Biosensors and Bioelectronics 87 (2017) 264–270

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

Hybrid hydrogel photonic barcodes for multiplex detection of tumor markers

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ARTICLE INFO

Article history:
Received 7 June 2016
Received in revised form
15 August 2016
Accepted 18 August 2016
Available online 21 August 2016

Keywords:
Tumor marker
Barcode
Hydrogel
Multiplex assay
Colloidal crystal

ABSTRACT

Barcodes-based suspension array have for demonstrated values in multiplex assay of tumor markers. Photonic barcodes which are encoded by their characteristic reflection peaks are the important supports for suspension array due to their stable code, low fluorescent background and high surface-volume ratio. Attempts to develop this technology tend to improve the function of the photonic barcodes. Here, we present a new type of hybrid hydrogel photonic barcodes for efficient multiplex assays. This photonic barcodes are hybrid inverse opal hydrogel composed of poly(ethylene glycol) diacrylate (PEG-DA) and agarose. The polymerized PEG-DA hydrogel could guarantee the stabilities of the inverse opal structure and its resultant code, while the agarose could offer active chemical groups for the probe immobilization and homogeneous water surrounding for the bioassay. In addition, the interconnected pores inverse opal structure could provide channels for biomolecules diffusing and reaction into the voids of barcodes. These features imparted the hybrid hydrogel photonic barcodes with limits of detection (LOD) of 0.78 ng/mL for carcinoembryonic antigen (CEA) and 0.21 ng/mL for α-fetoprotein (AFP), respectively. It was also demonstrated that the proposed barcodes showed acceptable accuracy and detection reproducibility, and the results were in acceptable agreement with those from common clinic method for the detections of practical clinical samples. Thus, our technique provides a new platform for simultaneous multiplex immunoassay.

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1. Introduction

Cancer has become one of the most devastating diseases worldwide due to its high mortality rates (Kanodra et al., 2015). People usually have terminal cancers when they are diagnosed because of lack of the incipient symptoms. Therefore, it's important to detect, treat and cure these terrible diseases earlier (Devi et al., 2015; Meng et al., 2015; Miller et al., 2014; Zheng et al., 2014). The tumor marker has significant roles in early screening of cancer, evaluating the severity of disease and monitoring the response of cancer therapy. However, because of its limited specificity, a single tumor marker is usually not sufficient to diagnose cancer. In this point, multiplex assay of tumor markers can avoid this dilemma to improve the diagnostic accuracy (Li et al., 2014b, 2015; Liu et al., 2013; Zhao et al., 2009). To achieve the multiplexing, clinical laboratories still employ a parallel single-analyte assay by detecting one tumor marker at a time and then combining these results together. This method usually needs more sample consumption, longer assay time and higher cost.

Up to now, various approaches have been devised to realize simultaneous multiplex analysis (Freeman et al., 2013; Lee et al., 2014; Ye et al., 2014; Zou et al., 2015). A successful example of these approaches is the biochips, in which probes are bound on the flat substrate and encoded by their two-dimensional positions. In order to avoid some drawbacks of the biochips, such as slow diffusion of molecules and low sample throughput, barcodes based suspension arrays, in which probes are immobilized on the surface of fluorescence or quantum dots encoded microparticles, have become an alternative approach for multiplex assay (Li et al., 2014a; Yang et al., 2014; Yu et al., 2009; Zhang et al., 2006; Zhao et al., 2011). These barcodes have several advantages, including

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http://dx.doi.org/10.1016/j.bios.2016.08.063
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higher flexibility for new analytes and faster reaction kinetics in solution. However, the fluorescent or quantum dots barcodes are still with several disadvantages, including the photobleaching during storage and the potential interference of encoding fluorescence with analyte-detection fluorescence.

Recently, photonic crystal (PhC) barcodes have been suggested as a new type of microcarriers for suspension array (Shang et al., 2015; Shen et al., 2011; Shi et al., 2013; Song et al., 2015; Wang et al., 2011; Zhao et al., 2014). As their encoded elements are the characteristic refection peaks originated from their periodical structure-induced photonic band gap (PBG), the PhC barcodes are extremely stable, and the controversial fluorescent signal is not aroused (Kanai et al., 2010; Lee et al., 2015; Sim et al., 2014, 2015; Yang et al., 2008; Zhao etal., 2015). These properties make them suitable for multiplex detection. However, most of the PhC barcodes are composed of silica nanoparticles or inert hydrogel, both of which are with dull surface chemistry and can only provide limited surfaces for the probe immobilization and target detection. These issues have restricted many practical applications of the PhC barcodes. Thus, the creation of novel PhC barcodes with active composed materials and functional structures are still anticipated.

In this paper, we proposed a new type of hybrid hydrogel PhC barcodes with these desired features (Fig. 1). The hybrid hydrogel could be constructed by cross-linking distinct classes of polymer monomers, such as synthetic and biological macromolecules, through covalent or non-covalent method. Due to the elaborate combination of the different monomers, these hybrid hydrogels were usually imparted with distinct functions. Here, we employed a poly(ethylene glycol) diacrylate (PEG-DA) and agarose hydrogel to construct inverse opal PhC barcodes. The polymerized PEG-DA hydrogel could guarantee the stabilities of the inverse opal structure and its resultant structural color code, which impart the barcodes with distinctive encoded information for multiplex assays. The agarose could offer active chemical groups for the probe immobilization and homogeneous water surrounding for the bioassay (Jokerst et al., 2011). In addition, the interconnected pores inverse opal structure could provide channels for biomolecules diffusing and reaction into the voids of the barcodes. It was demonstrated that the PhC barcodes showed high accuracy, detection reproducibility, and acceptable agreement with common clinic method in the multiplex assay of tumor markers carcinoembryonic antigen (CEA) and α-fetoprotein (AFP) for practical clinical samples. Thus, this new PhC barcodes would find many applications in analytical and clinical areas.

2. Experimental section

2.1. Materials

Human AFP, CEA, mouse monoclonal anti-human AFP antibody, anti-human CEA antibody were purchased from Shenzhen Constant Medical Engineering Company, China. Cy3 labeled rabbit polyclonal anti-human AFP antibody, anti-human CEA antibody were purchased from Micro Biological Technology Company, Shanghai, China. Bovine serum albumin (BSA) was obtained from Sigma-Aldrich, Shanghai, China. Clinical serum samples were obtained from Zhongda Hospital, China. Phosphate buffer saline (PBS, 0.05 M, pH 7.4) and PBS containing 0.05% Tween-20 (PBST) were self-prepared. Epoxy chloropropane (ECH) was purchased from Aladdin Industrial Corporation. 2 M NaOH was used for activating agarose with ECH. Agarose was purchased from Biosharp Company, America. Poly (ethylene glycol) diacrylate (PEG-DA) with molecular weights of 700 and 2-hydroxy-2-methylpropiophenone (HMPP) photoinitiator were purchased from Sigma-Aldrich, Shanghai, China. All buffers were self-prepared using water

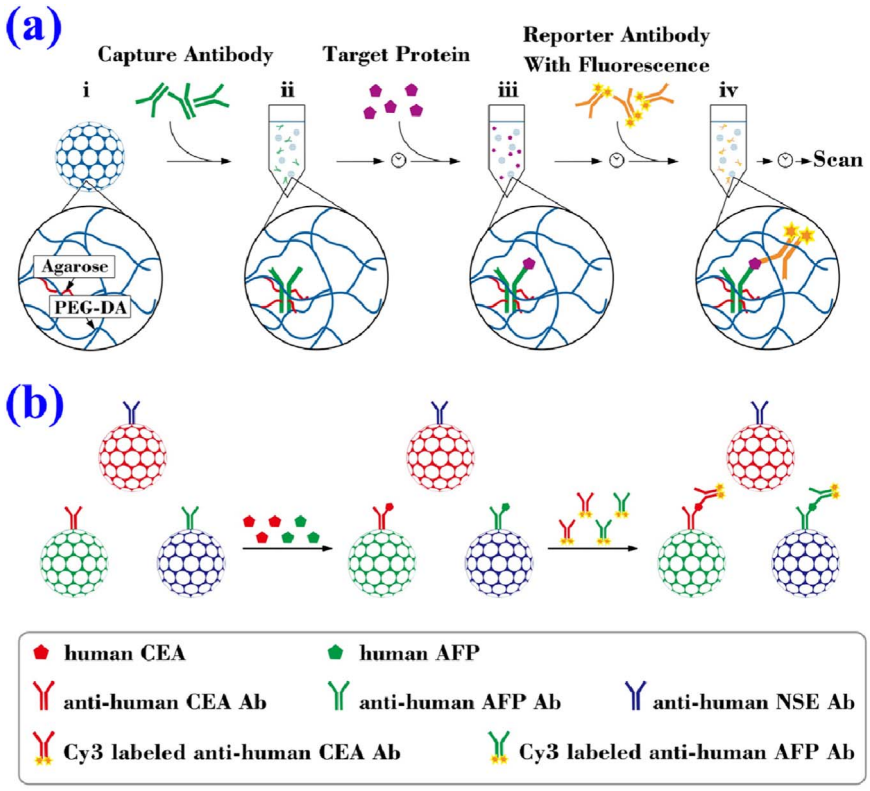

Fig. 1. (a) Schematic diagram of the structure of the hybrid hydrogel PhC barcodes and the procedure of single marker detection. The hybrid hydrogel PhC barcodes are composed of agarose and PEG-DA. The probe antibodies are immobilized on the barcodes by hydroxyl groups of agarose. (b) The procedure of multiplex detection based on the optical encoding property of the barcodes.

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