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Review

Nanomaterial-based biosensors and immunosensors for quantitative determination of cardiac troponins

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ABSTRACT

Cardiovascular diseases (CVDs) are the most frequent mortality cause in many countries. The acute myocardial infraction (AMI) is one of the most common types of CVDs. Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) as predominant cardiac infarction biomarkers considered as "gold standard" for diagnosis of acute myocardial infraction (AMI). The restrictions of traditional methods have encouraged the development of highly sensitive and specific methods for cTnI and cTnT detection. The rapid, early, reliable, and cost-effective diagnosis of CVDs not only helps with patient survival, but also save cost and time to prosperous prognosis. In recent years, the concept of biosensors has opened new horizons in high precision detection. Once combined with nanomaterials, nano-scale biosensors provide powerful analytical platforms for diagnosing of cTnI and cTnT. In this article, after a brief overview of the cardiac troponins, a classification and description of the research progresses of biosensors and immunosensors for the detection and quantitative determination of cardiac troponins based on optical and electrochemical platforms are presented.

Contents

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1. Introduction

Cardiovascular diseases (CVDs) are a group of the heart and blood vessels disorders. Based on 2017 World Health Organization (WHO) report, CVDs are the main cause of death globally estimated that 31% of all global deaths (~17.7 million deaths) in 2017 was related to CVDs [1]. According to new European cardiovascular disease statistics, CVDs cost nearly € 210 billion in a year [2]. Therefore, the quick, early and low cost diagnosis of CVDs not only helps with patient survival, but also save cost and time to prosperous prognosis. One of the most common types of the CVDs is acute myocardial infraction (AMI). After blockage of a coronary artery and lack of blood supply (ischemia), myocardial muscle getting damaged and leading to the AMI [3]. Because of myocardial necrosis is irreversible and 85% heart damage progresses within the first two hours after the onset of a heart attack, it seems that accurate diagnosis and instant treatment is important to increment the survival rate [3]. The main factor to establish the AMI happening is the determination of the concentration of biomarkers in the blood sample.

The most important cardiac infarction biomarkers include the following; cardiac troponin I (cTnI), cardiac troponin T (cTnT), C-reactive protein (CRP), myoglobin, lipoprotein-associated phospholipase, interleukin-6 (IL-6), interleukin-1 (IL-1), myeloperoxidase (MPO) and tumor necrosis factor alpha (TNF-α) [4–8]. Due to outstanding specificity and supreme sensitivity for acute myocardial cell damage, cTnI and cTnT preferred for diagnosis and these biomarkers considered as "gold standard" to AMI diagnosis [7,9]. After the onset of AMI, troponins levels elevate within 4 h; half-life is about 2 h and persist in the blood for 4–10 days. The normal value of cTnI is about 0.4 ng mL^{-1} and levels higher than 2.0 ng mL^{-1} indicate risk for future serious heart events [10–12]. Troponin T found in cardiac and skeletal muscle, whereas troponin I only found in cardiac muscle and Troponin C is selectively expressed in skeletal muscle cells [13,14]. A schematic view of troponin is shown in Fig. 1.

As routine tests, immunoenzymometric assays (ELISAs) have been used for cTnI and cTnT quantification [15]. Because of time limitation in terms of diagnosis and treatment, we need highly sensitive and low cost methods with stable characteristics and fast response time. In the last decade, special attention has been paid to biosensors, because of their high sensitivity, low cost, rapid and reliable determination [16].

Biosensor is an analytical device capable of generating specific quantitative or semi-quantitative analytical information using a biological recognition element integrated to a transducer unit [18]. Optical and electrochemical platforms are two accessible types of biosensors [19]. With notable achievements in nanoscience, especially nanoparticles (NPs) introduce unique properties for designing biosensors and immunosensors and display great potential for simple, swift and sensitive monitoring of biomarkers [20]. Biosensor can help in rapid diagnosis, providing better health care and reducing the waiting time for results dissemination which is highly stressful to the patients. A variety of methods such as colorimetric [21], chemiluminescent immunoassays [22], electrochemical [23,24], fluoro-immunoassays [25], fluorescent [26,27], chemiluminescence [15] and have been developed for the determination of cTnI and cTnT. In this review, we have collected the developments in the application of biosensors and immunosensors for the determination of predominant cardiac troponins (cTnI and cTnT); also highlighted the major clinically relevant parameters such as their detection limit/range and designing of the bioassay.

2. Electrochemical-based determination of cTnI

Typically, electrochemical biosensors are detected output of an electrode transducer generated following specific binding or catalytic reactions of surface modifier biomaterials such as aptamer, enzyme, antibody, or nucleic acids on the surface of a metal or carbon electrode [28,29]. Electrochemical techniques attracted considerable attention because of special features like simplicity, sensitivity and enable performing rapid analysis. For this reason, electrochemical biosensors are the most commercialized platforms for biomedical analysis and early determination or monitoring of diseases' biomarkers [30].

2.1. Electrochemical immunosensors for cTnI determination

Because of outstanding characteristics such as the low cost, high accuracy and high sensitivity, immunosensors have become advantageous tools for diagnosis of different agents in patients. Generally, in these methods, interaction between antigens and antibodies which are immobilized on electrodes are converted into an electrical signal. This signal can be amplified by enzymatic reaction [31]. The first report of this method for measuring cTnI were presented by Guo et al. [32] based on the dual monoclonal antibody "sandwich" principle using colloidal gold as a labeled substrate. They used an anodic stripping voltammetric method for the determination of cTnI at MCM-41 mesoporous material modified carbon paste electrode (MCM-MCPE). A linear range (LR) 1–20 ng ml^{-1} and a limit of detection (LOD) of 0.8 ng ml^{-1} were obtained [32]. Ko et al. developed electrochemical microchip by assembling a surface functionalized poly (dimethylsiloxane) (PDMS) microchannel with an interdigitated array (IDA) gold electrode. First, anti-cTnI immobilized on protein G layer (generated by silanization) in the internal surface of the PDMS channel. Then, the PDMS channel was assembled with an IDA chip after surface treatment to reduce electrode fouling. Cardiac TnI, alkaline phosphatase (AP)-labeled anti-cTnI, and p-aminophenylphosphate were injected for detection. Finally, based on concentration of enzymatic product (p-aminophenol), cyclic voltammograms were obtained. The anti-cTnI concentration of 30 μg mL^{-1} was optimal packing density for the highest electrochemical signal. The detection limit was 148 pg mL^{-1} with an 8 min detection time [33].

In another report, gold nanoparticles (AuNPs) immobilized on indium tin oxide (ITO) were applied for detection of antibody-antigen interaction by measuring open circuit potential (OCP) (Fig. 2A). In this platform, monoclonal antibody against to cTnI as immunoassay capture proteins was immobilized onto the AuNPs-ITO electrode surface by self-assembly. When HRP-conjugated anti-troponin antibody were added to hybrid between the cTnI as target protein and capture protein, HRP enzyme acted as a barrier in the electron transfer procedure and a remarkable redox current decrease was observed. The novelty of this strategy was measuring the changes of OCP, to obtain electrical signal generated by the enzyme-based immunocatalytic reaction. The LR of this method was 1–100 ng mL^{-1} [34]. In this way, Bhalla et al. deposited citrate-capped AuNPs on screen printed electrodes and then was characterized by atomic force and field emission scanning electron microscopies (Fig. 2B). Anti-cTnI antibodies were immobilized onto