Acoustic wave biosensors	
Calorimetric	

Abbreviations: SPR, surface plasmon resonance; BRET, bioluminescence resonance energy transfer; FRET, fluorescence resonance energy transfer; and QCM, quartz crystal microbalance.

The basic concept of biosensors was proposed by Leyland C. Clark in 1962 (Newman and Setford, 2006). The first published paper concerning the biosensor dated back to 1982, but the development in the field of biosensors was phenomenal. More than 4000 papers concerning the biosensor published annually in the last five-year period (ISI Web of Knowledge database, Thomson Reuters) (Fig. 1). The huge development of biosensors has expanded considerably the range of applications which included biochemistry, clinical analysis, drug screening, and environmental monitoring (Long et al., 2013; Shankaran et al., 2007). Currently, About 37% of articles dealing with biosensors have been published in Chemistry, 32% in Biochemistry molecular biology, while the rest were published in the fields such as Instruments instrumentation, Material sciences, Medical laboratory technology, and Electrochemistry. The classification of published scientific papers by research areas is shown in Fig. 1.

3. Strategies for SNP genotyping based on biosensors

3.1. Strategy 1: nucleic acid analogs-based biosensors

Nucleic acid analogs, as the research tools and diagnostic agents, have been synthesized by interspersing natural nucleobases with artificial nucleobases or modifying internucleoside linkages. The use of nucleic acid analogs has experienced a significant upsurge of interest during the past decade. The nucleic acid analogs are becoming increasingly important in the field of biosensors because of their high selectivity, chemical stability, and affinity toward complementary DNA/RNA.

3.1.1. Peptide nucleic acid-based methods

Peptide nucleic acid (PNA) is a neutral DNA mimic in which the sugar phosphate backbone of natural nucleic acid is replaced by the pseudopeptide backbone composed of N-(2-amino-ethyl)-glycine units (Wittung et al., 1994). Since PNA was first introduced by Nielsen et al. in 1991, it has been confirmed that PNA could efficiently bind to complementary DNA or RNA strand in a Watson–Crick hydrogen bonding rule, with high specificity and affinity (Nielsen et al., 1991). The better thermal stability and higher association constant have been revealed in the