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Research review paper

Nanomaterial based electrochemical sensors for in vitro detection of small molecule metabolites

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ABSTRACT

Small molecule metabolites secreted by pathological processes can act as molecular biomarkers for clinical diagnosis. In vitro detection of the metabolites such as glucose and reactive oxygen species is of great significance for precise screening, monitoring and prognosis of metabolic disorders and relevant diseases such as cancer, and has been under intense research and development in clinical chemistry and molecular diagnostics. In this review, we summarize recent developments in nanomaterial based electrochemical (bio)sensors for in vitro detection of glucose and reactive oxygen species and the progress in utilizing lightweight and flexible electrodes and micro/nanoscale electrodes for flexible and miniaturized sensors.

Contents

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1. Introduction

The translation of increasing fundamental understanding in biology systems and the increasing demands for rapid and point-of-care medical diagnosis have stimulated tremendous interest in the development of in vitro tests (Eletxigerra et al., 2015; Feyzkhanova et al., 2014; Misra et al., 2015; Vashist et al., 2015b), which are primarily used for detecting molecular and cellular targets in samples such as blood/serum, urine, sweats, saliva, interstitial fluid and tissue isolated from biological systems (Chi et al., 2012a,b; Jin and Hildebrandt, 2012). In comparison with in vivo tests conducted in living organisms such as animals, human body and plants, in vitro tests hold several advantages over in vivo tests in: i) relatively simple environmental settings by eliminating the dynamic environment in living systems; ii) less clinical and regulation limits towards practical uses; iii) using minimally invasive analytical instruments that improve the quality of life of patients; and iv) the possibilities for applications in remote settings, which are of particular importance for rapid on-site diagnosis and reducing biological risks of infectious diseases (Braga and Panteghini, 2014; Zhou et al., 2015).

In vitro diagnostics require the definite biomarkers for disease diagnosis (Wang and Qu, 2013b). In biological fluids (blood, serum, and urine), small molecule metabolites, such as glucose and reactive oxygen species with their concentrations related to specific pathological process can serve as molecular biomarkers for in vitro diagnostics (Chi et al., 2012a,b). For example, blood glucose level is a crucial index in many endocrine metabolic diseases such as diabetes. In clinic diagnosis, diabetes (hyperglycemia) reflects the disorder management of the glucose level in body. The diabetes can be diagnosed in case of a plasma glucose concentration of ≥7.0 mM (or ≥11.1 mM 2 h after a 75-g oral glucose load). During the past few years, the incidence of hyperglycemia keeps rising and becomes a serious public health problem worldwide because of the associated complications including circulatory disease, stroke, amputation, blindness, kidney failure, tissue damage and nerve degeneration (Lane et al., 2006). On the other hand, the diabetic emergencies such as hypoglycemic (low glucose) episodes cause blackouts, and severe ones are life-threatening (Hasslacher et al., 2012 and Wang, 2001). According to statistics released by the International Diabetes Federation (IDF), the global diabetes population in 2014 was 387 million, and, based on current projections, diabetes will be the 7th leading cause of death as of 2030 (Arakawa et al., 2016) with the global diabetes population reaching 590 million by 2035 (Mena et al., 2014). Diabetes is among the top five ranked diseases in medical expenses for all countries worldwide, requiring constant blood glucose monitoring for diabetic individuals.

On the other hand, chemically reactive small molecule metabolites, such as reactive oxygen species (ROS), e.g., superoxide anion (O_2^{-}•), hydroxyl radical (HO•), and hydrogen peroxide (H_2O_2), which is usually considered a ROS precursor, are natural byproducts of the normal metabolism of oxygen, and play an important role in cell signaling and homeostasis (Devasagayam et al., 2004). Recent research has disclosed that deregulated ROS can lead to the expression of proteins that control inflammation, cellular transformation, and tumor development. In particular, many cancer risk factors interact with cells through the generation of ROS (Gupta et al., 2012). Hence, the in vitro detection of ROS is of great significance for screening, monitoring and diagnosis of cancer and other related diseases (Minder et al., 2013). This trend has been attracting tremendous academic and commercial efforts to develop analytical methods and high-performance instruments.

In this review, we first outline the development of nanomaterial (NM) based electrochemical (EC) sensors towards in vitro detection of small molecule metabolites of interest. The functions of several NMs in the EC sensors and the performance of these sensors in in vitro tests have been discussed in detail. The NMs used in different EC sensing system (i.e., EC enzymatic, nanozymatic and nonenzymatic sensors) play diverse roles in improving the sensing performances, highly depended on their nanostructure and composition. Owing to their high sensitivity, selectivity, stability, fast response time, etc., the NM based EC sensors can be used in in vitro detection of glucose in human samples and real time tracking ROS from living cells. Furthermore, we present recent advances in NM based innovative electrode systems such as lightweight and bendable electrodes and micro/nanoscale electrodes, and outlook their promising applications in flexible and miniaturized sensors for in vitro tests.

2. Development of NM based EC sensors for in vitro diagnoses

2.1. Fundamental characteristics of analytical performance for in vitro tests

The in vitro tests for detecting and quantifying targets from the complex biological components, as being defined by World Health Organization, should be ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable to end-users (Peeling et al., 2006). Therefore, the fundamental characteristics of analytical performance for in vitro tests should be considered in terms of sensitivity and selectivity (for analytical reliability), detection limit and response time (for analytical capacity), repeatability and reproducibility (for analytical variability), operational easiness and speed (for analytical procedure), portability and affordability (for analytical equipment). Among these, the analytical reliability, capacity and variability are the quantity parameters for a given analytical procedure, where the sensitivity and selectivity are reflected by the slopes of analytical calibration curve of the analytes of interest and that of a particular interference, respectively. The detection limit and response time are defined by the concentration/quantity derived from the smallest signal that can be detected with acceptable degree of certainty, and the time after adding the analyte for the sensor response to reach a certain degree (e. g., ~95%) of its final value, respectively. And the repeatability and reproducibility underpin the close matching of the results of successive measurements carried out in the same (repeatability) or different (reproducibility) conditions (Justino et al., 2010). Overall, the in vitro detection of small molecule metabolites should feature a wide linear range, a low detection limit, fast response time, high sensitivity and selectivity specific to the targets. For example, the in vitro detection of glucose requires a wide linear range that can meet the needs of measuring blood glucose for both hypoglycemia and hyperglycemia, and the low detection limit that allows for noninvasively detecting trace glucose in human urine samples. Furthermore, these parameters are also crucial