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Biosensors: Types, features, and application in biomedicine

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ABSTRACT

Fast and precise diagnostic techniques are required for the treatment of many disorders. Biosensors are one of the diagnostic devices that are applicable in biological and medical sciences. Biosensors could be utilized to recognize biological molecules with high sensitivity. Biosensors are consisted of different components and have different types. Each type of biosensor is used in a particular field according to its specific features. Nanobodies are a novel class of antibodies with small size, high affinity, and specificity to their target. The unique properties of nanobodies make them appropriate tools for diagnostic applications. In this paper, we review biosensors, and their features and roles in medicine. Antibody/nanobody-based biosensors are also specifically discussed.

KEYWORDS: Biosensor; Nanobody-based biosensor; Antibody-based biosensor; Biomedicine; Biotechnology

1. Introduction

Biosensors are one of the technological achievements that have been developed greatly over the past few years. Biosensors are analytical devices that use intelligence to detect biological substances and components and react with them. This reaction may produce chemical, optical, or electrical signals[1]. Biosensors are sensitive and fast devices that are used for the detection of a wide range of pollutants and pathogens[2,3]. The majority of biosensors used for biological applications can detect different parameters such as temperature, pressure, pH, Ca^{2+}, *etc*. Moreover, they can be utilized for the detection of biological elements such as enzymes, antibodies, antigens, and microorganisms[4,5]. Biosensors are applicable in various fields, one of which is biomedicine. According to studies, it can be stated that the first biosensor in biomedicine was invented to detect blood glucose[6−8]. In this article, we review different parts/components of a biosensor and their application in biomedicine. In addition, we briefly discuss biosensors that are affected by different biological elements.

2. Different parts of a biosensor

A biosensor is an analytical device consisting of a bio-recognition element, detector or transducer, processor, and display[3,9,10]. Analytes are the components that can be recognized by biosensors. This recognition can take place upon binding of analytes to transducers through surface absorption, micro packaging, detention, crosslinking, and covalent bond[4,5]. Figure 1 demonstrates a schematic diagram of biosensors.

2.1. Bio−receptors (Bio−recognition elements)

Bio-receptors are molecules that are designed to interact with a specific analyte of interest. Organelles, cells, lipids, enzymes, antigens, and antibodies could be used as bio-recognition elements[11,12]. Table 1 summarizes some of the features of these biological elements.

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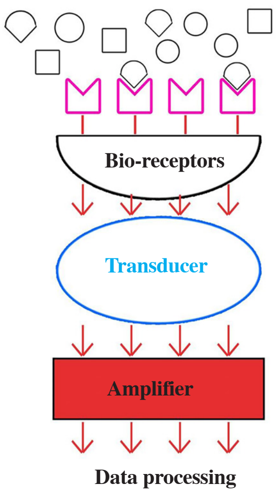

Figure 1. Schematic view of different sections of biosensors.

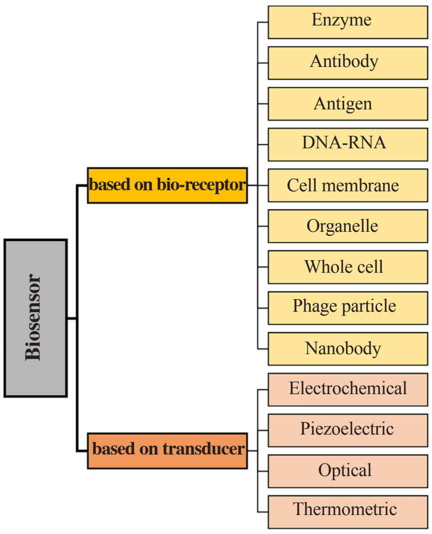

Figure 2. Classification of biosensors based on transducers and recognition elements.

2.2. Transducers

After interaction of analyte and bio-receptors, transducers can detect the type and the amount of interaction and transform/translate it to a readable signal and convert it to processors[11,13]. Figure 2 depicts different classifications of biosensors based on their transducers and biological elements. Transducers are also categorized into different groups based on the input signals. These transducers include electrochemical, optical, thermal, and piezoelectric[2,14].

2.3. Biosensors' processors

This part is responsible for the display of the results. Generally, biosensors are one of measuring devices that are designed to recognize specific analytes. This recognition is dependent on biological components and physicochemical detectors[11,13].

3. Biosensors based on bio-transducers

Sensors are powerful tools to recognize biological molecules. Electrochemical biosensors are suitable candidates for this technology due to their simplicity, high sensitivity, and favorable features[15-17]. These biosensors are based on chemical interactions of molecules, ions, or electrons that result in the modification of measurable electrical features such as electrical flow, ionic power, and potential[17-19] and could be utilized for detection of glucose, lactate, cholesterol, DNA, antigen, antibody and cancer[20,21]. The second group is optical biosensors that operate based on fluorescence and are applicable when the measuring signal is light. Optical biosensors are extremely useful because of their safe diagnostic applications. These biosensors are small and could measure intracellular parameters in small environments[22,23].

Other types of biosensors are thermal biosensors that are consisted

Table 1. Features of biological elements of biosensors.

Elements	Features	References
Antibodies	High sensitivity/strong bond (high affinity)/high selectivity	[2]
Enzymes	Binds to the sample of interest/high selectivity/catalytic activity/fast	[23]
Nanobodies	Small/can be used instead of antibodies/high affinity/suitable for structural analysis of proteins	[64]
RNA-DNA	Establishing strong bonds/known as a cost-effective method in the treatment of different diseases/utilizing this recognition element enables for early detection or diagnosis of the disease before the symptoms are presented at molecular levels	[76,83]
Cells	Low cost/flexible/requires fewer facilities/portable/does not require expert technicians	[84,85]
Bacteriophage	High sensitivity/high selectivity/low cost/often used in the diagnosis of plant diseases	[86]

Table 2. Features of biosensors based on their transducers.

Biosensors	Features	References
Electrochemical	Simple/high-sensitivity/fast/high tolerance against sample turbidity and absorbent compounds in biological samples/used for the detection of pollutants and applicable in biomedicine	[15-17]
Thermal	Thermal measurement capabilities/sensitivity changes with temperature change	[23]
Optical	Safe/small/able to detect intracellular parameters/uses different optical systems/used for the detection of pollutants	[21,22]
Piezoelectric	Detection of subtle fluctuations in human/small and durable/functions without energy source	[4,25,26]

of a combination of immobilized biomolecules and thermal sensors and are used for thermal measurement[23,24].

Another type of biosensors is piezoelectric biosensors (sensitive to mass) consisting of biological elements and piezoelectric components. The piezoelectric components are normally quartz crystals with gold coating[4,25–27]. Table 2 summarizes advantages and features of each biosensor.

4. Biosensors' features

Biosensors should possess certain features to make them applicable in different fields, such as sensitivity and repeatability. Sensitivity is the ability of a biosensor to recognize and differentiate a molecule of interest from other components in the sample[28]. The higher the sensitivity, the faster this recognition would be[28–30].

Repeatability is another important feature that a biosensor should have. This means that a biosensor should be able to repeat the same process of recognition and yield the same results[28–30]. Stability, simplicity, small size, and low cost are other features of biosensors[30].

5. Biosensors based on bio–receptors

5.1. Enzyme–based biosensors

Enzymes are generally used as bio-receptors due to their specific catalytic capabilities. Bio-catalytic activity of enzymes helps analytes to undergo biochemical interactions[31,32]. In enzyme-based biosensors, concentration or ionic changes can be easily detected with sensors[4].

5.2. DNA–based biosensors

Biosensors that are capable of detecting specific disease-related DNA sequences are necessary for medical diagnosis[33,34]. This approach is mostly based on immobilizing ssDNA on the sensors which enables hybridization of specific DNA sequences, recognition of complementary strands of DNA of interest, and signal transduction[35,36].

The basis of DNA-based sensors is the recognition of nucleic acid and is known as an affordable method in the treatment of various genetic and infectious diseases. In this technique, results are translated into readable analytical signals under controlled circumstances[37,38].

5.3. Antibody–based biosensors

Antibodies are considered a standard among biological elements due to their affinity to molecular targets. Studies have focused on the function of antibodies, their features, *etc*[39]. Each antibody has two antigen binding sites that bind to a specific epitope of an antigen[2]. Polyclonal antibodies recognize several epitopes at the same time; therefore, they are not commonly used in biosensor systems. On the other hand, monoclonal antibodies recognize only a single epitope and are more specific[40]. Antibody-based biosensors utilize antibodies or antigens as biological recognition elements[2] and could be optical or electrochemical based on the transducer, In addition, antibody-based biosensors that are extremely sensitive and have high detection capabilities[2,41] are applicable in various fields such as cancer. The SRC (proto-oncogene tyrosine-protein kinase)-associated mitosis protein (SAM68) is known as KHDRBS1[42]. Upon early detection of SAM68, we can prevent the development of cancer. In a study, an antibody-based biosensor against SAM68 was designed that could prognose pathologic state of lung cancer[43].

5.4. Nanobody–based biosensors

The process of producing antibodies is time-consuming, expensive, and challenging. It takes a lot of time to prepare antibodies so that they can be used as biological elements in biosensors. Thus, researchers came up with the idea that smaller parts of antibodies could be utilized instead of a whole antibody[44–50].

Nanobodies are single-domain antibodies. Unlike antibodies, nanobodies have smaller size around 10-12 kDa[47,48,51–58]. Moreover, they are more stable against detergents and are less toxic in physiologic environments[59–61]. Nanobodies are derived from the variable region of antibodies' heavy chain (HcAbs)[62,63]. Figure 3 demonstrates a schematic diagram of an antibody and a nanobody. Nanobodies can be used instead of antibodies in biosensors[64]. Smaller size and higher affinity of nanobodies[65] to biosensors make them a promising biological element to detect and analyze structural changes of proteins of interest[64]. In addition, a small size enables them to penetrate the cells and therefore makes them suitable recognition elements for analyzing intracellular protein structures[50,57,66–69]. Indeed, studies on the application of nanobody-based biosensors in biomedical fields are promising[44,64]. A study investigates PARP1 biosensors as nanobody-based biosensors. PARP1 has a pivotal role in DNA repair and has been considered in cancer treatment. PARP1 biosensor is designed based on PARP1 nanobody that can control and repair DNA damages in live cells[70]. In another study, nanobody-based biosensors were compared with antibody-based biosensors and it was observed that nanobody-based biosensors have more advantages than antibody-based biosensors[70]. Another study used RH5 nanobody in bioluminescence resonance energy transfer (BRET-based biosensors) that can affect Rho (Ras homologous) activity. Because of the nanobody used in BRET-based biosensor, small molecules are also affected and can be monitored by this biosensor[71,72]. In a study, E10, D10, and G10 nanobodies were used in the structure of epidermal growth factors. It was observed that these nanobodies were sensitive to EGFR and acted as biosensors[52,59]. According to these studies, it can be stated that utilizing nanobodies in biosensors could have remarkable advantages in the diagnosis and treatment of different disorders.

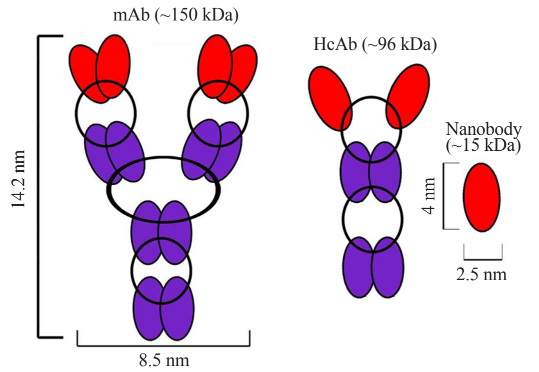

Figure 3. Structures of monoclonal antibody (mAb), heavy chain antibody (HcAb), and nanobody.

6. Biosensors used in biomedicine and their role in disease diagnosis

Biosensors are used in various fields such as medicine, marine sciences, and food industry[23,28,73]. In medicine, biosensors can quickly detect overall health status, initiation of the disease, and its progression. Biosensors can be cost-effective, sensitive, and fast and are applicable in most types of cancers, cardiovascular and other diseases[74]. They can also be utilized in biomedical studies and in particular in the diagnosis and treatment of different disorders, diagnosis of diseases at genome level and pathogens, measurement of therapeutic drugs, discovery of new drugs, and evaluation of their efficacy, as well as measurement of analytes in biological samples. Unlike other methodologies and techniques, operating biosensors does not require expert technicians and can provide fast diagnosis[1,74,75]. Biosensors also serve as a novel approach to the diagnosis and detection of cancers and tumors[76,77]. Currently, several biosensors have been designed to be utilized in the diagnosis and treatment of breast, ovarian, prostate, liver, and colon cancers, and melanoma[6,28]. Glucose biosensors are another type of biosensors that are widely used in the diagnosis of diabetes[6]. Because of an alarming increase in diseases due to high cholesterol levels, researchers have designed an enzyme-based biosensor that helps in the early recognition of cholesterol increase[78]. In a study, an antibody-based biosensor was designed and used in the early detection of two types of *Mycobacterium*[79]. Advances in molecular biology and genetic engineering enabled researchers to design biosensors based on DNA, RNA, and cells that can specifically recognize analytes of interest at molecular levels. There are biosensors for recognition of ArsR transcription factor and also biosensors with RNA-aptamer sensors that can recognize theophylline[80,81]. In cancer research and cancer treatment, biosensors can diagnose whether a tumor is benign or malignant by measuring the size of tumor-specific proteins and also help in eradicating or decreasing the population of tumor cells[76,77]. The majority of tyrosine-related disorders result in the increases of tyrosine levels. Evaluating tyrosine levels can be useful in the management of disorders. By using genetic engineering techniques, a biosensor was designed to easily quantitate tyrosine levels which helped in monitoring tyrosine levels[82].

7. Conclusion

Due to the innumerable advantages of biosensors, studies about their application in medical and biological fields have been increasing. Biosensors have different parts and are classified into different categories based on their transducers and their recognition elements and can be utilized in various medical fields. Biosensors are widely used in medicine due to their low cost and simplicity and also their capability to detect/diagnose diseases quickly. Different biosensors have different features. Antibody-based biosensors and nanobody-based biosensors are two main types of biosensors. In an antibody-based biosensor, the recognition element is an antibody. These biosensors are powerful and sensitive; however, because of some of their disadvantages, nanobody-based biosensors are generally used instead of them. Nanobody-based biosensors not only have the advantages of antibody-based biosensors but also are smaller in size, more stable, and more specific which makes them a suitable substitution for antibody-based biosensors. Studies on the application of biosensors in the treatment of different diseases are ongoing and more in-depth researches are required. Overall, it can be concluded that biosensors are promising tools in the diagnosis and treatment of various diseases such as cancer.

Conflict of interest statement

The authors declare there is no conflict of interest.

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Authors' contributions

EK: Collected data, and prepared draft of manuscript. FKL: Conceptualization, supervision, writing, review and editing.

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