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Quartz crystal microbalance biosensor for label-free MDA MB 231 cancer cell detection via notch-4 receptor

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ABSTRACT

Breast cancer is the most common cancer in women with increasing insidance. Breast cancer occurs as a result of some molecular changes, such as aberrant or dysregulated expression of receptors, in breast epithelial cells. Therefore, breast cancer cells can be detected through their membrane receptors using specific antibodies. This study aims to form a quartz crystal microbalance (QCM) biosensor to detect breast cancer cells. Notch receptor signaling directs many pathways in developing breast tissue and its expression is found to be aberrant or dis-regulated in metastatic breast cancer cells. Its involvement in malignant transformation makes it a potential drug target. The human metastatic breast cancer cells, MDA MB 231 cells, are used here as a model due to the overexpression of notch-4 receptor on their membranes. First, to increase the surface area of the chip poly(2-hydroxyethyl methacrylate-PHEMA) nanoparticles were synthesized and were placed on QCM chip surface. Then, the surface was further modified and functionalized by binding notch-4 receptor antibody using carbodiimide. Nanoparticle coated and antibody attached QCM chips were characterized via FTIR-ATR, ellipsometry, contact angle measurements and by atomic force microscopy. MDA MB 231 cell samples ranging in numbers between 50-300 cells/ml were introduced to the functionalized QCM chip at a flow rate of 1.0 mL/min and the resonance frequency (f_0) was recorded. Then, cell samples were applied to the QCM biosensor and the resonance frequency was monitored. The binding mode fitted best to Langmuir isotherm model. Sensitivity is found to be high and the selectivity as tested by competitive adsorption of L929 mouse fibroblast cells showed that QCM biosensor was 17.5 times more selective for MDA MB 231 cells than the fibroblast cells. The chip was reusable and was stable over 3 months. These results indicate that, the notch-4 receptor antibody PHEMA nanoparticle QCM biosensor is highly selective and efficient system that may be used for cancer cell detection.

1. Introduction

Breast cancer is the most common cancer in women with increasing incidence. Malignancy occurs as a result of some molecular alterations in the cell [1]. Abnormalities in the flow of information including aberrant receptor expression or signaling molecules usually set the stage for malignant transformation [2]. Breast cancer stems from breast epithelial cells modified by these changes and appears in various levels of differentiation, receptor expression and metastatic potential [3,4].

The current clinical methods used in breast cancer diagnosis include imaging systems such as ultrasonography, mammography, MRI as well as tissue and blood tests. However, current diagnostic tests are based on complex and time consuming processes and are rather costly [5]. Biosensors, which are composed of a receptor and transducer, are designed by modifications that enable specific detection of a certain molecule and real time detection is achieved by using a variety of transducers. Designing of the receptor part is the main task to obtain specificity in detecting cancer cells with high precision. Breast cancer cells can be detected through their membrane receptors using specific antibodies that will serve as the receptor part of biosensors [6-8].

Among current biosensor systems, piezoelectric biosensors play an important role in biochemical sensing. Piezoelectric biosensors including the quartz crystal microbalance (QCM) is based on the sensitivity of piezoelectric crystal resonance to perturbations in the surrounding environment [9,10]. Any mass added on the QCM resonator leads to a change in the resonator oscillation frequency. Thus, one can detect biomolecular/chemical interactions by simply measuring the shift in the frequency of the resonator, which correlates with the mass change on the resonator surface [11]. QCM has become the most common, simple, inexpensive and high-resolution mass sensing

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technique in piezoelectric sensing, operating with mechanical acoustic waves as the transduction mechanism [12,13]. The QCM biosensors allow the monitoring of interactions by employing an oscillating crystal with the biomolecules immobilized on its surface [14]. Also, the QCM biosensors were reported to detect protein C [15], cytochrome c [16], amantadine [17], sialic acid [18], lipoprotein [19], cannabinoids [20]. Therefore, QCM is selected here to form a biosensor, which can detect nanoscale mass changes on its surface.

Notch-4 receptor signaling directs many pathways in the developing breast tissue and is overexpressed in metastatic breast cancer cells. Its role in malignant transformation and cancer progression have presented it as a widely studied potential drug target. MDA MB 231 cells are human breast cancer cells having high metastatic potential, are used here as a model as they overexpress this molecule on their membrane [21].

First, as they play an important role in increasing the surface area of sensor surface Poly (2-hydroxyethyl methacrylate) nanoparticles (PHEMA-NPs) were synthesized and attached on the surface of QCM chip. Nanoparticles are important scientific materials that have applications in the biosensor systems. Nanoparticles have superior properties such as high electrical conductivity, high surface-volume ratio, and interface reactivity [22]. These materials have attractively combined with the QCM biosensor system for detection of various targets such as *E- coli* O157:H7 [23], lysozyme [24], *Campylobacter jejuni* [25], lead(II) [26], and HIV-1 antigen [27].

Here, PHEMA-NPs were also proved to be effective in increasing the intensity of the signal and reaching lower limits of detection. Then, the PHEMA-NPs surface of QCM chip was further modified and functionalized by notch-4 receptor antibody (Ab-NPs QCM chip). Therefore, it was aimed to detect MDA MB 231 human breast cancer cells via notch-4 receptors with high selectivity and sensitivity. The ultimate goal of designing this Ab-NPs QCM biosensor for breast cancer cells is to demonstrate that systems designed by targeting the changes on the cell membrane can detect these cells, especially the ones in circulation, with high precision by a rapid and cost effective process.

2. Materials and methods

2.1. Materials

Hydroxyethyl methacrylate and ethylene glycol dimethacrylate as monomer, cross linker and the notch 4 receptor polyclonal antibody was obtained from Sigma chem. Co., St. Louis, USA. Poly (Vinyl alcohol) was obtained from Aldrich (Munich, Germany). Gold QCM chips were purchased from Maxtek Inc. (New York, USA). All other chemicals were in analytical grade and purchased from Merck A.G. (Darmstadt, Germany). The water used for all experiments was purified using a Barnstead (Dubuque, IA, USA) ROpure LP® reverse osmosis unit (R = 18.2 MΩ).

2.2. MDA MB 231 cells

Human breast cancer cells, MDA MB 231 (ATTC-HTB-26) and L929 mouse fibroblast cells were cultured in dMEM supplemented with 10% FBS, 2 mM L-glutamine and 1% antibiotic-antimycotic solution under the atmosphere containing 5% carbon dioxide and 95% oxygen at 37° C. Cells were first washed with PBS and counted by trypan blue test using a hemocytometer. Different samples containing 50-300 cells in PBS were applied to the QCM chip.

2.3. Preparation and characterization of PHEMA-NPs

PHEMA-NPs were synthesized according to the literature procedure by using mini-emulsion polymerization technique as reported previously [13,28]. Briefly, 93.7 mg Poly (Vinyl alcohol) (PVA; Mw:100000), as the stabilizer, dissolved in 50 mL of deionized water to form the continuous phase. Then, 14.4 mg SDS and 11.7 mg sodium bicarbonate were added to the PVA solution. On the other hand, 50 mg polyvinyl alcohol, 50 mg SDS in 100 mL deionized water, 0.45 mL of HEMA and 1.05 mL of EGDMA were added to the first solution and was homogenized at 50000 rpm for 30 min at room temperature. Then, 0.44 mg/mL potassium persulphate (KPS) as the initiator was added to the first solution and nitrogen gas was blown through the medium for about 2 min to remove dissolved oxygen. The polymerization was completed in 24 h at 40° C at 600 rpm. The average size, size distribution and polydispersity of PHEMA-NPs was determined by using a zeta-sizer (nanoS, Malvern Instruments, London, UK).

2.4. Preparation of Ab-NPs QCM chip

Before the preparation of PHEMA-NPs QCM chips, the gold surface of the QCM chip was washed with ethanol, deionized water and then acidic piranha solution as mixture ratio of 3:1(v/v) of H_2SO_4 and H_2O_2 for 10 min, respectively. The QCM chip was then dried in the vacuum oven (200 mmHg, 37 °C) and 10 µL of PHEMA-NPs were dropped on the surface of the chip. PHEMA-NPs QCM chip was dried in the oven at 37 °C. Then, the PHEMA-NP coated QCM biosensor surface was washed with ethyl alcohol and deionized water and finally dried in a vacuum incubator under 200mmHg pressure at 40 °C. Notch-4 receptor antibody was attached to the PHEMA-NP QCM chip surface with carbodiimide. For attachment, the PHEMA-NPs QCM chip was dipped into the 1/10000 diluted solution of notch-4 receptor antibody with 5 mg carbodiimide solution and mixed in an incubator at 100 rpm for 24 h. Finally, QCM chip coated with PHEMA-NPs and functionalized with notch-4 receptor antibody (Ab-NPs QCM chip) was washed with 0.5 M NaCl, phosphate buffer solution (PBS) pH: 7.4 and deionized water, respectively (Fig. 1). Also, the nanoparticles were analyzed by FTIR-ATR. The FTIR-ATR analysis was carried out using the FTIR-ATR spectrophotometer (Thermo Fisher Scientic, Nicolet iS10, Waltham, MA, USA).

2.5. Characterization of Ab-NPs QCM chip

The Ab-NPs QCM chip was analyzed by ellipsometry, contact angle measurements and atomic force microscopy. The contact angle of the surface of QCM chip was determined with a KRUSS DSA100 (Hamburg, Germany) instrument. Measurements were made by the sessile drop method. The calculated values for the QCM chip surfaces represent the average of ten different measurements.

The layer thickness analysis of QCM chip was done by an ellipsometer (Nanofil EP3, Germany). The wavelength of all measurements were made at 532 nm with an angle of incidence of 62 °. Also, AFM observation was carried out using an AFM in tapping mode (Nanomagnetics Instruments, Oxford, UK).

2.6. Real time MDA MB 231 cell detection

In order to determine the kinetics of binding, the Ab-NPs QCM chip was equilibrated with PBS. MDA MB 231 cell samples, ranging 50-300 cells/mL were introduced to the QCM chip surface for 3 min at a rate of 1.0 mL/min and the resonance frequency (f_0) was monitored and when the equilibrium is reached in about 8 minutes, 1.0 M NaCl was applied to detach the cells from the chip surface. Data was evaluated with a RQCM (Maxtek) software system. For converting the frequency to mass, considering the geometrical and physical properties of quartz crystal, the Sauerbrey equation [29] is used. The equation shows the linear relationship between the changes in the resonance frequency of quartz crystal and the mass of a thin rigid film added to its surface.

$$\Delta f = -\frac{2f_0^2}{\rho_q \nu_q}\frac{\Delta m}{A} \quad (1)$$

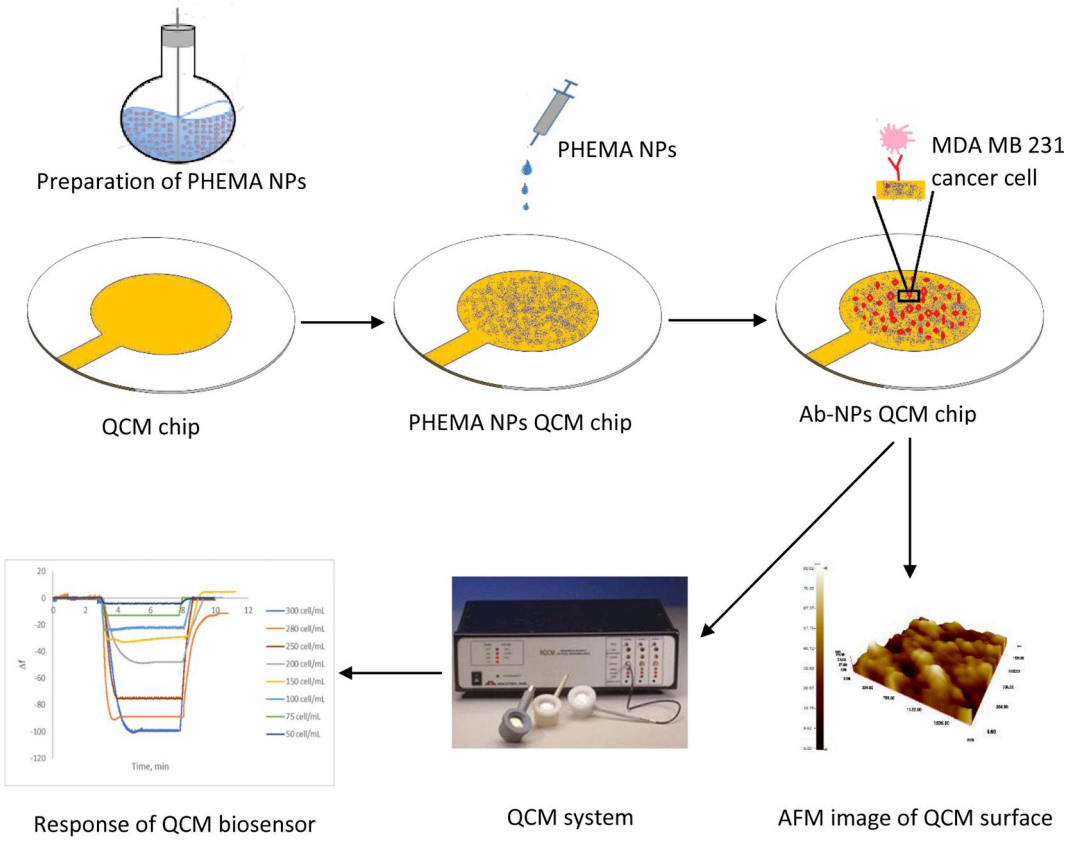

Fig. 1. Schematic view of QCM chip.

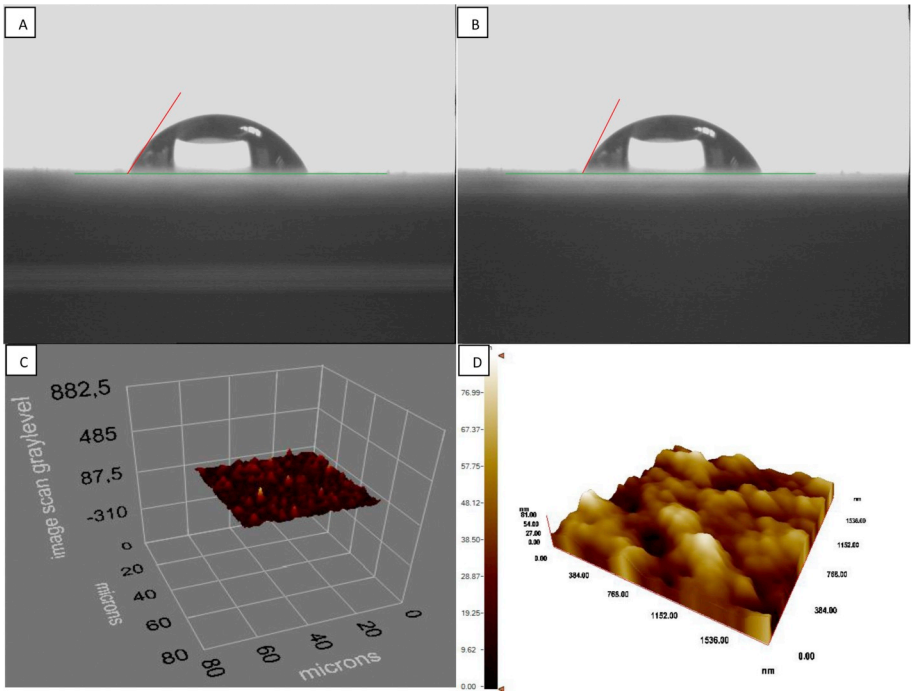

Fig. 2. Contact angles of Ab-NPs QCM chip (A), Contact angles of PHEMA NPs QCM chip (B), Ellipsometry (C) and AFM images of Ab-NPs QCM chips (D).

f_0, ν_q, ρ_q, Δm, and A are resonance frequency, shear wave velocity, density, shear modulus and active electrode of quartz crystal. To determine the selectivity of functionalized QCM chip, L929 mouse fibroblast cells were used. 150 cells/ml in PBS (pH 7.4) of mouse fibroblast cells were applied to the QCM chip surface. To check the affinity of the receptor antibody to the cells, 150 cells/ml was applied to PHEMA NPs QCM chip that was prepared by similarly without attaching notch 4 antibody. Ab-NPs QCM chip was reused 5 times and tested over a 3 months' period to analyze the reusability and stability of the QCM chip.

3. Results

3.1. Characterization of PHEMA NPs QCM chip

The size distribution of PHEMA NPs was determined and the average size of PHEMA NPs was found to be 62.18 nm with polydispersity of 0.185 (Figure Supplementary (S) 1.A). The low size of PHEMA NPs may increase the sensitivity of QCM biosensor [23]. Large surface area, fine particles and quantum confinement of NPs provide special materials that improve sensor system performance [30]. The large surface due to PHEMA NPs may allow more protein, in this case notch 4 antibody, absorption. The specific surface area of the PHEMA NPs was found to be 1899 m^2/g. PHEMA NPs were also characterized by FTIR-ATR. The band at 1713 cm^{-1} belongs to carbonyl of the ester group of HEMA while the wide band at 3000–3700 cm^{-1} belongs to the hydroxyl group of HEMA. Furthermore, the C=C double bonds belonging to the HEMA monomers which give a band at 1649 cm^{-1} were not detected in the PHEMA FTIR-ATR spectrum which shows that polymerization was complete (Figure S1.B)-.

3.2. Characterization of Ab-NPs QCM chip

The contact angle measurements were carried out in order to determine the degree of hydrophobicity of QCM chip surface. Ab-NPs and PHEMA NPs QCM chips, (with and without notch-4 receptor) had contact angles of 66.9 ± 0.32 and 66.1 ± 0.1, respectively (Fig. 2A and B). These data show that the –OH groups of PHEMA NPs increase the hydrophilic properties of the chip. The depth of the surface layer of Ab-NPs QCM chip was analyzed by using an ellipsometer. As seen in Fig. 2C, the depth of notch-4 Ab NPs QCM chip was 89.6 ± 2.9 nm. This is in agreement with zeta-sizer measurements. The Ab-NPs QCM chip surface was also visualized with AFM (Fig. 2D). The surface thickness was found to be 81.01 nm. According to the results, the Ab-NPs QCM chip surface was homogenously coated as a monolayer.

3.3. Real time MDA MB 231 cell detection

Ab-NPs QCM chip was first equilibrated with 0.1 M PBS buffer. Then, MDA MB 231 cell samples in 50–300 cells/mL density were applied to QCM system and as shown in Fig. 3B, the increase in density of cells caused a significant increase in the QCM biosensor response. The plateau was reached after 5-8 min. The response of QCM system increased linearly and the plateau was obtained after 8 min. 1.0 M NaCl solution was injected onto the QCM system for removing of cells. The whole cycle consisting of binding, removing and regeneration was completed about 12 min.

The detection limit was found to be 12 cells/mL. The data obtained from applications of increasing number of cells is used to determine the limit of detection (LOD) value. Limit of detection were calculated by equation (2):

$$\mathrm{LOD} = 3.3S/m \tag{2}$$

where S is the standard deviation of the intercept and m is the slope of the regression line [31-33]. This indicates that the QCM biosensor detects MDA MB 231 cells quantitatively.

A summary of the different detection methods for MDA MB 231 cells is given in Table 1. The table gives the limit of detection of cancer cell-targeted sensors previously reported in the literature. In our study, we showed a glamorous selective and sensitive method by using the advantages of nanoparticles and QCM biosensor technique for cell sensing.

Modeling of the equilibrium data was performed using the Langmuir, Freundlich and Langmuir-Freundlich isotherm model and given as follows [42]:

$$\text{Langmuir: } \Delta m = \frac{\Delta m C}{KD} + [C] \tag{3}$$

$$\text{Freundlich: } \Delta\ m = \Delta m_{max}[C]^{1/n} \tag{4}$$

$$\text{Langmuir–Freundlich: } \Delta\ m = \{\Delta m_{max}[C]^{1/n}/K_D + [C]^{1/n}\} \tag{5}$$

where Δm defines the amount of increased mass on the unit area of a QCM biosensor (cells/cm^2); C is the cell number (cells/mL); 1/n is the Freundlich exponent; k_a (cells/mL) and k_d (s^{-1}) are forward and reverse kinetic rate constants; K_A (cells/mL) and K_D (mL/cells) are forward and reverse equilibrium constants; and subscripts ex, max, and eq indicate experimental, maximum and equilibrium, respectively. After carrying out the equilibrium kinetic analysis, we have calculated slopes of curves and plotted concentration vs. slope curve to determine ka and k_d, respectively.

Langmuir, Freundlich and Langmuir–Freundlich isotherm models were applied to describe the binding behavior and the possible interactions between cells and Ab-NPs QCM biosensor. Equilibrium analysis and langmuir, Freundlich and Freundlich-Langmuir isotherm parameters are given in Table 2, Fig. S2. Results are in good agreement with the Langmuir model indicating that the QCM chip surface is a homogeneously distributed monolayer with co-energy and minimal lateral interaction.

3.4. Selectivity studies

Selectivity is one of the most important parameters in order to examine the binding ability of Ab-NPs QCM biosensor to MDA MB 231 cells. Therefore, the Ab-NPs QCM biosensor was used for competitive adsorption of L929 mouse fibroblast cells (150 cells/mL). As seen in Fig. 4A, the Ab-NPs QCM biosensor was more selective for MDA MB 231 cells as compared to fibroblast cells. The following terms and equations are used to analyze the selectivity of the Ab-NPs QCM biosensor:

$$\text{Distribution coefficient: } K_d = \frac{C_i - C_f}{C_f} \tag{6}$$

$$\text{Selectivity coefficient: } k = \frac{K_{d\ (Breast\ cell)}}{K_{d\ (Fibroblast)}} \tag{7}$$

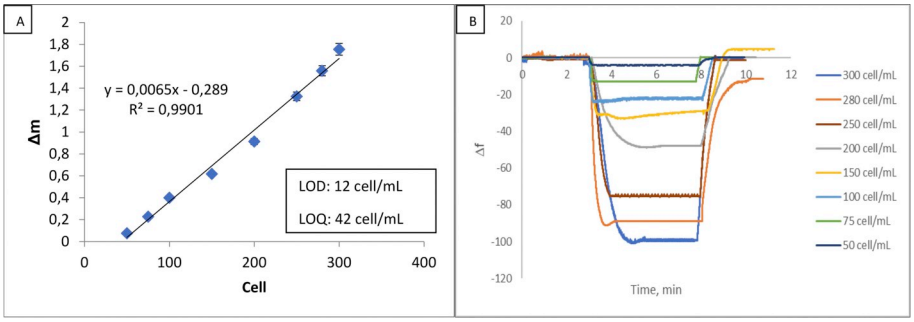

Fig. 3. Kinetics of QCM biosensor (A, B).

Table 1
The comparison of various cells detection methods.

Detection Systems	*Detection Cells*	LOD (cells/mL)	Ref.
QCM biosensor	*human lung carcinoma*	100	[34]
Chitosan-based QCM biosensor	*breast cancer*	430	[35]
Aptamer based QCM biosensor	*leukemia*	1160	[36]
Leaky surface acoustic wave aptasensor array	*MCF-7*	32	[37]
QCM biosensor	*MDAMB 231*	500	[13]
Electrochemical impedance cytosensor	*MDAMB 231*	10	[38]
Electrochemical impedance spectroscope	*MCF-7*	10	[39]
Electrochemical impedance spectroscope	*SW 620*	79	[40]
Differentialpulse voltammograms	*HepG2*	30	[41]
QCM biosensor	*MDAMB 231*	12	This study

Table 2
Calculated value of isotherms.

Langmuir		Freundlich		Langmuir- Freundlich	
Δm_{max},	1.4	Δm_{max},	1.6	$\Delta m_{max,}$	0.68
K_A, cells/mL	0.002	1/n	1.24	1/n	0.69
K_D, mL/cells	407.1	R^2	0.90	K_A, cells/mL	0.021
R^2	0.99			K_D, mL/cells	47.31
				R^2	0.91

Relative selectivity coefficient: $k' = \frac{k_{Ab-NPs\ QCM\ biosensor}}{k_{NPs\ QCM\ biosensor}}$ (8)

Here, C_i (cell/mL) is initial and C_f (cell/mL) is the final MDA MB 231 cell numbers. The selectivity coefficients (k) and relative selectivity coefficients (k') for Ab-NPs QCM biosensor and PHEMA NPs QCM biosensor respectively are given in Fig. 4A. As seen in the figure the system is highly selective for notch-4 receptor.

3.5. Reusability

The equilibration-binding-regeneration cycles were repeated for five times using 100 MDA MB 231 cell/mL. As shown in Fig. 4B, Ab-NPs QCM showed that there was not any decrease in the binding capacity during five cycles. Therefore, QCM chip can be used repeatedly for cell detection. Furthermore, the stability of QCM chip was tested at 1, 2 and 3 months (Fig. 4C) and the results showed the stability of QCM chip was acceptable.

4. Conclusion

A label-free and highly selective QCM biosensor is successfully developed to detect MDA MB 231, breast cancer cells. Sensitivity and selectivity of the sensor are found to be high. Firstly, Poly (2-hydroxyethyl methacrylate) nanoparticles (PHEMA-NPs) were synthesized for increasing the surface area of sensor surface. Then, these nanoparticles were attached on the surface of QCM chip. The QCM biosensor was prepared by modified and functionalized with notch-4 receptor antibody (Ab-NPs QCM chip). Therefore, it was aimed to detect MDA

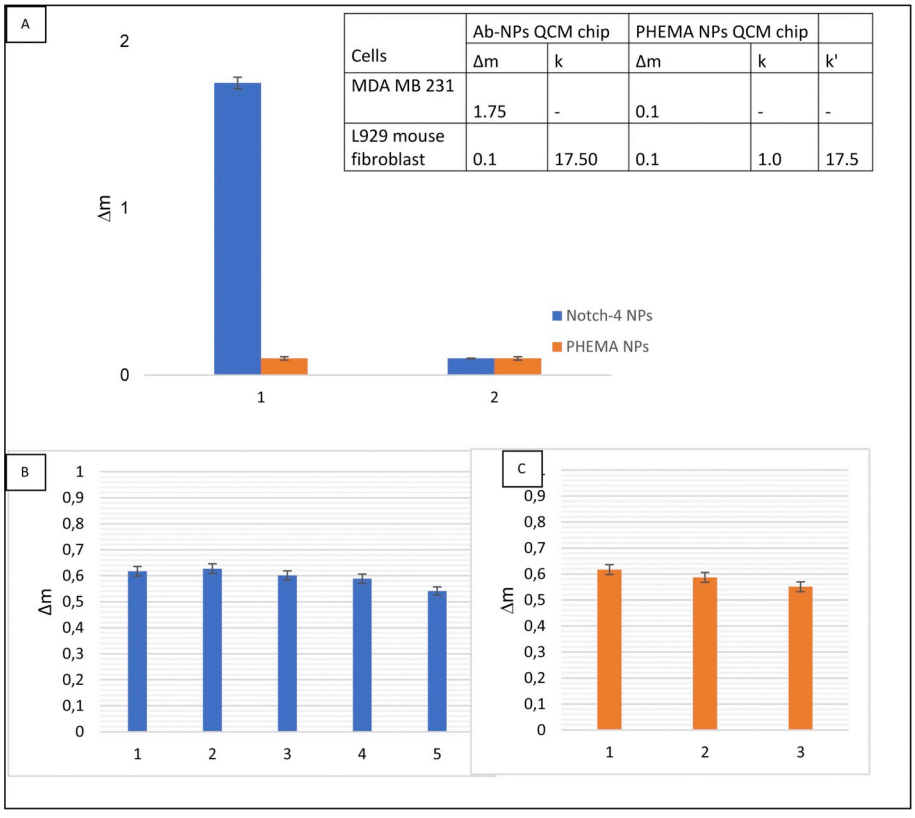

Fig. 4. Selectivity (A), reusability (B) and stability (C) of Ab-NPs QCM biosensor.

MB 231 human breast cancer cells with high selectivity and sensitivity. The PHEMA-NPs were characterized via FTIR-ATR and Ab-NPs QCM chip surfaces were characterized via ellipsometry, contact angle measurements and by atomic force microscopy. The detection limit was found to be 12 cells/mL. Furthermore, it is reusable and stable for long periods. These results show that this is an efficient system that binds MDA MB 231 cells and it may serve as a useful tool in cancer cell detection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2019.06.060.

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