In-Situ Detection of C-Reactive Protein Using Silicon Nanowire Field Effect Transistor

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Abstract: Label-free, sensitive, and real-time c-reactive protein (CRP) sensor was fabricated using p-type silicon nanowire (SiNW) based structures configured as field effect transistors (FET) using the conventional 'top-down' semiconductor processes. The width of SiNWs were distributed 80 nm to 400 nm. Among them to improve signal-to-noise ratio and sensitivity of SiNW FET, 221 nm-SiNW was chosen for biosensing of CRP. Antibody of c-reactive protein (anti-CRP) was immobilized on the SiNW surface through polydimethylsiloxane (PDMS) microfluidic channel for detection of CRP. Specific binding of CRP with anti-CRP on the SiNW surface caused a conductance change of SiNW FET and various injections from 10 and 1 mu g/ml to 100 ng/ml solutions of CRP resulted in the conductance changes from 39 and 25 to 16%, respectively. Label-free, in-situ and very sensitive electrical detection of CRP was demonstrated with the prepared SiNW FET.

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In-Situ Detection of C-Reactive Protein Using Silicon Nanowire Field Effect Transistor

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Label-free, sensitive, and real-time c-reactive protein (CRP) sensor was fabricated using *p*-type silicon nanowire (SiNW) based structures configured as field effect transistors (FET) using the conventional 'top-down' semiconductor processes. The width of SiNWs were distributed 80 nm to 400 nm. Among them to improve signal-to-noise ratio and sensitivity of SiNW FET, 221 nm-SiNW was chosen for biosensing of CRP. Antibody of c-reactive protein (anti-CRP) was immobilized on the SiNW surface through polydimethylsiloxane (PDMS) microfluidic channel for detection of CRP. Specific binding of CRP with anti-CRP on the SiNW surface caused a conductance change of SiNW FET and various injections from 10 and 1 μg/ml to 100 ng/ml solutions of CRP resulted in the conductance changes from 39 and 25 to 16%, respectively. Label-free, *in-situ* and very sensitive electrical detection of CRP was demonstrated with the prepared SiNW FET.

Keywords: Silicon Nanowire Field Effect Transistor, Top-Down, Biosensor, C-Reactive Protein, Label-Free, Real-Time.

RESEARCH ARTICLE

1. INTRODUCTION

The detection and quantification of biological species are essential to many areas of healthcare and the life sciences, ranging from the diagnosis of disease to the discovery of novel drug molecules. The FET-type device is one of strong candidates for detecting charged molecules.[1] The two-dimensional planar FET can be configured as a sensor by modifying the gate oxide with molecular receptors. And then binding of receptors with the charged molecules results in depletion or accumulation of carriers within the FET structure.[2] But the planar-type FET devices have limitations in device structure and electrical properties such as integration of nm-scale devices and reduction in signal intensities caused by lateral current shunting.[3] To overcome these limitations, SiNW FET can be suggested because its one-dimensional structure and nm-scale of the NW leads to depletion or accumulation of carriers in the 'bulk' rather than 'surface' of the NW when the charged molecules bind to the NW surface.[4] Therefore, SiNW FET is substantially more sensitive than conventional planar FET because, generally, carriers in a narrow channel are more efficiently affected by charges on the gate insulator than those in a wide channel. Consequently, SiNW FET is a suitable candidate for a highly sensitive, label-free and real-time detection of biomolecules.[1, 5]

In this paper, we fabricated the SiNW FET by using 'top-down' process technology. Integration issue of 'bottom-up' process can be solved by 'top-down' process which has advantages of good device uniformity, high yield and scalability.[6–8]

The CRP biomarker is an acute phase reactant and a well-accepted indicator of inflammation.[9, 10] In an attempt to improve global cardiovascular risk prediction, considerable interest has focused on CRP.[11] For detection of CRP, anti-CRP was immobilized on the SiNW surface by injecting chemical solutions through the microfluidic channel. And then real-time conductance change caused by binding of CRP with anti-CRP on the SiNW surface was measured.

2. EXPERIMENTAL DETAILS

2.1. Fabrication of SiNW FET Biosensor

A *p*-type silicon-on-insulator (SOI) wafer with a 1 μm buried oxide layer and a 100 nm silicon device layer was used to fabricate SiNW FET. Boron ions were injected into the silicon device layer by ion implantation method with a

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carrier concentration of 1×10^{18} cm^{-3}. I-line stepper was used to pattern photoresist (PR) with a line width (LW) of 350 nm to 600 nm by increment of 50 nm. The PR pattern was reduced to the LW of 80 nm to 400 nm by oxygen plasma.[12] Reactive ion etching (RIE) was used to fabricate SiNW channels. To characterize ohmic contact of source and drain, boron ions were implanted with a concentration of above 10^{20} cm^{-3} into source and drain. Silicon oxide was deposited on the SiNW channels by plasma enhanced chemical vapor deposition (PECVD). And then metal contact layer for source and drain and passivation layer were deposited. Finally, for modification of SiNW surface, the region of SiNW channel was opened. Figure 1 shows field emission scanning electron microscope (FESEM) image of the fabricated SiNW FET with a SiNW width of 221 nm.

2.2. Functionalization of SiNW

Microfluidic channel was used for SiNW surface modification and isolation of metal pads from a variety of solutions when the surface of SiNW was modified. For fabrication of a PDMS microfluidic channel, SU-8 PR was used as a template. Liquid PDMS was poured on the template and was annealed in the vacuum oven. The fabricated PDMS microfluidic channel was bonded to SiNW FET by using oxygen plasma. To detect the CRP using the SiNW FET, surface modification of SiNW was needed for antigen-antibody reaction. Before the anti-CRP immobilization on the SiNW surface, the −OH groups were attached to the SiNW surface by oxygen plasma treatment. After that, the SiNW was exposed to 5% 3-aminopropyltriethoxysilane (APTES) in ethanol for 1 h to form amine groups and then exposed to 25 wt% glutaraldehyde with sodium cyanoborohydride ($NaBH_3CN$) for 3 h to form aldehyde groups.[4, 13] This is because aldehyde groups were bound easily with amine groups in anti-CRP.[8] Also, $NaBH_3CN$ was known for reducing agent and catalyst of amide

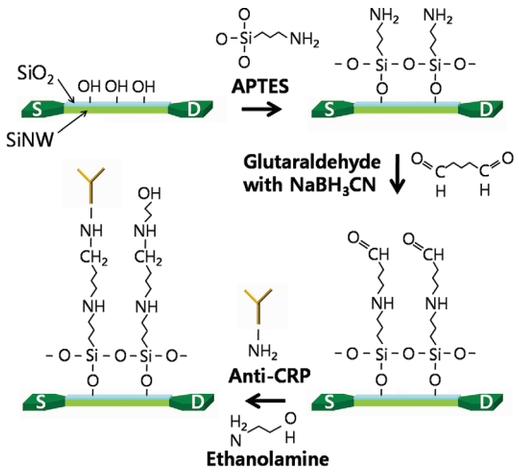

Fig. 2. Schematic diagram of the chemical process for functionalization of SiNW surface.

reaction.[14] After the formation of aldehyde groups on the SiNW surface, the anti-CRP with a concentration of 100 μg/ml was injected and preserved for 2 h. Finally, the SiNW was exposed to ethanolamine for 1 h to block non-specific binding. All of these modification processes are summarized in Figure 2.

3. RESULTS AND DISCUSSION

Before the immobilization of anti-CRP on the SiNW surface, we measured source-drain current (I_{sd}) by using semiconductor characterization system (Keithley 4200-SCS) to investigate electrical characteristics of SiNW FET. As shown in Figure 3, the I_{sd} increased linearly with increasing source-drain voltage (V_{sd}) under back gate voltage of 0 V. This result shows that there is no electrical problem such as schottky barrier in the metal contact, implying that ohmic contact was well-established in the

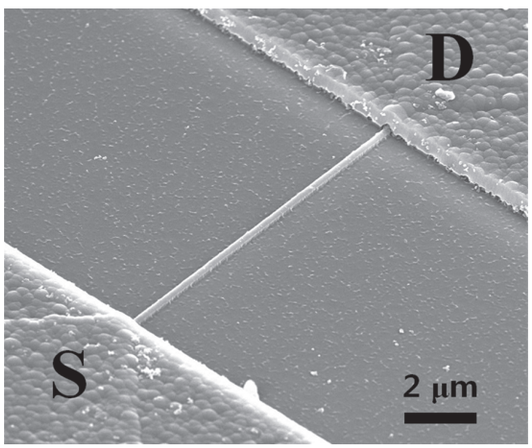

Fig. 1. SEM image of SiNW FET.

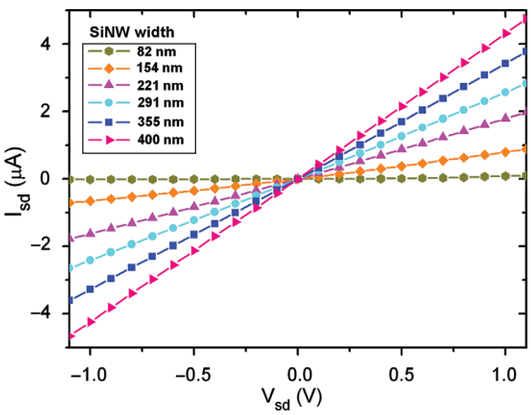

Fig. 3. Source-drain current versus source-drain voltage characteristics of the SiNW FETs depending on the width of SiNW. Back gate bias value was 0 V.

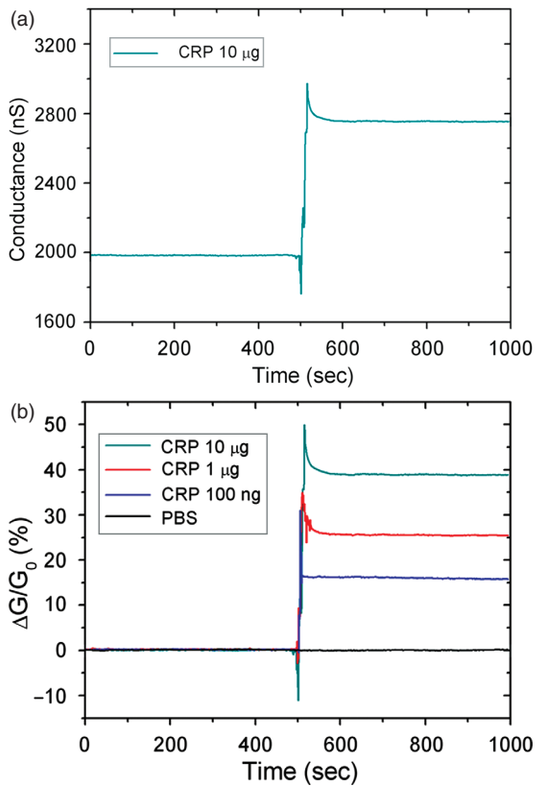

Fig. 4. Real-time sensing results of the SiNW FET. (a) Conductance change of SiNW FET by injection of 10 μg/ml CRP. (b) Sensitivity of SiNW FET depending on the concentration of CRP.

source and drain of SiNW FET. As we expected, resistance of the SiNW decreased with increasing the width of SiNW.

Among the SiNW FETs with different width of SiNW, we chose one with 221 nm-SiNW to do experiment for detection of CRP. The reason is as follows: as shown in Figure 3, if the width of the SiNW is too narrow, current level is too low so that signal can be affected by noise. On the other hand, if the width of the SiNW is too wide, current level is too high so that sensitivity of the SiNW FET is decreased. Therefore, in this work, the SiNW FET with a middle width (221 nm) SiNW was chosen to insure both signal-to-noise ratio and sensitivity.[17, 18]

We prepared the following three concentrations of CRP: 10 μg/ml, 1 μg/ml and 100 ng/ml by mixing with phosphate buffered solution (PBS). Before injection of CRP, PBS was injected through the microfluidic channel and then the I_{sd} was measured while 0.5 V of bias was applied between source and drain. After 500 seconds, the 10 μg/ml CRP was injected through microfluidic channel. As a result, the conductance increased from 1985 nS to 2756 nS due to reaction between CRP and anti-CRP as shown in Figure 4(a) and the sensitivity (defined as $\{(G_{CRP}-G_0)/G_0\} \times 100(\%)$,) of the SiNW FET was about 39% as shown in Figure 4(b), where G_{CRP} is the conductance of SiNW after CRP is coupled to anti-CRP on the SiNW surface, and G_0 is the conductance before the SiNW is exposed to CRP. In the case of *p*-type SiNW FET, the I_{sd} increases when a negative voltage is applied to the gate because positive charges are accumulated in the SiNW channel. Since the isoelectric point (pI) of CRP (about 4.8) is smaller than the PBS (pH 7.4) the overall net charge is negative.[15, 16] Thus, the conductance increment occurred after binding of CRP with anti-CRP on the SiNW surface. In the same way, 1 μg/ml and 100 ng/ml CRP were injected and the conductance change was measured. As a result, the sensitivity was 25% and 16%, respectively, as shown in Figure 4(b).

4. CONCLUSION

We have fabricated *p*-type 221 nm-SiNW FET by 'top-down' process technology. The I_{sd}–V_{sd} curves of these devices indicate that they showed good FET characteristics and can be used as biosensors. For detection of CRP, SiNW surface was modified with anti-CRP through PDMS and even at the minimum solution of 100 ng/ml CRP injected through microfluidic channel the conductance was changed up to 16%. This means that the label-free and *in-situ* detection of CRP could be done with 221 nm-SiNW FET and this 'top-down' process for SiNW fabrication is useful to enhance the reproducibility and the reliability of SiNW FET biosensor.

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RESEARCH ARTICLE

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