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An integrated giant magnetoimpedance biosensor for detection of biomarker

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ABSTRACT

A Dynabeads-labeled magnetic immunoassay (MIA) has been developed by using an integrated giant magnetoimpedance (GMI) biosensor for the detection of alpha-fetoprotein (AFP). The GMI biosensor (Cr/Cu/NiFe/Cu/NiFe/Al_2O_3/Cr/Au films) integrated magnetic sensing elements and a biomolecular immunoplatform. Au film was modified with 11-Mercaptoundecanoic acid (11-MUA) for the immobilization of AFP monoclonal antibody. Double antibody sandwich immunoassay was used to specifically capture and label AFP antigen. Functionalized Dynabeads were conjugated to AFP antigen by streptavidin–biotin binding assay. GMI responses were measured for sensitive detection of AFP from 1 to 10 ng/ml. Our results revealed that the presence of AFP on the biosensor improved the GMI effect owing to the induced magnetic dipole of superparamagnetic Dynabeads, and the GMI ratio was greatly increased at high frequency. Specificity of MIA was tested through the use of 1% bovine serum albumin (BSA). The underlying biophysical mechanisms responsible for the enhanced GMI effect in the detection of AFP were discussed. This work provides a complex lab-on-chip MIA for the detection of biomarker, which may open up a new way for the development of GMI-based MIA in clinical trials.

1. Introduction

In recent years, many efforts have been made to develop a new generation of compact bioanalytical system incorporated with magnetic sensor. Fluxgate sensor (Heim et al., 2009), hall sensor (Lee et al., 2009a), giant magnetoresistance sensor (Pannetier et al., 2011) and spin valve sensor (Ferreira et al., 2002) have been proposed as a biosensor for biomagnetic measurements. Giant magnetoimpedance (GMI) effect has become an interesting topic in magnetic materials research due to its potential for the development of high-performance magnetic sensors (Vacher et al., 2007; Phan and Peng, 2008; Tehranchi et al., 2011; Moulin et al., 2011). GMI effect is the great change of the alternating current (AC) impedance in soft magnetic materials when an external magnetic field is applied (Panina and Mohri, 1994; Panina et al., 1995). In soft magnetic thin films, the GMI effect is caused by the skin effect (Jackson, 1975; Landau and Lifshitz, 1975) as a consequence of the changes in the penetration depth induced by the direct current (DC) applied magnetic field through modification of the transverse permeability (Panina and Mohri, 1994; Panina et al., 1995; Phan and Peng, 2008). This effect has been extensively studied in soft amorphous ferromagnetic wires (Qin et al., 2010; Zhukov et al., 2012), thin films (Zhou et al., 2001; Peksoz et al., 2010; NazariNejad et al., 2013 and ribbons (Phan et al., 2006; Dwevedi and Markandeyulu, 2010; Laurita et al., 2011) for the development of GMI-based sensors in the last decade. GMI sensors have attracted considerable attention because of their several advantages over the conventional magnetic sensors (Ripka et al., 2001; Panina et al., 1995; Phan and Peng, 2008), such as higher sensitivity, smaller size, quicker response and lower cost. The GMI sensors have been introduced into the field of biosensing as a biosensor prototype (Chiriac et al., 2005, 2007; Chiriac and Herea, 2007; Kim et al., 2008; Blanc-Béguin et al., 2009; Yang et al., 2010; Chen et al., 2011) in order to develop a new generation of bioanalytical system.

Magnetic beads have appealed considerable research interest because of their wide applications in magnetic labeling and separation (Sun et al., 2008; Shen et al., 2012; Zhang et al., 2012; Liang et al., 2012; Suaifan et al., 2013; Chen et al., 2013). Dynabeads are uniform polymer spherical magnetic beads that have been made magnetizable and superparamagnetic. Streptavidin-coupled Dynabeads are the gold standard for isolation and handling of biotinylated nucleic acids, antibodies or other biotinylated ligands and targets.

Detection of biomarkers shows great promise for early prediction of related disease. Alpha-fetoprotein (AFP) is a major plasma protein that is produced mainly by the yolk sac and the liver during fetal development. AFP level in serum albumin is related to many diseases, for instance, AFP has been used as a biomarker for monitoring hepatocellular carcinoma, and a raised AFP level is often

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used in the clinical diagnosis of primary liver cancer (Johnson, 2001). Moreover, elevation of AFP is also used as one factor in the diagnosis of other diseases (Szabó et al., 1990; Johnson, 2001; Rosen and D'Alton, 2005; Taylor and Byrd, 2005; Sturgeon et al., 2009; Krantz et al., 2010). Until now, a variety of methods (Chester et al., 1991; Ito et al., 1999; Lee et al., 2009b; Zhang et al., 2011) have been used for the detection of AFP. However, few works have been done for the detection of AFP using an integrated GMI biosensor.

In the GMI-based biosensing experiment, detection of biological analyte can be realized by measuring the GMI responses of two sets of samples: samples with magnetic-labeled analyte and label-free samples. The functionality basis is supposed to be similar to that proposed earlier for biosensors working on the principle of magnetic field measurements (Baselt et al., 1998; Miller et al., 2002; Kurlyandskaya, 2009): the fringe fields induced by the magnetic particles employed as analyte labels provide a means for transfer of information. In the phase of the analyte detection, the GMI responses are compared for two states: with and without magnetic particles in a tested sample. The differences between the GMI responses can be used to determine the presence, level or absence of the analyte. In this study, an integrated GMI biosensor combined with double antibody sandwich immunoassay was firstly employed to detect AFP. The aim of this study is to explore the possibility and clinical significance of the GMI-based MIA for early diagnosis of cancers.

2. Experimental section

2.1. Reagents

Human AFP antigen, mouse anti-human AFP monoclonal antibody, and Biotinylated mouse anti-human AFP monoclonal antibody were purchased from LNC-Bio (Shanghai Linc-Bio Science Co., Ltd.,). N-Hydroxysuccinimide (NHS) was purchased from Medpep

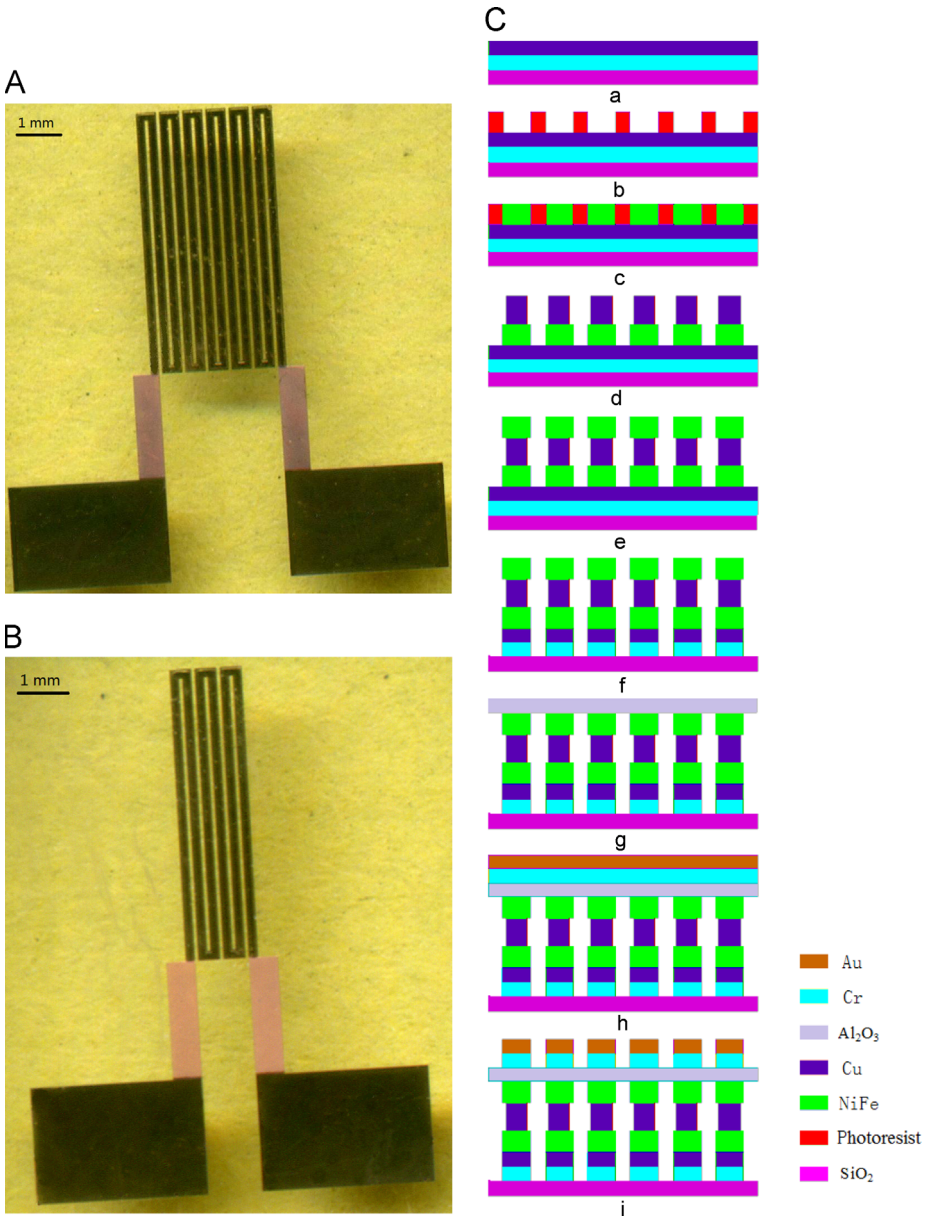

Fig. 1. The integrated GMI biosensor with a meander-line structure. (A) Top view of the sample with 6 turns. (B) Top view of the sample with 3 turns. (C) Illustration of the stepwise process for GMI biosensor fabrication.