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Review

Trends in DNA biosensors

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ABSTRACT

Biosensors have witnessed an escalating interest nowadays, both in the research and commercial fields. Deoxyribonucleic acid (DNA) biosensors (genosensors) have been exploited for their inherent physicochemical stability and suitability to discriminate different organism strains. The main principle of detection among genosensors relies on specific DNA hybridization, directly on the surface of a physical transducer. This review covers the main DNA immobilization techniques reported so far, new micro- and nanotechnological platforms for biosensing and the transduction mechanisms in genosensors. Clinical applications, in particular, demand large-scale and decentralized DNA testing. New schemes for DNA diagnosis include DNA chips and microfluidics, which couples DNA detection with sample pretreatment under in vivo-like hybridization conditions. Higher sensitivity and specificity may arise from nanoengineered structures, like carbon nanotubes (CNTs) and DNA/protein conjugates. A new platform for universal DNA biosensing is also presented, and its implications for the future of molecular diagnosis are argued.

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Contents

1. Introduction 607
2. Fundamentals of hybridization DNA biosensors 607
3. DNA-probe immobilization techniques 608
4. New biosensor platforms 609
5. Transduction mechanisms in genosensors 609
   5.1. Optical 609
      5.1.1. Optical fibers 609
      5.1.2. SPR and evanescent waves 610
      5.1.3. Gold nanoparticles 610
      5.1.4. Quantum dots 611
      5.1.5. Other systems 611
      5.1.6. Commercial optical biosensors 612
   5.2. Piezoelectric (mass-sensitive) 612
   5.3. Electrochemical 613
      5.3.1. Enzyme indirect detection 613
      5.3.2. Label-based (indirect) detection 613
      5.3.3. Label-free (direct) detection 614
   5.4. Magnetic particles 616
   5.5. Bibliographic revision on limit of detection of DNA biosensors 619
6. A new paradigm: MS DNA sensing and the universal biosensor 619
7. Conclusions 620
   Acknowledgment 620
   References 620

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1. Introduction

The enormous amount of genetic information brought by extensive genome sequencing has raised the need for simple, fast, cheap and high-throughput miniaturized and mass-producible analytical devices to attend the growing market of molecular diagnostics, thus accomplishing the basic criteria for decentralized DNA testing. Genome sequencing has allowed detecting, respectively, inherited disease-causing point mutations and human pathogens through their peculiar, specific nucleic acid sequences. Drug screening, monitoring of differential gene expression and forensic analysis have also benefited from the ongoing research in biosensor technology. Such analytical devices, known as biosensors, convert a biochemical reaction or interaction into an analytical signal that can be further amplified, processed and recorded. Among them, DNA biosensors consist of an immobilized DNA strand to detect the complimentary sequence by DNA–DNA hybridization. In a wider conception, DNA biosensors may still be conceived to detect other analytes, with the probe molecule usually in the form of an aptamer [1], but the study of these sensors is beyond the scope of this review. For their importance, large variety and widespread applications compared to other types of DNA biosensors, those based, for instance, on distinctive interactions of small analytes with single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) and in polymerase chain reaction (PCR) amplicon detection without hybridization are the subject of hybridization-based DNA biosensors justifies, by itself, a new and comprehensive overview, something that this paper intends to be. Compared to enzyme biosensors and immunosensors, there is still a scarcity of DNA biosensors available in the market and/or under research and development. Unlike enzymes or antibodies, DNA forms biological recognition layers easily synthesizable, highly stable and reusable after simple thermal melting of the DNA duplex [2]. In general, the underlying mechanism of quantitative DNA detection through DNA biosensors is the highly specific hybridization between two complimentary DNA chains which, unlike in conventional solid-state hybridization formats, occurs directly on the surface of a physical transducer. Conventional DNA microarrays also make use of sequence-specific DNA detection, but their efficiency is usually hampered by the typically large size of biological samples and by their complex treatment, which also makes it difficult to obtain real-time outputs. Moreover, their technology is still too expensive to turn them valuable in point-of-care diagnosis. In theory, DNA biosensors are able to surpass these handicaps, allowing easier, faster and cheaper results than in traditional hybridizing assays, while keeping high sensitivity and specificity of detection. A truly high performance biosensor with an immobilized DNA-probe should be able to discriminate as few as a single base-pair mismatch between different target DNA-strains. DNA multiplexed analysis of complex biological samples and related gene expression patterns have been performed with microarrays of multiple DNA biosensors, integrated with bioinformatics-processed data. In general, they are produced in the form of DNA biochips, inspired by the unending advances in planar silicon-based circuitry. The very high density of individual hybridization spots is a major highlight in microchip-based genetic analysis. However, this technology is highly costly and, unlike individual biosensors, biochip surfaces must be scanned for acquisition of full information about the genomic hybridization profile [3]. The newly developed concept of 'lab-on-a-chip' (or micro total analytical system, μTAS) integrates, in a single chip, modules for DNA extraction, purification, amplification and detection. Some advantages of these printable miniaturized devices for analyte detection include smaller sample and reagent requirements, lower cost and lower tendency for sample contamination than other detection schemes. Enhanced rapidity, high performance and high automation ability are also additional advantages. Disposability is also an advantage, especially when dealing with infectious agents. Innovative efforts have been assayed towards the development of electrical-driven microfluidic flow formats as advantageous alternatives to mechanical pumps and valves. The paper also covers some recent developments in nanotechnology, namely CNTs and DNA/protein conjugates, which are responsible for improved sensitivity and selectivity in DNA detection. Despite not being a hybridization-based platform for DNA detection – the ultimate subject of this paper – important applications of the mass-spectroscopy (MS)-based T5000 Universal Biosensor, from Ibis Biosciences, is also mentioned. This pioneering system, by using sets of broad-range primers, is able to amplify PCR products from a large number of closely related organisms without prior knowledge of their specific genomic sequences. By accurately determining the nucleotide composition (the amount of each nucleotide) of the unknown sequence through mass spectroscopy (MS), the identification of PCR products may be carried out almost instantaneously. The following text gives an overview of the DNA biosensors research and background, as well as current trends for the forthcoming future.

2. Fundamentals of hybridization DNA biosensors

Conventional methods for specific genomic sequence analysis include nucleic acid sequencing and hybridization, the later more routinely used in clinical laboratories due to its higher simplicity [4]. DNA hybridization usually occurs between a known DNA sequence (probe) and an unknown counterpart (target), but DNA–ribonucleic acid (RNA) and RNA–RNA hybridizations can also occur [5]. The duplex formation can be detected following the association of an appropriate hybridization indicator or through other changes accrued from the binding event. DNA probes may be produced by chemical methods or by molecular biology; in this case, a probe may be obtained by reverse-transcription (RT) of a previously isolated and specific messenger RNA (mRNA), or inferring its nucleotide sequence based on the amino acid sequence of the protein expressed by that DNA, despite the validity of this last strategy may be limited due to the genetic code degeneracy [6]. Conventional nucleic acid hybridization methods, like gel electrophoresis and Southern blotting, are usually lengthy and labor-intensive [7], and is also the intrinsic biomolecular recognizing event of most genosensors. However, in this case, it occurs directly on the surface of a physical-transducer [8]. In this way, the immobilized DNA-chain is a part of the biosensor itself. Both in vivo as onto a transducer surface (solid support), nucleic acid hybridization is stronger and more specific when the complimentarity degree between two DNA chains increases. The specificity and stability of the linkage reach a maximum in the case of full (100%) complimentarity. However, the molecular mechanisms of hybridization over solid supports are still greatly unknown and unpredictable, owing to the difficulty of accurately determine the concentration of the immobilized nucleic acid. Even so, it is commonly assumed that the relevant events in the solid/liquid interface are the analyte diffusion towards the surface of the sensor, bidimensional diffusion, adsorption and desorption [9]. Despite the similarity between the hybridization processes in solution and at an interface, the hybridization rate is typically dozens of times higher in the former case, assuming identical DNA sequences and conditions. This may be due to the partial unavailability of many linking groups in the immobilized chain, eventually involved in that immobilization process. The hybridization rate also decreases with the secondary structure level of one or both chains. This fact can be easily avoided with a proper selection of the probe-sequence. Moreover, the

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