Analytical Biochemistry 515 (2016) 40–46

Contents lists available at ScienceDirect

Analytical Biochemistry

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

Determination of collagen type IV by Surface Plasmon Resonance Imaging using a specific biosensor

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ARTICLE INFO

Article history:
Received 2 August 2016
Received in revised form
21 September 2016
Accepted 3 October 2016
Available online 4 October 2016

Keywords:
Biosensor
Surface Plasmon Resonance Imaging
Collagen IV

ABSTRACT

Serum collagen type IV (COLIV) is a promising tumor marker. High COLIV concentrations have been found in the serum of patients with colorectal, gastric, lung, liver and breast cancers. The aim of this work was to develop a biosensor for use with the Surface Plasmon Resonance Imaging (SPRI) technique for COLIV determination. The biosensor consists of glass covered with gold and immobilized monoclonal mouse anti-human collagen type IV antibody via cysteamine linker. The biosensor works selectively within a dynamic response range between 10 and 300 ng mL^{-1}, with LOD 2.4 ng mL^{-1} and LOQ 8 ng mL^{-1}. The precision of determination is 4.7% at a 150 ng mL^{-1} COLIV spike and 8.0% at a 20 ng mL^{-1} spike, with recoveries of 101% and 106% respectively. A 100-fold excess of collagen I, albumin, laminin and fibronectin is tolerated. The average COLIV blood plasma concentration of healthy donors determined by the developed method was 69 ± 10 ng mL^{-1}, while the median of six results available in the literature was approximately 80 ng mL^{-1}. The average COLIV blood plasma concentration of breast cancer patients was 360 ± 68 ng mL^{-1}, showing the high potential of COLIV as a marker of this type of cancer.
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1. Introduction

Surface Plasmon Resonance Imaging (SPRI) is a promising tool for the development of sensitive sensors for biologically active species. It is potentially able to compete successfully with the commonly used ELISA method in the determination of diagnostically significant biologically active species – in terms of selectivity, dynamic response range, LOD and LOQ, accuracy and precision, as well as time and cost of a single determination. SPRI is a 'label-free' and direct technique, and does not require the use of radioisotopes, special substrates, etc. Change of wavelength and polarization angle is the SPR signal which reacts to the increase in mass. In the SPRI technique, this signal is converted into an image. The increase in mass is caused by the specific or highly selective capture of the species to be determined by the biosensor from the analyzed solution. Capture of this species on the biosensor surface is caused by a previously immobilized antibody specific to the species. Alternatively, an inhibitor can be used for capturing an analyte from the solution, if it is an enzyme that is to be determined. In both cases only the species to be determined participates in the creation of the analytical signal. There are numerous examples of successful use of SPRI for the determination of diagnostically significant species such as 20S proteasome [1], cathepsin G [2], ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) [3], aromatase [4], podoplanin [5], mucin [6], angiopoietin-2, human epidermal growth factor receptor 2 (HER2), matrix metallopeptidase-1 (MMP-1) [7], matrix metallopeptidase-9 (MMP-9) [8], transgelin-2 (TAGLN2) and gene activated leukocyte cell adhesion molecule (ALCAM) [9]. Several successful SPRI applications for clinical research have been reported [10–12]. SPRI is thus capable of competing with ELISA; however, it also provides an alternative to the ELISA determination necessary in the validation of any method.

Serum collagen type IV (COLIV) is a promising tumor marker. The protein is a major component of the basement membrane acting as a barrier separating the epithelium from the underlying stroma [13]. The basement membrane also surrounds the cancer vasculature. COLIV is synthesized during angiogenesis and is deposited around the endothelial cells and pericytes. It may be a marker of angiogenic activity [14]. This activity is significantly enhanced in the case of tumor. High COLIV concentrations were determined in the serum of patients with colorectal, gastric, lung and liver cancers as well as metastatic breast cancer [15,16]. Mazouni et al. [17] found that serum COLIV concentration in

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http://dx.doi.org/10.1016/j.ab.2016.10.002
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patients with breast cancer is significantly higher than in a control group. Elevated collagen IV concentration compared with the control was also found in patients with liver cirrhosis and chronic renal diseases [16,18].

All available literature data concerning COLIV concentration in human blood serum were obtained using enzyme immunoassays known as the ELISA method [17,19–23]. ELISA is the method most popularly used for the determination of biologically active species. However, it is an indirect method. In the case of COLIV determination, an analytical signal is created by oxidation of 3,3′,5,5′−tetramethylbenzidine (TMB) by hydrogen peroxide catalyzed by horseradish peroxidase (HRP). All commercially available ELISA kits for COLIV use this reaction for creation of the analytical signal. This reaction, like all catalytic reactions used in chemical analysis, exhibits both high sensitivity and vulnerability to the presence of impurities. It should be noted that none of the ELISA kits for COLIV are intended for diagnostic purposes; they are recommended only for use in research.

The aim of this work was to develop a biosensor for use with the SPRI technique for COLIV determination. The biosensor was based on the interaction of collagen IV with a specific antibody. The analytical parameters of the SPRI biosensor were optimized and the biosensor's ability to determine COLIV in biological samples was tested.

2. Materials and methods

2.1. Apparatus

SPRI measurements were performed on a home-made apparatus which has been successfully used and described previously [1–3]. The apparatus consists of a HeNe laser (JDS Uniphase, Edmund Industrial Optics, USA), two glass lenses L1 (f = 3 mm) and L2 (f = 300 mm), two polarizers (P1 and P2), a mirror, a prism and a CCD camera (QICam, QImaging, Canada). NIH Image J version 1.42 software was used for evaluation of the SPRI images in 2D form.

2.2. Reagents

Purified monoclonal mouse anti-human collagen type IV (Tebubio, France), collagen type IV, collagen type I, fibronectin (all three Sigma, Steinheim, Germany), albumin (Calbiochem, Darmstadt, Germany), laminin (Abcam, Cambridge, USA), 2-amino-ethanethiol hydrochloride (cysteamine hydrochloride), N-ethyl-N′-(3-dimethylaminopropyl) carbodiimide (EDC), N-hydroxysuccinimide (NHS) and 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid sodium salt (HEPES) (Aldrich, Steinheim, Germany) were used, as well as absolute ethanol, acetic acid, ethylenediaminetetraacetic acid disodium salt (EDTA), magnesium chloride, potassium chloride, potassium phosphate, sodium acetate, sodium carbonate, sodium chloride, sodium hydroxide, sodium phosphate (all POCh, Gliwice, Poland), HBS-ES solution pH 7.4 (0.01 M HEPES, 0.15 M sodium chloride, 0.005% Tween 20, 3 mM EDTA), acetic buffer pH 3.79–5.57, Phosphate Buffered Saline (PBS) pH 7.2, phosphate buffer pH 7.17–8.04, carbonate buffer pH 8.50–9.86 (BIOMED, Lublin, Poland), photopolymer ELPEMER SD 2054, and hydrophobic protective paint SD 2368 UV SG-DG (Peters, Kempen, Germany). Aqueous solutions were prepared with milliQ water (Simplicity® Millipore). ELISA kit for collagen type IV determination (Echelon Biosciences. Salt Lake City, Inc. USA) was used.

2.3. Blood plasma samples

Blood plasma samples from healthy donors were provided by the Blood Donor Centre in Bialystok, Poland. Blood plasma samples from patients with breast cancer were provided by the Maria Sklodowska-Curie Oncology Center in Bialystok, Poland. All samples were provided after obtaining the consent of the Bioethical Commission.

Blood samples were centrifuged at 2500 cycles/min for 15 min. The blood plasma samples were stored at −20/−70 °C until use. Patients samples were diluted 10 times with PBS buffer prior to measurement.

2.4. Procedures

2.4.1. SEM measurements

The Scanning Electron Microscopy (SEM) measurements were performed with a commercial SEM Hirox SH-4000m with EDS System Bruker Quantax 100 Easy EDX System.

Microscopic examination was performed with using the accelerating voltage of 10 kV at magnifications of 1000x and 8000x and using the secondary electron detector (SE).

2.4.2. Chip preparation

Biosensors for COLIV determination were manufactured on glass chips as described previously [2]. The chips were covered with gold (50 nm under a 1 nm thick chromium layer) with the surface covered with photopolymer and hydrophobic paint. An array of 9 × 12 free gold surfaces was made (see Fig. 1a and b). Without mixing the tested samples, nine different solutions can be

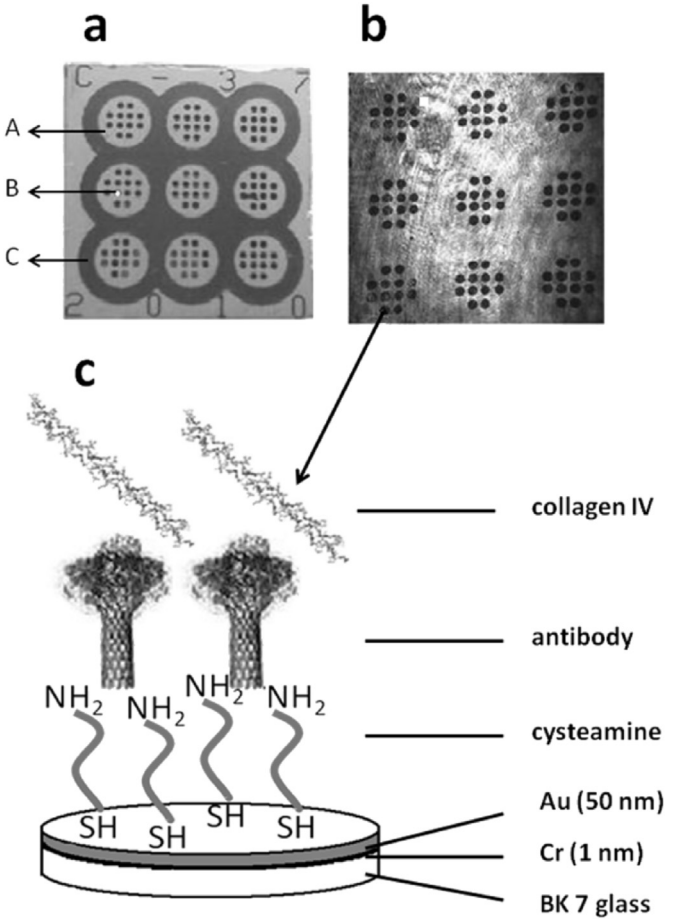

Fig. 1. a) Picture of chip (A-photopolymer, B-free gold surface, C-hydrophobic paint), b) the SPR image of the chip obtained using a CCD camera, c) the schematic illustration of the sensor active part.

simultaneously measured and twelve single measurements can be made from each solution. Twelve individual SPRI signals for each sample can be obtained.

2.4.3. Antibody immobilization and COLIV entrapment

The chips' surface was subsequently rinsed with absolute ethanol and water, dried in a stream of nitrogen and immersed in 20 mM cysteamine ethanolic solutions for a minimum of 2 h. The chips with immobilized linker were rinsed again and dried. For antibody immobilization, 50 μL of antibody solution (6 μg mL^{-1}, apart from the experiments for optimization of antibody concentration) was mixed with 250 μL of 50 mM N-hydroxysuccinimide (NHS), 250 μL of 200 mM N-ethyl-N′-(3-dimethylaminopropyl) carbodiimide (EDC) and 100 μL of carbonate buffer, placed on the amine-modified surface, and incubated at 37 °C for 1 h. The surface of the prepared biosensor was rinsed five times with water. The schematic illustration of the sensor active part is presented on Fig. 1c. The chip was then treated with the analyte solution (containing COLIV) for 10 min, rinsed with the buffer and dried, and the SPRI measurement was performed.

SEM pictures was used to confirm the creation of subsequent layers: gold, thiol (cysteamine), antibody and immobilized collagen IV. Fig. 2 shows a representative picture of the SEM measurements. Pictures are taken of bare gold (Fig. 2a), cysteamine (Fig. 2b), antibody (Fig. 2c) and immobilized collagen IV (Fig. 2d). The presented SEM pictures confirm that the described stages of the creation of each layer on the biosensor surface has really taken place. This may be concluded on the basis of the creation of different structures after each stage.

The developed biosensor for COLIV determination is able to cooperate with our home-made SPRI apparatus, however its basic architecture including gold and thiol layers and antibody receptor is basically able to work with any SPR or SPRI instrument.

2.4.4. SPRI measurement

A fixed angle of incident light was maintained during the measurements, and the reflectivity was simultaneously measured across the entire chip surface. The contrast values obtained for all pixels across a particular sample single spot were integrated. Thus the SPRI signal was integrated over the single spot area. A background correction was applied (it is the signal difference between the place of the receptor-analyte complex and the receptor-free space treated only with PBS buffer. Non-specific binding was monitored by measuring the signal SPRI in place on the chip without the receptor (ligand). Minimization of the non-specific binding obtained by preparing samples in PBS buffer (NaCl an KCl concentration ~200 mM) at pH 7.4 near the isoelectric point of the protein. Non-specific binding in the case of natural samples is eliminated by a background correction. It is the signal difference between the place of the receptor-analyte complex and the receptor-free space treated with natural sample.

The signal was measured twice based on the registered images, after immobilization of the antibody, and then after interaction with the sample containing COLIV. The SPRI signal, which is proportional to the mass of entrapped COLIV, was obtained as the difference between the signals before and after interaction with the analyzed sample, for each spot separately.

2.4.5. Statistical analysis

Student's t-test was used for statistical analysis. All results are given as mean ± confidence limit. A value of $p < 0.05$ was considered significant. Data obtained by SPRI biosensor and ELISA for natural samples was analyzed using Pearson's correlation.

3. Results and discussion

3.1. Influence of antibody concentration on the analytical signal of collagen IV

Apart from collagen IV (COLIV) concentration, the analytical response of the biosensor depends on the antibody concentration. Therefore, antibody concentration was optimized. Experiments

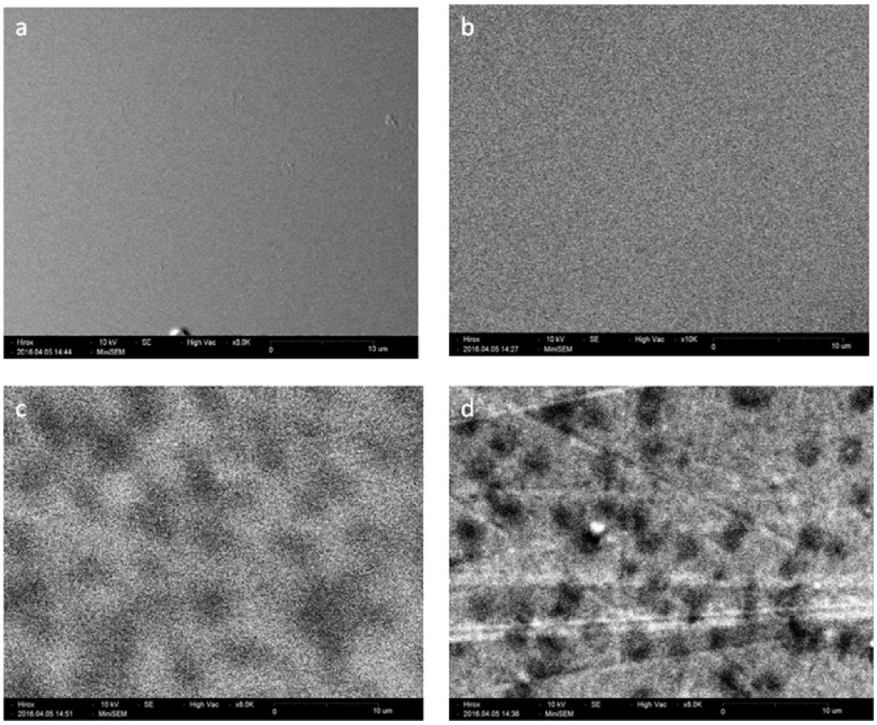

Fig. 2. SEM images of the individual layers on the gold chip surface, a) the pure gold; b) the cysteamine layer; c) the antibody layer; and d) the collagen IV layer.

were performed at pH = 7.4 and at a constant collagen IV concentration equal to 300 ng mL^{-1}. Antibody concentration varied between 1 and 15 μg mL^{-1}. The experiment was performed as described in previous sections. The results are shown in Fig. 3. A Langmuirian type of dependence was obtained, with a clear plateau for antibody concentrations equal to or higher than 6 μg mL^{-1}. This value was selected as optimal for further experiments.

3.2. Analytical response of the sensor to COLIV concentration. Calibration curves

A calibration curve was plotted within the range 10–1000 ng mL^{-1} at constant pH (7.4) and antibody concentration (6 μg mL^{-1}). The results are shown in Fig. 4. Linearity of the dependence is observed up to 300 ng mL^{-1} (R^2 = 0.9921). The absence of linearity above 300 ng mL^{-1} is caused by the saturation of active points with COLIV.

3.3. Recovery and precision of the developed method. LOD

Three series of measurements were performed for the determination of recovery, precision, and limits of detection (LOD) and quantification (LOQ). In each series 24 single measurements were made. The first series was 'blank', i.e. performed without a COLIV spike; this series was used for LOD and LOQ determination on the basis of 3SD and 10SD respectively. COLIV spikes of 20 ng mL^{-1} and 150 ng mL^{-1} were used in the subsequent two series. The results are shown in Table 1.

Both precision and recovery are typical for this kind of determination, and are satisfactory. Both analytical parameters are slightly worse at low concentration, which is typical. The LOD of the developed method is equal to 2.4 ng mL^{-1}, and the LOQ is equal to 8 ng mL^{-1}.

Recovery of the developed method was also checked by the addition of standard solution of COLIV into nine different samples of human plasma – Table 2. The spike of COLIV was 70.0 ng mL^{-1}. Recoveries are within the range of 99–103% and show no significant matrix effect.

3.4. Selectivity of the developed method

The selectivity of the developed method is a crucial factor for its potential application. Collagen I, albumin, fibronectin and laminin

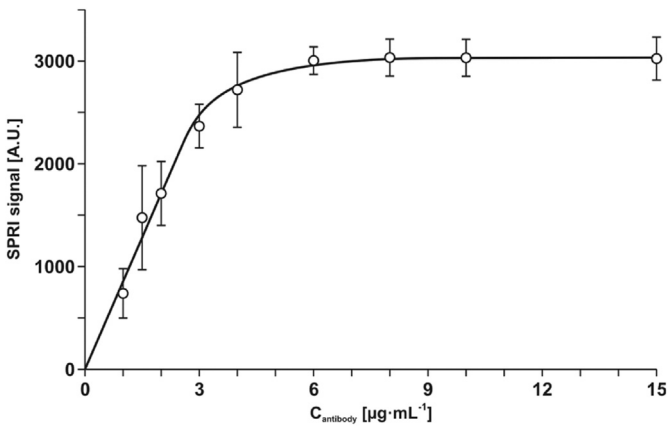

Fig. 3. Dependence of SPRI signal (Arbitrary Units) on monoclonal mouse anti-human collagen type IV antibody concentration. COLIV concentration: 300 ng mL^{-1} pH = 7.4. Error bars were calculated for 12 independent measurements for each concentration at a 95% confidence level.

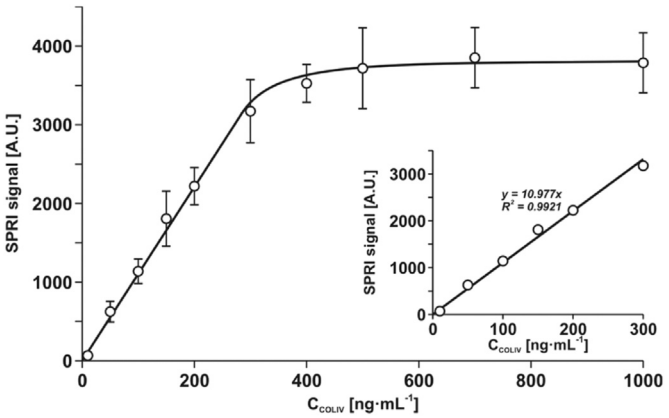

Fig. 4. Dependence of the SPRI signal (Arbitrary Units) on collagen IV concentration. Monoclonal mouse anti-human collagen type IV antibody concentration: 6 μg mL^{-1} pH = 7.4. Error bars were calculated for 12 independent measurements for each concentration at a 95% confidence level.

were investigated as potential interferents. COLIV concentration was selected as 150 ng mL^{-1}, i.e. the middle value of the dynamic response range of the method. The excess of interferents varied from 1:1 to 1:100. The results are shown in Table 3.

No significant influence of these substances on COLIV determination was observed at 100-fold excess. Thus, the developed method can be classified as highly selective.

3.5. Determination of COLIV in real samples

Using the developed method, COLIV concentration was determined in nine samples of blood plasma from patients with breast cancer and nine samples from healthy volunteers. The aim of this experiment was to demonstrate the potential of the method with typical real samples. The determination was performed as described in previous sections. The results are shown in Table 4. The available literature data, though limited in quantity, are also included.

The results for patients with breast cancer (360 ± 68 ng mL^{-1}) are on average five times higher than for healthy volunteers (69 ± 10 ng mL^{-1}), which indicates the high diagnostic potential of the method for determination of circulating COLIV. The only available data [17] also show a statistically significant higher level of COLIV in the blood plasma of breast cancer patients as compared with the control (166 vs. 115 ng mL^{-1}). Those authors state that serum collagen IV levels are elevated in patients with breast cancer relative to healthy women because of increased angiogenic activity in the cancer. This conclusion is strengthened by the results in Table 4, because the control results of Mazoumi et al. [17] (115 ng mL^{-1}) are probably too high, as compared with published results for COLIV in the blood serum of healthy volunteers ([19–21,23] and Table 3). The average serum COLIV concentration from these sources is approximately 70 ng mL^{-1}. On the other hand, Nystrom et al. [22] reported a serum COLIV concentration of 106 ± 35 ng mL^{-1}, with the confidence interval hardly covering the level of 70 ng mL^{-1}.

A significant conclusion from Table 3 is that the results for serum COLIV concentration obtained in this work are located around the mid-point of the results reported by other authors and obtained by different methods. This fact enhances the credibility of the results obtained by the developed method. Although the methods used for COLIV determination in those papers were described only marginally or not at all, it can be assumed that the ELISA method was used, since it is so far the only method routinely

Table 1
Recovery and precision of the developed method.

Series	Number of measurements	Spiked [ng mL^{-1}]	Found [ng mL^{-1}]	SD [ng mL^{-1}]	Sr [%]	Recovery [%]
1	24	0	0	0.8[a]	–	–
2	24	20	21.3	1.6	8.0	106
3	24	150	150.6	7.1	4.7	101

[a] Standard deviation of the blank (buffer).

Table 2
Recoveries of collagen IV in blood plasma samples.

No of samples	COL IV concentration without spike [ng mL^{-1}]	Added standard concentration [ng mL^{-1}]	Determined [ng mL^{-1}]	Recovery [%]
1	75.6 ± 1.3	70.0	147.9 ± 1.9	103
2	93.1 ± 1.3	70.0	163.4 ± 2.5	102
3	55.2 ± 1.1	70.0	124.3 ± 1.4	99
4	63.1 ± 1.3	70.0	134.4 ± 1.1	102
5	74.6 ± 1.5	70.0	143.8 ± 1.3	99
6	57.5 ± 1.9	70.0	128.3 ± 1.9	101
7	77.9 ± 0.9	70.0	148.5 ± 2.0	100
8	76.4 ± 2.1	70.0	148.8 ± 2.1	103
9	59.3 ± 1.7	70.0	130.2 ± 1.9	101

Table 3
Selectivity of COLIV determination with the developed method in the presence of potential interferents: collagen I, albumin, fibronectin and laminin-5.

Potential interferent	COLIV concentration [ng mL^{-1}]	Excess over COLIV	Found COLIV [ng mL^{-1}]	SD [ng mL^{-1}]	Recovery [%]
	150	–	150.6	7.1	101
Collagen I	150	1:1	151.1	2.8	101
		1:10	153.4	2.2	102
		1:100	153.1	3.3	102
Albumin	150	1:1	150.8	3.2	101
		1:10	156.0	2.7	104
		1:100	156.4	2.6	104
Fibronectin	150	1:1	152.1	4.0	101
		1:10	154.0	3.2	103
		1:100	154.1	5.3	103
Laminin-5	150	1:1	152.1	4.0	101
		1:10	154.0	3.2	103
		1:100	154.1	5.3	103

Table 4
Concentration of collagen type IV in human blood plasma of patients with breast cancer and healthy volunteers as measured by the developed method.

	Collagen type IV concentration [ng mL^{-1}]	
	Healthy donors	Patients with breast cancer
1	58.0 ± 1.7	194.8 ± 19.2
2	93.8 ± 1.3	380.8 ± 54.3
3	78.9 ± 0.9	429.6 ± 68.2
4	76.5 ± 1.3	438.9 ± 33.4
5	75.2 ± 1.2	354.9 ± 18.1
6	55.0 ± 1.9	174.0 ± 29.3
7	81.7 ± 1.4	432.4 ± 36.0
8	50.4 ± 1.2	397.2 ± 29.0
9	51.4 ± 1.3	440.4 ± 37.1
Mean value ± confidence limit	69.0 ± 10.2	360.3 ± 67.9
Range	50.4–93.8	174.0–440.4
Literature mean value	115.0 [17]	166.0 [17]
	81.0 ± 17.0 [19]	
	79.8 ± 12.2 [20]	
	57.2 ± 18.04 [21]	
	106.0 ± 35.0 [22]	
	82.4 ± 13.7 [23]	
Literature range	61.0–339.0 [17]	85.0–327.0 [17]

applied.

In order to validate the developed method, comparative determination of COLIV concentration in the same samples by the commercial ELISA kit was performed. The results are shown in Fig. 5. The mean value of COLIV concentration obtained by ELISA is 67 ± 9 ng mL^{-1} (range: 49–90 ng mL^{-1}) for healthy volunteers and 355 ± 66 ng mL^{-1} (range: 182–432 ng mL^{-1}) for patients with breast cancer. Comparison between measurements of COLIV

concentration by SPRI biosensor and ELISA showed a generally good agreement although the results for ELISA are slightly lower than for SPRI ($C_{ELISA} = 0.90\ C_{SPRI}$ or $C_{ELISA} = 0.98\ C_{SPRI}$, for healthy volunteers and patients, respectively). The significant Pearson correlation coefficient value of 0.979 ($p < 0.00001$) for healthy volunteers and 0.987 ($p < 0.00001$) for patient confirms to be a very strong positive correlation between the results obtained by two methods.

In contrast to ELISA, the SPR-based biosensor is real-time, label-free, fast, and low-cost. It can quantitatively measure molecules of interest without the need for secondary antibodies to generate signals. In the case of ELISA kit, the test results are generally available within minimum 12 h after sample collection. Our SPR-based biosensor allows fast measurement in about 3–6 h. This time advantage may be crucial for making decisions in urgent situations. Generally, SPR-based biosensor is more sensitive than ELISA and has a similar specificity and detection limits.

4. Conclusions

The developed biosensor co-operating with SPR imaging measurement is suitable tool for collagen IV determination in blood serum. It is able to compete with ELISA method for such determination. The method is selective and sufficiently sensitive for COLIV determination in blood serum both healthy subjects and patients suffering with breast cancer without preliminary preconcentration. Recoveries and precision of COLIV determination are satisfactory. COLIV in blood serum of patients suffering with breast cancer is approximately 5 times higher in comparison with healthy subjects average concentration. Thus COLIV is potential breast cancer marker.

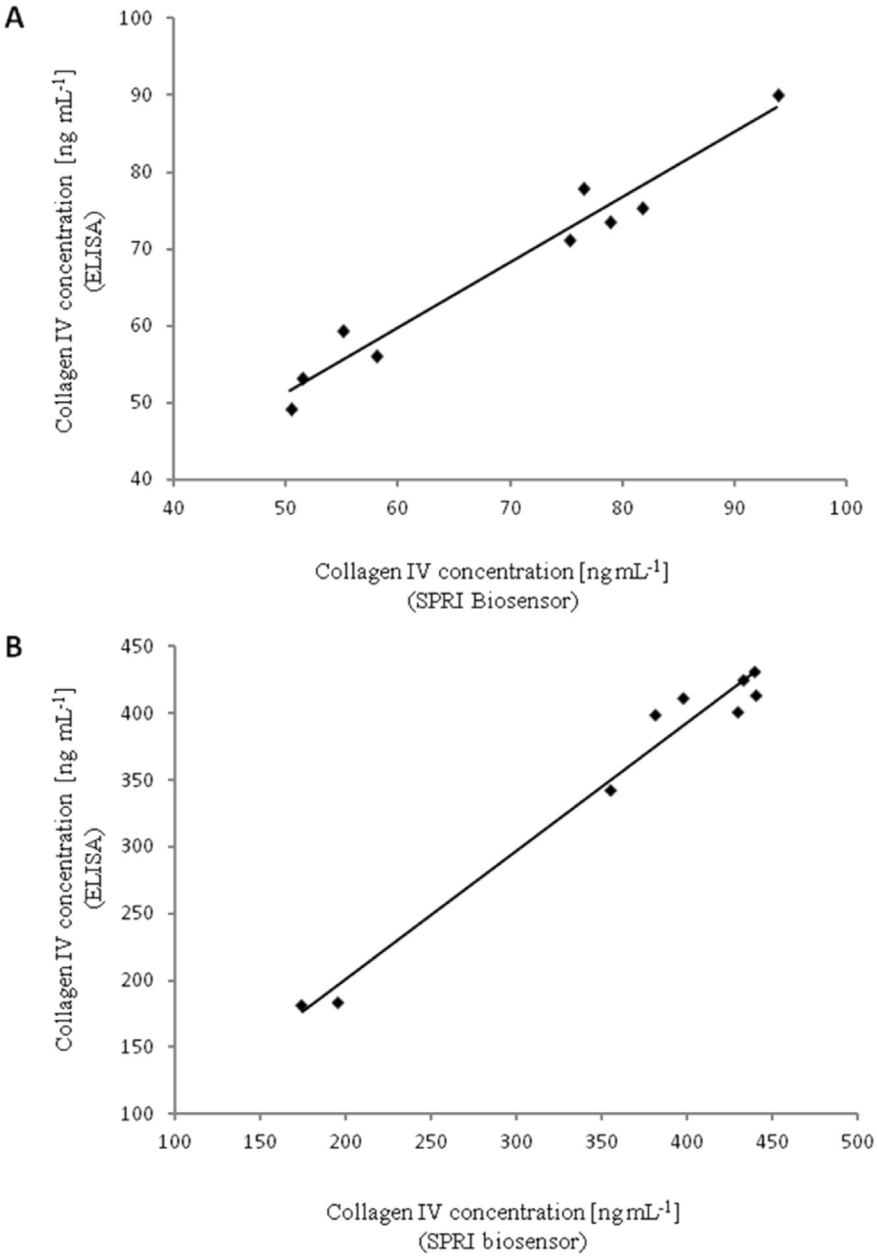

Fig. 5. Comparison of human plasma collagen IV concentrations from (A) healthy volunteers ($n = 9$, $r = 0.979$, $p < 0.00001$) (B) patients with breast cancer ($n = 9$, $r = 0.987$, $p < 0.00001$) determined by SPRI biosensor method and ELISA.

Acknowledgments

The authors thank engineer Adrian Karwatiuk from OPTA-TECH company for the performance of SEM images.

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