A Survey on Nano biosensor development and its functions

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Abstract: The aim of this survey is review of Nano biosensor development and conspiring its function in different field. Nano biosensors are capable of penetration and location at specific sites within single living cells, which is made possible through developments in Nano biotechnology. Advances in nanotechnology have led to the development of nanoscale biosensors that have exquisite sensitivity and versatility. The ultimate goal of Nano biosensors is to detect any biochemical and biophysical signal associated with a specific disease at the level of a single molecule or cell. Nanotechnology has bestowed some highly exciting ingredients for the improvement of sensing phenomenon. The use of diverse nanomaterials and nanoparticles has enabled faster detection and its reproducibility in a much better way. For example, a number of particles have slow response times and are burdensome to patients. The goal of this combination is to utilize the high sensitivity and selectivity of biological sensing for analytical purposes in various fields of research and technology. Their applications include detection of microorganisms in various samples, monitoring of metabolites in body fluids and detection of tissue pathology such as cancer. The ability to detect pathogenic and physiologically relevant molecules in the body with high sensitivity and specificity offers a powerful opportunity in the early diagnosis and treatment of diseases.
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1. Introduction

Over the past decade, many important technological advances have provided us with the tools and materials needed to construct biosensor devices. Since the first invention of the Clark Oxygen Electrode sensor, there have been many improvements in the sensitivity, selectivity, and multiplexing capacity of the modern biosensor. Before the various types of biosensor technologies and application are discussed, it is first important to understand and define ‘‘biosensor’’. According to IUPAC recommendations 1999, a biosensor is an independently integrated receptor transducer device, which is capable of providing selective quantitative or semi-quantitative analytical information using a biological recognition element.

Essentially it is an analytical device, which incorporates a biological or biological derived recognition element to detect a specific bio-analyte integrated with a transducer to convert a biological signal into an electrical signal. The purpose of a biosensor is to provide rapid, real-time, accurate and reliable information about the analytic of interrogation.

Ideally, it is a device that is capable of responding continuously, reversibly, and does not perturb the sample. Biosensors have been envisioned to play a significant analytical role in medicine, agriculture, food safety, homeland security, and bioprocessing, environmental and industrial monitoring. A biosensor consists of three main elements, a bioreceptor, a transducer and a signal processing system. A biological recognition element or bioreceptor generally consists of an immobilized biocomponent that is able to detect the specific target analyte. These biocomponents are mainly composed of antibodies, nucleic acids, enzyme, cell and etc. The transducer on the other hand is a converter. The reaction between the analyte and bioreceptor bring about chemical changes such as the production of a new chemical, release of heat, flow of electrons and changes in pH or mass. The biochemical signal is converted into an electrical signal by the transducer. Eventually, the electrical signal is amplified and sent to a microelectronics and data processor. A measurable signal is produced, such as a digital display, a print-out or an optical changeThere is a need for a simple, rapid and reagentless method for specific determination, both qualitative and quantitative, of various compounds in various applications. Hence, it is paramount to have fast and accurate chemical intelligence which is particularly conspicuous in human health care.

Advances in nanotechnology have led to the development of nanoscale biosensors that have exquisite sensitivity and versatility. The ultimate goal of nanobiosensors is to detect any biochemical and biophysical signal associated with a specific disease at

the level of a single molecule or cell. They can be integrated into other technologies such as lab-on-a-chip to facilitate molecular diagnostics. Their applications include detection of microorganisms in various samples, monitoring of metabolites in body fluids and detection of tissue pathology such as cancer. Their portability makes them ideal for pathogenesis of cancer applications but they can be used in the laboratory setting as well.

The ability to detect disease-associated biomolecules, such as disease-specific metabolites, nucleic acids, proteins, pathogens, and cells such as circulating tumor cells, is essential not only for disease diagnosis in the clinical setting but also for biomedical research involving drug discovery and development. Nanotechnology, with its enhanced sensitivity and reduced instrumentation size, will rapidly improve our current biodiagnostic capacity with respect to specificity, speed, and cost.

Reduction in sensor size provides great versatility for incorporation into multiplexed, transportable, portable, wearable, and even implantable medical devices. The integration of nanoscale ultrasensitive biosensors with other medical instruments will open the door to emerging medical fields, including point-of-care diagnostics and ubiquitous healthcare systems. The biomedical application of nanobiosensors is wide; moreover, the future impact of nanobiosensor systems for point-of-care diagnostics will be unmatched. This technology will revolutionize conventional medical practices by enabling early diagnosis of chronic debilitating diseases, ultrasensitive detection of pathogens, and long-term monitoring of patients using biocompatible integrated medical instrumentation.

There are different strategies for creating next generations of nanobiosensor devices: i) the use of a completely new class of nanomaterial for sensing purposes, ii) new immobilization strategies, and iii) the new nanotechnological approaches. In the second part of this chapter, current state-of-the art principles of nanobiosensor systems are discussed along with future perspectives.

Enzyme based sensor

Enzyme based biosensors were the earliest biosensors, introduced by Clark and Lyons– an amperometric enzyme electrode for a glucose sensor which used a ‘‘soluble’’ enzyme electrode. Since the first biosensor, enzyme based biosensors have faced a massive growth in usage for various applications up to the present.

Enzymes are very efficient biocatalysts, which have the ability to specifically recognize their substrates and to catalyze their transformation. These unique properties make the enzymes powerful tools to develop analytical devices. Enzyme-based biosensors associate intimately a biocatalyst-containing a sensing layer with a transducer. The working principal is based on catalytic action and binding capabilities for specific detection. They are made of an enzyme as bioreceptor which detects the targeted analyte from a sample matrix. The lock and key and induced fit hypothesis can apply to explain the mechanism of the enzyme action which is highly specific for this type of biosensor. This specific catalytic reaction of the enzyme provides these types of biosensor with the ability to detect much lower limits than with normal binding techniques. This high specificity of enzyme–substrate interactions and the usually high turnover rates of biocatalysts are the origin of sensitive and specific enzyme-based biosensor devices. Ideally enzyme catalytic action can be influenced by several factors such as the concentration of the substrate, temperature, presence of a competitive and non-competitive inhibitor and pH. Essentially the Michaelis– Menten equation can be used to further explain the detection limit of the enzyme based biosensor (Parkinson and Pejcic, 2005). Glucose oxidase (GOD) and horseradish peroxidase (HRP) are the most widely used enzyme based biosensors reported in literature. However, some recent studies have shown that enzyme based biosensors can be used to detect cholesterol, food safety and environmental monitoring, heavy metals and also pesticides. Moreover, recent studies have reported the used of enzyme catalytic implication incorporating a nucleic acid biosensor for DNA detection.

Nanomaterials for new biosensing principles

One of the first new nanomaterials to impact on amperometric biosensors was the carbon nanotube (CNT), which was blended into a number of formulations to improve current densities and overall performance of enzyme electrodes and enzyme-labelled immunosensors.

Amperometric enzyme electrodes benefited from enhanced reactivity of NADH and hydrogen peroxide at CNT-modified electrodes and aligned CNT ‘‘forests’’ appeared to facilitate direct electron transfer with the redox centers of enzymes. The most widely used nanomaterial in industry overall to date, however, is the silver nanoparticle. These have also been harnessed as a simple electrochemical label in a highly sensitive amperometric immunoassay intended for distributed diagnostics and as an inexpensive solution for immunoassays performed in developing countries. In this electrochemical sandwich immunoassay, silver nanoparticles are used as a robust label, which can be solubilised after the binding reaction has occurred, using thiocyanate, to form a silver chelate. This benign chemistry replaces earlier versions using aggressive chemical oxidants such as nitric acid. Once solubilised, the silver concentration

can be very sensitively determined using stripping voltammetry on a single-use screen-printed carbon electrode. The silver colloid aggregates due to the presence of thiocyanate and the negatively charged aggregates are attracted to the positive potential of the carbon electrode during the pre-treatment. Once in direct contact with the electrode surface, the silver is oxidised at 0.6 V to form soluble silver ions, which are immediately complexed by the thiocyanate and detected by the ensuing anodic stripping voltammetry. Hence, the analyte concentration yields a signal which is directly proportional to the anodic stripping voltammetry peak of silver. In one example, the cardiac marker myoglobin, was measured down to 3 ng mL-1, which was comparable with the conventional enzyme-linked immunosorbent assay (ELISA). Samples volumes of less than 50 mL could be handled and the assay worked in turbid solutions without the need for sample clean up.

A variety of other nanoparticle-based strategies have been described in the literature for electrochemical affinity assays. Most recently, nanostructured materials have been used to deliver label-free electrochemical immunoassays. Gooding's group in Australia described a direct electrochemical immunosensor for detection of veterinary drug residues in undiluted milk. They used a displacement assay for with a mixed layer of oligo (phenylethynylene) molecular wire, to facilitate electrochemical communication, and oligo (ethylenelycol) to control the interaction of proteins and electroactive interferences with the electrode surface. More recently, Turner et al. reported on the use of a highly conductive N-doped graphene sheet-modified electrode, which exhibited significantly increased electron transfer and sensitivity towards the breast cancer marker.

Despite using new nanotechnologies for biosensors the application of nanomaterials to bioanalytics in array-type assays or in vivo monitoring is currently a replacement of organic dyes, radioactive or metal labels and contrast agents by metal, oxide or luminescent nanocrystals. Such methods have to be used to investigate metabolic pathways on cellular levels where conventional device-based nanobiosensors have no chance to measure. Using such new labelling nanomaterials the bioanalytical and imaging methods remain mostly unchanged, whereas the tagged or labelled biomolecule is replaced by a bionano-system. The conjugation between biomolecule and nanocrystal is crucial for every bionano-system as it determines the overall biological properties of the conjugate.

Biomimetic sensor

A biomimetic biosensor is an artificial or synthetic sensor that mimics the function of a natural biosensor. These can include aptasensors, where aptasensors use aptamers as the biocomponent. Aptamers were reported for the first time in the early 1990s and described as artificial nucleic acid ligands. Aptamers were thus chemically related to nucleic acid probes, but behaved more like antibodies and showed surprising versatility compared to other bio-recognition components. Aptamers are synthetic strands of nucleic acid that can be designed to recognize amino acids, oligosaccharides, peptides, and proteins.

An aptamer has a few advantages over antibody based biosensors such as high binding efficiency, avoiding the use of animals and smaller and less complex. However, a common challenge facing the aptasensors is that they have the properties of nucleic acids such as structural pleomorphic and chemical simplicity which reduce the assay efficiency and also increase its production cost. Subsequently, some effort has been directed towards characterization and optimization of the aptamer to overcome this limitation. Aptamer properties such as their high specificity, small size, modification and immobilization versatility, regenerability or conformational change induced by the target binding have been successfully exploited to optimize a variety of bio-sensing formats. The aptamer based biosensor has been widely used in various ways. Recently sufficient progress has been made in biomimetics sensor and aptasensor for clinical application. This includes clinical diagnostics to detect pathogen, virus and infectious disease.

Immobilization Strategies at the Nanoscale

Since the development of the first biosensor, biosensors technology has experienced a considerable growth in terms of applicability and complexity of devices. In the last decade this growth has been accelerated due the utilization of electrodes -modified nanostructured materials in order to increase the power detection of specific molecules. Other important feature can be associated with the development of new methodologies for biomolecules immobilization. This includes the utilization of several biological molecules such as enzymes, nucleotides, antigens, DNA, amino acids and many others for biosensing. Moreover, the utilization of these biological molecules in conjunction with nanostructured materials opens the possibility to develop several types of biosensors such as nanostructured and miniaturized devices and implantable biosensors for real time monitoring. The interface between the nanostructure and the biomolecule requires significant attention as it dictates the biosensor performance and sensitivity. Based on the physical and chemical properties of both the nanostructure and the biolmolecule, a number of

immobilization methods have been proposed. The key problem during the immobilization is how to fully maintain the biomolecule's conformation and activity. Non-specific biomolecule adsorption onto the nanostructure is the initial stage of the degradation mechanisms that will ultimately compromise the functionality of the biosensor. The different methods of conjugation between nanostructures and biomolecules can be divided into three categories. The first category includes methods where biomolecules are bound non-covalently to nanoparticles. Therefore, nanoparticles are first derivatized with a chemisorbed monolayer or the capping agent from synthesis to have hydrophobic surfaces. In a second step, these hydrophobic nanoparticles are precipitated and redissolved in water within tensidic micelles. In principle, this method works with all common micelle building agents such as phospholipids and sodium dodecylsulfate. In a final step, biomolecules are coupled covalently to functional groups at the outer sphere of the micelles. A major advantage of this method is that the whole process, from non-polar/polar solvent transfer to the coupling, is relatively easy to perform. The bond between nanoparticles and biomolecules is based on hydrophobic interactions within the micelles. Therefore, the conjugate disintegrates relatively easily.

The second category contains methods in which biomolecules are chemisorbed onto nanoparticles by means of a 'linker'. This can be realized in two variations: first, the biomolecules contain surfaceactive groups such as, e.g., thiols, and are directly chemisorbed onto the nanoparticles. Second, a bifunctional molecule is chemisorbed onto the nanoparticles and biomolecules are coupled to these molecules in a second step, similar to the micelles from the first category.

Chemisorption of thiols onto gold surfaces is well known and as long as the adsorption energy is less than −40 kJ mol–1, this bond has mostly covalent character. However, from a practical point of view, on a longer time-scale these conjugates can disintegrate by desorption, what could become critical for long-term experiments in the range of days.

The third category of coupling methods includes methods in which biomolecules are bound covalently to modified nanoparticles. Therefore, the nanoparticles have to be derivatized with a cross-linked surface shell, which contains binding sites for biomolecules. This cross-linked surface shell could consist of functionalized polymers or inorganic networks like silica. Second, the biomolecules have to be coupled to these surface shells. Such conjugates are very stable due to covalent bonds. The major disadvantage of these methods is the sometimes difficult and costly preparation. Compared to the other categories these methods are recommended when long-term stability of the conjugate is necessary.

In conclusion, it can be stated that different methods of producing bionanosystems with different advantages and disadvantages are available. The major problem with all of them is that the biomolecule is turned into a colloid by attaching it to a nanocrystal. Because colloids have very different 'solubility' from biomolecules, there is always a tendency for coagulation within biological media.

Nano Biosensors in Nanomedicine

Nanomedicine involves cell-by-cell regenerative medicine, either repairing cells one at a time or triggering apoptotic pathways in cells that are not repairable. Multilayered nanoparticle systems are being constructed for the targeted delivery of gene therapy to single cells. Cleavable shells containing targeting, biosensing, and gene therapeutic molecules are being constructed to direct nanoparticles to desired intracellular targets. Therapeutic gene sequences are controlled by biosensor-activated control switches to provide the proper amount of gene therapy on a single cell basis. The central idea is to set up gene therapy "nanofactories" inside single living cells. Molecular biosensors linked to these genes control their expression. Gene delivery is started in response to a biosensor detected problem; gene delivery is halted when the cell response indicates that more gene therapy is not needed. Cell targeting of nanoparticles, both nanocrystals and nanocapsules, has been tested by a combination of fluorescent tracking dyes, fluorescence microscopy and flow cytometry. Intracellular targeting has been tested by confocal microscopy. Successful gene delivery has been visualized by use of GFP reporter sequences. DNA tethering techniques were used to increase the level of expression of these genes. Integrated nanomedical systems are being designed, constructed, and tested in-vitro, ex-vivo, and in small animals. While still in its infancy, nanomedicine represents a paradigm shift in thinking – from destruction of injured cells by surgery, radiation, chemotherapy to cell-by-cell repair within an organ and destruction of non-repairable cells by natural apoptosis.

Conclusion

Simple, easy-to-use measurement devices for a diverse range of biologically relevant analytes have an intuitive appeal as portable or pocket-sized analysers, and this has driven the diverse range of applications reported in the literature. However, both historical precedent and a critical analysis of potential markets leads to an indisputable conclusion that healthcare is and will continue to be the most important area for the application of biosensors. The maintenance of health

is one of the most laudable technological objectives challenging science and technology and diagnosis is an essential prerequisite for treatment and prevention of disease. Moreover, related applications of biosensors, such as the maintenance of food safety and environmental monitoring can be aligned with this central objective. The developing world has a desperate need for robust diagnostics that can be deployed in the field by both healthcare professionals and volunteers. Infectious diseases account for around a quarter of worldwide deaths, although they are projected to decline as a percentage of total deaths over the coming 20 years, as other cause become more prevalent. In developing countries we are faced with diseases of poverty such as HIV/AIDS and tuberculosis, where the former kills 1.8 million people each year and the latter still affects around a third of the world's population and accounts for an estimated 1.4 million deaths, according to the WHO (2012), although the incidence has been falling globally at a rate of 2.2% in recent years. In addition there are 2.5 million deaths from diarrheal infections and almost 800 000 from malaria. Of the estimated 57 million global deaths in 2008, 36 million (63%) were due to non-communicable diseases. Technology needs to offer more economic solutions and distributed diagnostics enabled by biosensors and enhanced by consumer products available over-the-counter are a key part of the solution. This is also commercially attractive, with in vitro diagnostics already worth an estimated US$40 billion per year. While glucose biosensors for diabetes have had the most profound effect ondisease management to date, biosensors for other metabolites promise utility for other noncommunicable diseases such as kidney disease, which is increasingly being recognised as an emerging problem in a rapidly ageing population. Multifarious affinity biosensors have been described to detect cardiac disease markers such as creatine kinase and troponin, while cancer markers and single cell cancer detection have attracted considerable recent literature.

We hope that this brief overview has illustrated that biosensors have achieved considerable success both in the commercial and academic arenas and that the need for new, easy-to-use, home and decentralized diagnostics is greater than ever. The enormous success of the glucose sensor serves as a model for future possibilities and should not overshadow the multifarious other applications that this versatile technology can address. Emerging science, driving new sensors to deliver the molecular information that underpins all this, includes the development of semisynthetic ligands that can deliver the exquisite sensitivity and specificity of biological systems without the inherent instability and redundancy associated with natural molecules. Currently aptamers, affibodies, peptide arrays and molecularly imprinted polymers are particularly promising research directions in this respect. Chances of success are enhanced by the potential utility of some of these materials for novel therapeutic, antimicrobial and drug release strategies, since these complimentary areas will drive investment in these approaches.

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