Gold nanoparticle enhanced detection of EGFR with a terahertz metamaterial biosensor

KAI LIU,1 RUI ZHANG,2,5 YAO LIU,3 XUEQUAN CHEN,1 © KAI DI LI,1 AND EMMA PICKWELL-MACPHERSON1,4,6 ©

1Department of Electronic Engineering, The Chinese University of Hong Kong, Sha Tin, Hong Kong, China
2Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, Guangdong Province, China
3Department of Biomedical Engineering, The Chinese University of Hong Kong, Sha Tin, Hong Kong, China
4Department of Physics, University of Warwick, Coventry, United Kingdom
5rui.zhang1@siat.ac.cn
6e.macpherson@warwick.ac.uk

Abstract: The epidermal growth factor receptor (EGFR) plays an important role in the proliferation of various cancers, and the expression level of EGFR in tumor tissues can provide a basis for the diagnosis and prognosis. Improving the detection technology of EGFR to achieve high sensitivity and faster speed will benefit the diagnosis of many types of tumors. Trace biological samples can be sensitively measured with terahertz (THz) metamaterial devices. Here, a bow-tie array THz metamaterial biosensor is presented and modified with gold nanoparticles (GNPs) and EGFR antibodies for specific EGFR detection. The effect of the size of the GNP on the sensitivity enhancement was also analyzed. Enhanced sensing for EGFR was achieved with the assistance of GNPs and EGFR antibodies. Importantly, the metamaterial functionalized by GNPs and antibodies with a bigger GNP diameter achieves a greater resonance frequency shift. The proposed metamaterial biosensor can also realize tiny-volume EGFR solution detection. Our proposed technique can therefore sense EGFR sensitively with high speed, and can potentially be applied to achieve quick and accurate detection of EGFR related tumors.

1. Introduction

The epidermal growth factor receptor (EGFR) is a transmembrane protein which is important in the occurrence and development of many types of cancer, for example, gastrointestinal cancer, lung cancer, oral squamous cell carcinoma [1–3]. Traditional EGFR detection methods mainly include direct sequencing of polymerase chain reaction (PCR), denaturing high performance liquid chromatography (DHPLC), and immunohistochemistry [4,5]. Quick and sensitive detection of EGFR is important for the diagnosis and prognosis of EGFR related diseases. However, most of these traditional methods cannot realize high detection speed and sensitivity at the same time.

Terahertz (THz) spectroscopy has been widely applied in the quantitation and recognition of various biological samples [6–9]. In particular, metamaterial biosensors are further introduced for the sensitive detection of bacterial, DNA, glucose and various proteins [10–14]. Metamaterials are artificial electromagnetic materials with periodic sub-wavelength structures, which exhibit specific enhancement to local electromagnetic fields and are particularly sensitive to the dielectric alternations on the surface [15–19]. Compared with traditional detection methods, THz sensing based on metamaterials is a promising technique for time-saving, low-cost, highly sensitive and non-destructive detection of trace amount biological samples.

Metal nanoparticles have excellent physical and chemical properties and biocompatibility, which have been widely used in molecular imaging, targeted drug development and photothermal therapy [20–22]. Nanoparticles with different shapes and sizes can also be developed according to
different application purposes. In recent studies, researchers combined gold nanoparticles (GNPs) with a specific antibody or ligand to detect target biomolecules based on THz metamaterials [23,24]. This can further increase the sensitivity and decrease the dosage required to detect the targeted biomolecules. Nonetheless, the effect of the size of GNPs on the sensitivity enhancement has not hitherto been revealed.

In this work, we present EGFR sensing results from our device based on a bow-tie array THz metamaterial. First, we designed and fabricated a bow-tie array metamaterial sensor. Then the EGFR antibodies were combined with GNPs of different sizes to react with EGFR peptides on the metamaterial sensor. The metamaterial resonance frequencies for EGFR detection with and without antibodies and GNPs were measured to verify the enhanced sensitivity. In particular, the nanoparticle size effect on the sensing sensitivity was also analyzed.

This work is an important extension for our conference abstract [25], in which only the preliminary experimental results were demonstrated. More content of the sensor design and fabrication, and the experimental procedures are contained in this article. The EGFR sensing experiments based on the functionalized metamaterial with GNRs of different diameters are also included.

2. Materials and methods

A bow-tie structure was chosen for our array because bow-tie metamaterials achieve stronger electric field enhancement and localization compared to square or rectangular structures, and this is advantageous for sensing applications [26,27]. The bow-tie array structure used for the base of our sensor is illustrated in Fig. 1(a). Each bow-tie consists of two identical equilateral triangles of side 50 µm and there is a 10 µm gap at the center of each unit. 2-mm-thick quartz was adopted as the substrate. First, the quartz substrate was cleaned by ultrasonic treatment with acetone and isopropyl alcohol (IPA) for 10 min, then washed with double distilled water, and dried by nitrogen. Then, positive photoresists were deposited onto the quartz and patterned the designed bow-tie array structure. 20 nm of chromium and 100 nm of gold (Au) layers were deposited separately with the rate of 1 Å/s by metal thermal evaporation process. We used a chromium sublayer to increase the adherence of the gold layer to the surface of quartz substrate. For the lift-off process, the fabricated device was immersed with acetone under ultrasonic treatment first and washed with double distilled water to finish.

![Fig. 1.](image)

The sensing experiments based on the fabricated sensor were conducted in a THz time-domain transmission system. More details of the system are given in a previous publication from our group [28]. The sensor was placed in the focal point of THz beam. The transmission amplitude spectra were calculated. A 40 ps window was applied to the time-domain waveform to select the
first transmitted main pulse and zero padding was applied to extend the signal length to 10 ns, upon Fourier transformation, this provided a frequency resolution of 0.1 GHz. The experimental spectrum of the fabricated metamaterial is shown in Fig. 1(b), with the resonance frequency at 2.292 THz and transmission dip amplitude of 16.15 dB. The full width at half maximum (FWHM) is 0.117 THz. The dynamic range of the signal transmitted through a 2 mm thick quartz wafer, which was used as our reference, was 30 dB at 2.3 THz, sufficient to resolve the attenuation of 16.15 dB at the resonant dip.

For EGFR detection, the metamaterial was functionalized with EGFR antibodies and GNPs to improve the sensitivity. First of all, we implemented the EGFR sensing experiment with only EGFR antibody (Ab) functionalized metamaterial. The procedures were as follows. Double distilled water was applied to prepare the EGFR solution (BIOSS Co., Ltd) and phosphate buffer saline (PBS) (Keygen Biotech) was used to prepare the antibody solution (BIOSS Co., Ltd) [29]. Firstly, 10 ul EGFR solution was added onto the bare metamaterial sensor (without Ab functionalization), air dried and measured as the control. The concentration of EGFR solution ranged from 10 fM to 10 pM. To detect the binding state of EGFR and Ab, we added 10 ul Ab solutions (10 pM) onto the sensing area of the sensor and incubated for 30 min. Then, 10 ul EGFR of different concentrations were mixed with the Ab on the sensor and stored at 4 °C; to bind with Ab, air dried and measured by the THz time-domain transmission system. The mean value of three repeated measurements for each concentration was adopted for further analysis.

Moreover, the GNPs were further introduced to improve the sensitivity. The schematic diagram for EGFR detection based on bow-tie metamaterial sensor with the addition of GNPs and antibodies is shown in Fig. 2. The experimental procedures are as follows. Firstly, the GNPs were functionalized with polyethylene glycol (PEG) (Laysan Bio Inc) via the thiol group. EGFR antibodies were linked to the GNPs with the PEG linker molecule, whose N-Hydroxysuccinimide (NHS) ester group can form covalent bonds with EGFR antibody. 10 nM GNP-PEG were mixed with 100 nM EGFR antibody solution. The mixture was incubated at room temperature for 120 min to form the nanoparticle-antibody complexes. Unreacted EGFR antibody was removed by centrifugation at 15000 rpm for 30 min. After removal of the supernatant, purified EGFR antibody modified GNPs (GNP-Ab) were acquired.

Dynamic light scattering (DLS) measurements were carried out to characterize the GNP modification results by EGFR antibodies. The Gaussian fitting results of the diameter measurement data are shown in Fig. 3. The intensity is normalized to 100% [29]. The GNPs with mean diameters of 5 nm, 15 nm and 25 nm were adopted and compared in this study (Fig. 3(a)). After EGFR antibody modification, the prepared GNP-Ab increases in size compared to the bare GNP. The DLS results of EGFR antibody modified GNPs with different diameters are shown in Fig. 3(b). An increase in diameter of nearly 10-15 nm is seen compared to the bare GNPs for different nanoparticle sizes, which demonstrates the successful modification of GNPs by the EGFR antibodies.

The GNP concentration was determined by the molarity of Au used for preparation and verified by the inductively coupled plasma mass spectrometry. For the GNP-Ab solution, the GNPs with bigger diameter may contain more antibodies due to the larger surface area for antibody modification, but it is difficult to measure the exact antibody molar numbers on the GNPs. Here the molarity of the GNP was adopted to represent the GNP-Ab concentration. To compare the resonant frequency shifts of GNP and GNP-Ab with different diameters, we used double distilled water to dissolve GNP or GNP-Ab to the concentration of 10 pM [30]. 10 µL GNP or GNP-Ab solution (10 pM) with different GNP diameters was dropped on the sensor center and air dried for detection. For EGFR detection, we dissolved EGFR antibody modified GNPs with PBS and diluted to 10 pM. The GNP-Ab modification procedures are nearly the same as EGFR detection with only antibody functionalization (without GNP). Firstly, 10 µL GNP-Ab solution (10 pM) was dropped on the sensing area of metamaterial and incubated for 30 min. After incubation, we
Fig. 2. (a) Schematic diagram of GNP modification and binding processes for EGFR detection. (b) Schematic diagram of EGFR sensing based on bow-tie array metamaterial biosensor.

Fig. 3. (a) DSL results of bare GNPs with different diameters. (b) DSL results of EGFR antibody modified GNPs with different diameters.

deposited 10 µL EGFR solutions of four different concentrations on the sensor and stored at 4 °C. The THz transmission responses were measured when the reaction was completely finished. For comparison, the THz transmission measurements of bare GNP or GNP-Ab with different diameters (10 µL solution (10 pM) dropped on the metamaterial without EGFR addition) were also implemented. The average result of three repeated responses for each measurement was used.

3. Experimental details and results

The transmission amplitude spectra of EGFR detected by the antibody functionalized metamaterial biosensor are shown in Fig. 4(a). With the increase of the concentration, the resonance frequency decreases slightly. We compare the resonance frequency shift of the metamaterial sensor without and with EGFR antibody functionalization (Fig. 4(b)). A higher detection sensitivity can be achieved with the EGFR antibody functionalized metamaterial [25]. Based on the bare metamaterial, EGFR cannot be detected when the concentration is smaller than 100 fM and can
only cause about 2 GHz resonance frequency shift at concentration of 10 pM. With the addition of EGFR antibodies, 10 fM EGFR can be detected and around 8.9 GHz frequency shift was measured at the concentration of 10 pM.

![Fig. 4.](a) Transmission amplitude spectra of EGFR detected with Ab functionalized sensor. (b) The resonance frequency shift of EGFR with bare sensor (blue line) and with Ab functionalized sensor (red line). Adapted from [25].]

GNPs usually have high refractive index, and can enable a larger frequency shift range when biological samples combine with them in THz metamaterial sensors [23,24]. To further investigate the sensitivity enhancement effect of GNPs with different diameters, we compared the GNPs with the mean diameter of 5 nm, 15 nm and 25 nm, respectively. 10 µl diluted GNP solutions (10 pM) with diameter of 5 nm, 15 nm and 25 nm were evenly injected at the center of the metamaterial sensor and then air dried, respectively. The THz transmission measurement results for bare GNPs are illustrated in Fig. 5. Compared to the bare metamaterial sensor, the GNPs red-shift the resonance frequency. The 25 nm-diameter GNPs cause the largest resonance frequency shift: a red-shift of ∼12.5 GHz was observed. While the 5 nm-diameter and 15 nm-diameter GNPs only have around 2.2 GHz and 6.7 GHz frequency shift, respectively. The trend of the frequency shift is illustrated in Fig. 5(b). It is worth noting that there is not a consistent trend in the amplitude, but this is usual for such measurements and the key parameter of interest is the frequency shift [31].

![Fig. 5.](a) The transmission amplitude spectra of GNPs with diameters of 5 nm, 15 nm and 25 nm at the concentration of 10 pM. (b) The resonance frequency shift of GNPs with diameters of 5 nm, 15 nm and 25 nm at the concentration of 10 pM.

After comparing the bare GNPs with different diameters, we modified the GNPs with EGFR antibodies. 10 µL GNP-Ab solutions with different GNP diameters at the concentration of 10 pM
were dropped on the sensor center and then under the incubation for 30 min. The experimental sensing results are shown in Fig. 6. The GNP-Ab with bigger GNP diameter causes a larger resonance frequency shift. Compared to the resonance frequency of the bare metamaterial, 5 nm GNP-Ab can cause a frequency shift of around 3.8 GHz, while 15 nm and 25 nm GNP-Ab have frequency shifts of 11.3 GHz and 14 GHz, respectively.

![Fig. 6. The transmission amplitude spectra of GNP-Ab with the GNP diameters of 5 nm, 15 nm and 25 nm at the concentration of 10 pM. (b) The resonance frequency shift of GNP-Ab with GNP diameters of 5 nm, 15 nm and 25 nm at the concentration of 10 pM.](image)

To further evaluate the sensitivity enhancement effect of GNP-Ab assistance, we used the same experimental procedures as the EGFR detection with the Ab functionalized sensor. 10 µl GNP-Ab solutions (10 pM) with different GNP diameters were dropped onto the bare metamaterial, air dried and measured as control, respectively. Then the EGFR was detected based on the metamaterial biosensor functionalized by GNP-Ab with different GNP diameters. The sensitivity enhancement effects of GNP-Ab with different GNP diameters were compared. The EGFR detection results based on the GNP-Ab functionalized metamaterial biosensor with different GNP diameters are shown in Fig. 7. For comparison, the resonance frequency shift results for EGFR detection without GNP (only Ab modification) are also listed in Fig. 7(d). Compared to the resonance frequency of the metamaterial, the sensors functionalized by GNP-Ab with GNP diameters of 5 nm, 15 nm and 25 nm have resonance frequency shifts of 15 GHz, 36.5 GHz and 39 GHz for 10 pM EGFR solution, respectively. However, only 8.9 GHz shift can be achieved with only Ab modification. The GNP-Ab functionalized metamaterial has a larger frequency shift range and a higher sensitivity for EGFR detection compared to the only Ab functionalized metamaterial. Furthermore, the metamaterial functionalized by GNP-Ab with bigger GNP diameter achieves a larger resonance frequency shift. The measurement results show the feasibility and effectiveness for sensitive detection of tiny-volume EGFR solution based on our designed THz metamaterial biosensor. The proposed strategy with GNP-Ab modification can significantly increase the detection sensitivity.

The reasons for the sensitivity enhancement effects of GNP-Ab with different GNP diameters are as follows. The metamaterial has strong electromagnetic field enhancement and localization and is highly sensitive to any fluctuations in dielectric properties on the surface [15–19]. In metamaterial sensing applications, the resonant frequency shift is mainly related to the real part of the complex refractive index of the sample being sensed [10]. Metal nanoparticles usually have a high refractive index and can help achieve higher sensing sensitivity when binding to biological samples. The GNP-Ab and EGFR complexes can be regarded as the isotropic medium film based on the effective medium theory [32]. A larger resonance frequency shift would be detected with a thicker sample film on the metamaterial [33]. An increase in GNP diameter could be regarded as a way to achieve a larger average sample thickness [34], which leads to greater
Fig. 7. (a) The transmission amplitude spectra of EGFR detected with 5 nm GNP-Ab functionalized sensor. (b) The transmission amplitude spectra of EGFR detected with 15 nm GNP-Ab functionalized sensor. (c) The transmission amplitude spectra of EGFR detected with 25 nm GNP-Ab functionalized sensor. (d) The resonance frequency shift results for EGFR detection based on the metamaterial functionalized with Ab (black line), 5 nm GNP-Ab (blue line), 15 nm GNP-Ab (purple line), 25 nm GNP-Ab (red line), respectively.

resonance frequency shift. Furthermore, owing to the differences of the surface areas of GNP with different sizes, the antibodies on GNPs with different diameters are different. The GNPs with bigger diameter may contain more antibodies on their surface. This is also a secondary factor for the larger enhancement effect with bigger GNPs. It is not beneficial for the GNP size to become too big (usually < 50 nm) due to the aggregation effect, because aggregations of GNP are generally too large to disperse at the strong field areas on the metamaterial [32].

In previous studies, when the sample is measured with a bare metamaterial sensor, the sensitivity needs to be further improved [10–14]. The presented GNP-Ab functionalized metamaterial biosensor requires less sample volume to realize highly sensitive sensing, which is desirable for very costly and precious samples. This detection strategy can be applied to different metamaterial designs and other frequency bands. The sensing performance could be further increased by optimizing the metamaterial design, for example by adopting a low-absorption substrate with thinner thickness and higher quality factor resonator [35,36]. Moreover, the microfluidic channels can be introduced to further improve the sensitivity [27]. As for the applications of this metamaterial biosensor, the sensitivity and specificity could be further optimized by adjusting the metamaterial parameters to coincide with the specific resonance frequency of the target bio-molecule. Apart from the biological applications on protein solutions, the proposed strategy can be applied in a wide range of areas, such as dried bacteria sensing, cancer cells sensing and even non-biological organic matter sensing.
4. Conclusion

In conclusion, we adopted a bow-tie array metamaterial and further introduced antibody and GNPs of different diameters to enhance the sensitivity for EGFR detection. The resonance frequency shift increases with the increasing EGFR concentration. In particular, the GNP-Ab functionalized sensor with bigger GNP diameter shows a higher sensitivity. The GNP-Ab modified metamaterial biosensor can be applied for quantitative EGFR measurement. The technique presented herein therefore shows great potential for quick recognition of EGFR relevant cancers.

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