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Application of Surface-Enhanced Raman Spectroscopy-Based Biosensors in Tumour Marker Detection

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Abstract. Malignant tumours represent a significant public health issue posing a grave threat to human life and health, garnering considerable attention in the field of biomedical science in recent years. Early screening and diagnosis of tumours provide patients with valuable treatment time, constituting a crucial measure in tumour prevention and management. Surface-enhanced Raman spectroscopy (SERS), with its advantages of ultra-high sensitivity, high precision, and multiplexing capabilities, has been widely applied in the detection of tumour markers. This paper examines SERS-based biosensors for three distinct tumour markers: prostate-specific antigen (PSA) for prostate cancer screening, alpha-fetoprotein (AFP) for primary liver cancer detection, and chromogranin A (CgA) for neuroendocrine tumour diagnosis. Compared to SERS technology, alternative early-stage tumour marker detection methods—such as chemiluminescent immunoassays, enzyme-linked immunosorbent assays, and real-time quantitative PCR—face limitations in widespread clinical adoption due to their higher costs, longer analysis times, and greater operational complexity. To address current clinical application challenges, future advancements in SERS-based biosensor detection of tumour markers will primarily be achieved through innovative improvements to the biosensor substrate.

Keywords: Surface-enhanced Raman spectroscopy, Tumour marker, Prostate-specific antigen, Alpha-fetoprotein, Chromogranin A

1. Introduction

Malignant tumours, also known as cancer, are diseases that seriously threaten human life and health. There will be about 19.3 million new cancer cases worldwide in 2020. It is estimated that by 2040, the global cancer burden will reach 28.4 million, an increase of 47% compared with 2020 [1]. In the face of the severe cancer prevention and control situation, early tumour screening and effective treatment can greatly improve the survival rate of malignant tumour patients. Tumour markers refer to substances that characteristically exist in malignant tumour cells during the development of malignant tumours, or substances produced by their abnormalities. They are generally detected in tumour tissue or other body fluids such as blood, urine and saliva, and are related to the occurrence, staging, and post-treatment of tumours. The detection of tumour markers is an effective means of early tumour screening and diagnosis, which has extensive scientific value and important clinical significance. Traditional tumour marker detection methods, such as low-dose computed tomography,

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enzyme-linked immunosorbent assay, immunofluorescence and immunocomics, have problems such as low sensitivity, cumbersome operation and high cost. Therefore, a more convenient, sensitive and specific tumour marker detection technology is needed in clinical practice. After the collision between photons and molecules, the frequency changes to produce inelastic scattering to form the Raman effect. Raman spectroscopy can provide unique structural information of molecules due to the Raman effect, its advantages of non-destructiveness, stability and specificity, so as to identify the molecules of biochemical substances such as proteins and nucleic acids. However, the low signal-to-noise ratio and weak signal peak intensity of Raman spectrum are not widely used in detection. Surface-enhanced Raman spectroscopy (SERS) technology uses rough surface metal nanostructure particles to absorb target molecules to enhance the electromagnetic field, greatly improve the Raman signal, and effectively solve the problem of weak Raman signal. As a non-destructive, highly sensitive, convenient and efficient detection method, SERS technology has received great attention in medical testing. The classification of tumour markers is very complex, mainly including protein markers, nucleic acid markers, sugar antigen markers and hormone markers, etc. [2].

This paper provides the application of biosensors based on SERS technology for the detection of three different tumour markers, namely prostate-specific antigen (PSA), the glucose antigen marker of prostate cancer, alpha-fetoprotein (AFP) in the serum of patients with primary liver cancer, and chromogranin A (CgA), a protein tumour marker of neuroendocrine tumours. At present, the research on SERS technology mainly focuses on substrate improvement and probe preparation. The combination of SERS technology and machine learning algorithms can finally accurately realise the detection of tumour markers, which can accelerate the development and application of this technology in the field of biomedicine.

2. Overview of surface-enhanced Raman spectroscopy

2.1. The principle of surface-enhanced Raman spectroscopy

Because the strength of the Raman signal itself is relatively weak, it is necessary to enhance the Raman effect on the surface to use Raman spectroscopy to identify unique molecular information. The mechanism is that the base surface of the biosensor uses rough precious metal nanoparticles, such as gold and silver, to form a surface plasma under light irradiation. The strong electromagnetic field generated by the surface plasma resonance makes the target molecule more adsorbed on the metal surface and the Raman signal is enhanced. The metal nanoparticle gap produces a high-intensity local electric field, which is the "hot spot" due to the action of the photoelectric field. When the molecule is in the "hot spot", it will produce a strong Raman scattering and present the characteristic fingerprint map of the target substance [3]. Surface-enhanced Raman technology can effectively enhance the weak biomolecular Raman scattering signal, provide molecularly rich fingerprint information, and use "hotspots" to achieve accurate and high-sensitivity detection of target markers.

2.2. Enhancement mechanisms in surface-enhanced Raman spectroscopy

There is a large number of free electrons on the metal surface, and free electrons are excited to form plasma under the irradiation of light. Because the substrate surface uses rough metal nanostructures, plasma is limited to the near-surface area, so it is also known as surface plasma. Surface plasma is excited by light irradiation to a higher energy level, producing surface plasma resonance, and electromagnetic enhancement through surface plasma resonance to achieve a significant

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improvement in Raman scattering. Electromagnetic enhancement is directly related to the electric field strength on the surface of precious metal nanoparticles. In the tip and slit area of metal nanoparticles, the surface plasma resonance phenomenon is prone to coupling, forming a "hot spot" area. Therefore, it will be important to analyse the impact of the "hot spot" area in the base, such as how to increase the number of "hot spot" areas, or make it easier for the tested object to be in the "hot spot" area. At present, the enhancement effect of the precious metal substrate is mainly improved through three aspects. By reducing the distance between metal nanoparticles, they can be arranged in an orderly manner at the interface between the molecules and the substrate, so as to form local "hotspots" in the particle gap to enhance the Raman scattering signal. Secondly, the surface metal nanoparticles with complex structures are prepared, such as flower-shaped, star-shaped, etc., which can form "hot spots" through the tip of the particles, and at the same time, a sufficiently small gap can be formed, which can also adsorb more signal molecules while generating "hot spots". In addition, nanoparticles formed by metal or metal compounds with other materials can be used to use the spherical shell structure, because the spherical shell structure can not only expand the range of surface plasma resonance to a certain extent, but also be relatively easy to synthesise [4].

3. Application of surface-enhanced Raman spectroscopy technology in the detection of three different tumour markers

3.1. Surface-enhanced Raman spectroscopy detection of prostate-specific antigen

In the early diagnosis of prostate cancer, the main goal is to detect whether the glycoprotein prostate-specific antigen (PSA) is overexpressed to determine whether there is prostate cancer. At present, the market mainly uses chemiluminescence immunoassay to detect the PSA level in human serum to screen for prostate cancer. Capturing the PSA in the serum by screening out antibodies that can produce a specific binding to PSA. Then it is labelled with a luminous substance, that is, another PSA antibody, to form a "sandwich" structure. Due to the specific immune reaction, the luminous substance undergoes a chemical reaction and emits photons, so qualitative or quantitative analysis is carried out by detecting the intensity of the light signal [5]. In fact, when detecting PSA, it is necessary to detect not only the serum total PSA (total prostate specific antigen, tPSA) level but also free PSA (free prostate specific antigen, fPSA). When only the tPSA level was detected, the diagnostic effect decreased, the specificity was only 48.6%, and the misdiagnosis rate was as high as 50% [6]. Therefore, the detection effect of using PSA alone as a tumour marker for the diagnosis of prostate cancer is not good. The chemiluminescence immunoassay method has certain limitations because it may have a hook effect [7] and the single information dimension cannot be multiply detected at the same time. Biosensors based on SERS technology to detect PSA mainly use precious metals silver (Ag) and polystyrene colloidal microspheres (PS) to build the substrate, adaptands (Apt) and Raman probe molecular methylene blue (MB) to form molecular identification elements, and Raman spectrometer to measure the surface-enhanced Raman spectroscopy of MB. In the production of SERS substrate, the silver (Ag) film is sputtered on the polystyrene colloidal microsphere (PS) template through magnetron sputtering technology, and the combination of precious metals with excellent surface enhancement effect and polystyrene colloidal microspheres (PS) with uniform size and easy pattern arrays can not only ensure the sensitivity of SERS, but also improve the SERS spectral reproducibility. In the process of composition of the ligand molecular identification element, the complementary DNA strand (SH-DNA) and PSA adaptor are gradually fixed on the PS@Ag substrate by using the sandwich structure, and the Raman probe molecular methylene blue (MB) is introduced through the interaction with the guanine base on the Apt. Before

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detecting the target PSA, the Raman characterisation of the ontology MB was measured, and 1623cm–1 was selected as the characteristic peak for subsequent analysis according to the Raman spectroscopy. When the target PSA is introduced to the chip, due to the reaction of the adapter and PSA, the MB-attached adaptor is released from the chip. At this time, the MB molecular weight reduction is detected by Raman spectrometer to find that the characteristic peak intensity at 1623 cm–1 is reduced, so as to achieve the detection of PSA [8]. In the reducibility test of this technology, there is no obvious deviation in the intensity of the Raman peak between 10 randomly selected points. In the stability test, even if it is placed at 4℃ for two weeks, the intensity of SERS can still be maintained by more than 90%. Compared with other methods for detecting PSA, the detection of PSA based on SERS technology has significant advantages in terms of spectral reproducibility and selectivity.

3.2. Surface-enhanced Raman spectroscopy detection of Alpha-fetoprotein

Primary liver cancer usually originates in liver tissue, one of the most common malignant tumours worldwide, and is also one of the main causes of cancer-related deaths [9]. At present, the clinical methods for diagnosing primary liver cancer mainly include electronic computed tomography (CT), magnetic resonance imaging (MRI), serological index detection and puncture biopsy. As imaging examinations, CT and MRI are not a means of extensive screening to identify small liver cancers with poor sensitivity and potential health hazards. In the detection of serological indicators, the detection of alpha-fetoprotein (AFP) by chemiluminescent immunoassay is used. Although its sensitivity and specificity are high, the high detection cost is not suitable for daily mass detection. The detection of AFP by enzyme-linked immunosorbent method has the advantages of high throughput analysis and good specificity, but it requires a long analysis time. There are obvious disadvantages. As the gold standard, puncture biopsy is more demanding for doctors and the risk of spreading cancer cells is usually not the first method for early screening of primary liver cancer. AFP is the most commonly used protein tumour marker for primary liver cancer screening. The content of A-fetoprotein has a certain correlation with primary liver cancer, and the content of A-fetoprotein in the serum of patients with primary liver cancer will increase. At present, the level of AFP has a large range of changes in the diagnosis of early liver cancer, with a specificity of about 76% to 96% and a sensitivity of about 40% to 65% [10]. Therefore, a high-precision, highly sensitive, economical and easy-to-operate detection technology is needed to meet the clinical early detection of AFP. Biosensors based on SERS technology to detect AFP use silver nanoparticles to assemble on silicon dioxide wafers to build a substrate. AFP adaptors and Raman signal molecules ROX modified by the complementary sequence of AFP adaptors form molecular identification elements. ROX is in the "hot spot" area between silver nanoparticles to enhance Raman signals. Due to the specific binding of AFP to the adaptor, the addition of AFP will compete with the complementary sequence to bind to the AFP adaptor, and the Raman spectral signal of ROX decreases with the increase of AFP content, thus realising the quantitative detection of AFP. Compared with the traditional clinical detection technology of AFP, the detection limit (LOD) of biosensors for detecting AFP is about 145fg/ml, and its detection limit will be increased by an order of magnitude [11].In terms of the specificity and anti-interference characteristics of the SERS sensor for detecting A-fetoprotein, even if the interference object is added under the same conditions, the detected ROX Raman spectrum peak signal strength is basically the same, with strong specificity and anti-interference, and also reflects the good affinity between the ligand and the A-fetoprotein. Biosensors based on SERS technology to detect AFP have the advantages of good sensitivity, strong specificity, strong anti-interference ability, low detection limit and simple economy, but the

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reproducibility between batches and the accuracy of detection in complex environmental samples have yet to be improved.

3.3. Surface-enhanced Raman spectroscopy detection of chromogranin A

Neuroendocrine Neoplasm (NENs) is a rare heterogeneous tumour originating from the body's neuroendocrine cells. Compared with other tumours, the incidence of neuroendocrine tumours has increased more rapidly in recent years, which has attracted the attention of more clinicians. According to the degree of tumour differentiation, it can be divided into highly differentiated Neuroendocrine tumour (NET) and poorly differentiated Neuroendocrine carcinoma (NEC). Neuroendocrine cells are all over the body, so neuroendocrine tumours can occur in any part of the body, but the most common are mainly neuroendocrine tumours that occur in the stomach, intestines and pancreas, accounting for about 55%~70% of all NENs [12]. Since the early clinical symptoms of neuroendocrine tumours are not obvious, it is very important to find an indicator that can effectively screen and monitor NENs. Chromogranin A (CgA) is widely distributed in neuroendocrine cells and endocrine systems. The level of CgA in patients with neuroendocrine tumours will increase, which is the core diagnostic marker of neuroendocrine tumours at present. At present, clinical diagnosis mainly relies on pathological immunohistochemical detection, but its low incidence is easy to cause misdiagnosis. Only pathological consultation with large-scale diagnosis and treatment experience can ensure correctness. The ELISA method is used to detect the difference between batches of CgA, and the long detection time cannot meet the needs of automated clinical detection, and the chemiluminescence immunology method affects the fluorescence sensing efficiency due to the insufficient antibody connection effect. Therefore, a fast, sensitive and specific technology is needed to meet the needs of clinical testing. Based on SERS technology to detect CgA, the biosensor uses magnetic nanoparticles and silver nanoparticles to build a substrate, and uses the domain Z-specific binding antibody Fc segment modification substrate on Staphylococcus aureus protein A as a molecular identification element. The paired antibodies of CgA are used to identify CgA in the sample, and the pull Whether the peak value of the Mann signal map is enhanced is the basis for whether it contains CgA. CgA is detected by Staphylococcus aureus protein A and coupled SPA domain Z respectively. The new Raman probe modified with coupled protein has a stronger ability to identify CgA and a lower false positive rate. Through the detection of CgA samples of different concentrations, the minimum detection concentration is 1ng/mL, which fully meets the clinical requirements. Re-test overnight under the condition of 4℃, with no obvious change in the peak value of the Raman spectrum map, it can reflect the strong stability of the Raman probe [13]. The clinical plasma detection of CgA can screen neuroendocrine tumours at an early stage and improve the efficiency of patient diagnosis and treatment. Based on SERS technology to detect CgA, the existence of CgA can be judged through the specific elevation of the peak of the Raman peak map. At the same time, the detection limit is as low as 1ng/mL. An ultra-sensitive and rapid detection technology for neuroendocrine tumour markers has been established, but it has not been applied to actual clinical detection. In the future, a large number of experimental verifications will be required to apply SERS technology in the early screening of relatively rare neuroendocrine tumour diseases.

4. Conclusion

Tumour marker detection based on SERS technology has developed rapidly. Due to its advantages of high sensitivity, high selectivity, strong specificity and convenience and speed, the technology can

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identify different molecular structure information, which is very important for the early screening and treatment of a variety of malignant tumours at present. This article introduces that biosensors based on SERS technology are used for the detection of prostate-specific antigens, A-fetoprotein and pheochromate protein A respectively. Compared with traditional detection methods, their advantages can be reflected, and there is also room for optimisation and improvement. In complex serum samples, there may be biomolecules that interfere with the Raman probe and reduce the stability of the Raman signal. The substrate composed of precious metal nanoparticles may be contaminated, resulting in poor reproducibility and high cost-effectiveness of precious metals. In addition, combining SERS technology with artificial intelligence to establish a diagnostic model and prepare a biological sensor that can be used for POCT will become the main development trend. In the future, a large number of experimental verifications are still needed to apply this optical biosensor based on surface-enhanced Raman spectroscopy technology to the clinical detection of more tumour markers.

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