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Advances in Surface-Enhanced Raman Scattering for Lung Cancer Diagnosis and Treatment: Substrate Design and Detection Strategy Innovations

Yuxin Lin

Biopharmaceuticals Department, School of Life Science and Techology, China Pharmaceutical University, Nanjing, China
2020240258@stu.cpu.edu.cn

Abstract. Recently, surface-enhanced Raman scattering (SERS) has proven to be an effective method for lung cancer diagnosis and therapeutic applications. It exhibits ultra-high sensitivity and superior molecular fingerprint recognition capability. It also shows powerful adaptability to complex biological samples. The present review highlights the latest progress in SERS-enhanced substrates and novel detection approaches. It lays particular emphasis on their utility in lung cancer early detection and treatment monitoring too. We also discuss future trends of research towards clinical translation of SERS-based lung cancer care.

Keywords: Surface-enhanced Raman scattering, lung cancer, enhancement substrate, detection strategy

1. Introduction

Lung cancer remains the most common and deadly form of malignancy, posing a major public health risk worldwide. Although medical technology has advanced continuously in recent years, the mortality rate of lung cancer continues to increase yearly [1]. This disturbing trend is primarily attributed to the vague and nonspecific symptoms of early-stage lung cancer. As a result,the disease is often detected late. A high percentage of patients receive a diagnosis only after the disease has progressed, at which point therapeutic options are no longer viable [2]. Hence, developing highly sensitive and specific diagnostic techniques for early detection has become a major focus of current research. However, current clinical diagnostic methods have several limitations. Traditional imaging techniques have low resolution and involve radiation exposure [3]. Sophisticated imaging modalities like PET-CT involve high expenses, making them impractical for widespread screening programs. What's more, existing diagnostic and treatment technologies require prolonged processing durations. As a reault, intervention is likely to be postponed and patients' prognosis will be negatively affected [4].

Surface-enhanced Raman scattering (SERS), a robust spectroscopic method, offers a promising way to overcome the limitations of lung cancer detection. Originally reported by Fleischmann et al. [5,6] in 1974, the SERS phenomenon is driven by LSPR from noble metal nanostructures, leading to

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significant enhancement of Raman signals from surface-bound molecules. Compared with traditional analytical methods, SERS exhibits significant advantages in trace detection and molecular identification.These advantages come from its unique enhancement mechanism that combines electromagnetic and chemical contributions [7,8]. Benefiting from its outstanding sensitivity,molecular specificity,precise compatibility and biocompatibility,SERS boasts remarkable potential. It has bright prospects for clinical use in the treatment and monitoring of lung cancer [9-14]. This review summarizes recent progress in SERS-based enhancement substrates and detection strategies for lung cancer diagnosis and therapy, aiming to provide new insights for future research.

2. Enhancement substrates for SERS

The amplification of SERS signals primarily arises from electromagnetic enhancement caused by LSPR [15]. The strength and spatial profile of the LSPR effect are primarily governed by the substrate's material, structure, and surface geometry. To meet the requirements of lung cancer diagnosis and treatment for high sensitivity, high specificity, and complex sample analysis, researchers have developed a variety of SERS enhancement substrates with diverse properties.

2.1. Gold-based substrates

Gold nanoparticles (AuNPs), owing to their unique optical properties and excellent SERS performance, have become one of the most important materials in SERS substrate research. The surface of AuNPs possesses abundant tunable structures and high surface energy, which facilitate strong interactions with molecules. Sharp edges and interparticle gaps serve as regions of intense field localization, markedly boosting the surrounding electromagnetic environment and leading to substantial Raman signal enhancement. In addition, AuNPs exhibit high flexibility in surface modification, enabling functionalization for the highly selective recognition of various target molecules [16]. Guo et al. [17] designed a sea-urchin-like gold nanocluster (AuNC) probe, whose abundant nanobridges and sharp tips markedly enhanced SERS activity and signal uniformity. Integration of targeted molecular beacons enabled precise and sensitive identification of EGFR mutations linked to lung cancer.To address the demand for high-throughput clinical applications, Qian et al. [18] constructed a microfluidic SERS platform using a gold nanocone array (AuNCA). Its periodic conical structure generated dense and reproducible "hot spots." By combining enzymatic amplification with catalytic hairpin assembly (CHA), the platform achieved highly specific and sensitive identification of circulating tumor DNA, providing a new approach for monitoring lung cancer treatment response.

2.2. Silver-based substrates

Silver nanoparticles (AgNPs)are the earliest discovered SERS enhancement substrates. They boast an extremely potent electromagnetic enhancement effect and enable single-molecule-level detection [19]. AgNPs exhibit a strong charge transfer capability and excellent adsorption stability toward polar molecules, which considerably enhances its chemical enhancement effect. The sophisticated manufacturing procedure of sliver-based substrates grants them prospects for mass production at a low cost. As a result, they are extensively applpied in lung cancer diagnosis and therapy. Because of their superior enhancement performance and biocompatibility, AgNPs have demonstrated great advantages in practical applications. Huang et al. [20] integrated silver into a metal–organic framework to develop a multifunctional AgNPs@ZIF-67/g-C3N4 membrane for solid-phase

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extraction. Within this system, AgNPs create abundant SERS-active sites, ZIF-67 enriches target analytes, and g-C3N4 extends the interaction duration between aldehyde molecules and the substrate surface. These components exhibit a remarkable synergistic effect, lowering the detection limit significantly. Kun et al. [21] introduced AgNPs onto the surface of lung tissue slices. In comparison with slices without AgNPs, the number of surface "hot spots" increased greatly. COMSOL simulations of the electromagnetic field distribution on a SiO_2 substrate revealed a higher density of "hot spots" and stronger electric field intensity in the gaps between AgNPs. The fabricated samples showed potent Raman enhancement effects.Such effects enabled the collection of additional biochemical spectral data and provided fresh perspectives on the wider clinical utility of SERS-based tissue slice analysis.

2.3. Bimetallic composite substrates

Bimetallic composite substrate is a combination of advantages of microstructure modification and electronic structure modulation. Bimetallic composite substrates can resolve the problems of monometallic substrates for SERS amplication. It has the advantages of good stability, specificity, and biocompatibility [22]. Zhao et al. [23] fabricated patterning plasmonic trimers ($Au@Al_2O_3$–Au–$Au@Al_2O_3$) based on two coupled plasmonic units and one trapping unit, namely central nanostructures.The system ensures high-field areas of target analytes, ensuring that the probe is placed precisely where the strongest electromagnetic enhancement occurs. In the trier structure, it could highly proportionate signal contribution molecules, offering the SERS detection at the single molecule level. It shows significant applications prospect in lung tumors' detailed pathological diagnosis and tumor subtypes' diagnosis via SERS. Geng et al. [24] prepared AgPb bimetallic core–shell nanoparticles with thermoelectric characteristics. The nanoparticles minimize thermal injury to biomolecules and provides tunable optical properties to maximize the SERS signal, which can be used to detect low concentration of carcinoembryonic antigen sensitively. Xia et al. [25] reported a SERS platform based on Au– Ag bimetallic nanowires functionalized by hairpin DNA probe.It can be seen that dense "hot spots" were developed at the agNWs/AuNPs interface and significant signal amplification of Raman signals ensued.

2.4. Microfluidic-integrated substrates

In contrast to monometallic and bimetallic substrates, microfluidic-integrated substrates boast more distinct merits. These merits cover sample manipulation, detection efficacy and signal consistency [26]. Microfluidic-integrated substrates are able to reduce sample usage to a minimum. At the same time, they significantly streamline operational workflows [27]. Additionally, they enable multiplexed detection, thereby enhancing detection efficiency [28]. Cao et al. [29] introduced an innovative dual-amplification approach using a pump-free microfluidic SERS chip integrated with CHA chemistry. Once the target is introduced, CHA-mediated hybridization immobilizes Pd–Au core–shell nanorods on magnetic beads (MBs). Also, SERS probes accumulate on the Au–AgNBs array, creating a large number of "hot spots". Subsequently, the composite structures are assembled under a magnetic field, achieving dual amplification of the SERS signal. This approach enables rapid, multi-analyte, and ultra-sensitive detection and quantification. This approach enables rapid, multi-analyte, and ultra-sensitive detection and quantification. Chen et al. [30] constructed a microfluidic SERS platform enhanced by deep learning algorithms. The chip utilized a composite material of AuNCs and polystyrene microspheres (Figure 1a), which was functionalized to form SERS-active capture probes. This platform provides fast processing speed, low sample consumption,

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and excellent sensitivity. It holds great potential for the early screening and subtyping of NSCLC. Gu et al. [31] developed a microfluidic SERS device for parallel, high-efficiency detection of two NSCLC-linked microRNAs. When target strands are present in the sample solution, they hybridize in a one-step pairing reaction with the corresponding hairpin DNA (hpDNA) immobilized on the hairpin-DNA-functionalized Au–Ag nanobowl (Au–AgNBs) array, thereby amplifying the SERS signal. With high specificity, reproducibility, and stability, the chip supports NSCLC early diagnosis and prognostic evaluation.

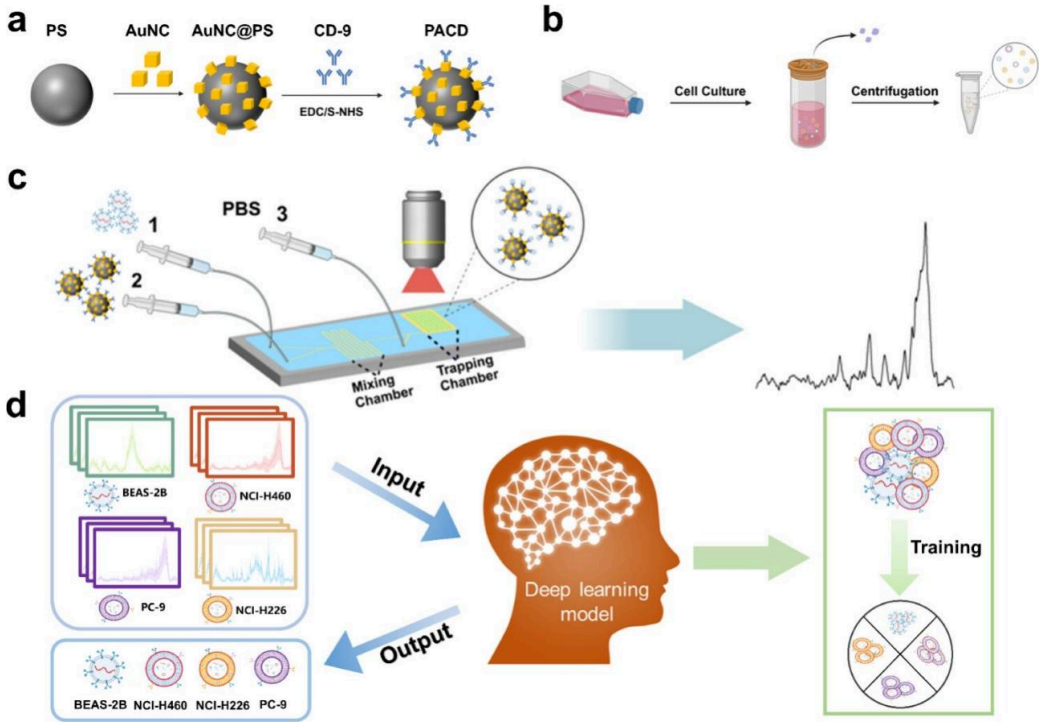

Figure 1. Schematic illustration of a microfluidic platform integrated with label-free SERS and deep learning to characterize exosomes for the subtyping of NSCLC. (a) The synthesis of the exosome capture probe PACD. (b) Extraction of exosomes. (c) Microfluidic-SERS Chip for exosome capture and SERS detection. (d) Overview of deep learning-based classification of NSCLC exosomes using SERS signal patterns. Adapted from reference [30]

2.5. Special substrates

With ongoing research, an increasing number of special substrates have been developed and applied in lung cancer diagnosis and treatment. Compared with conventional substrates, these special substrates exhibit unique advantages in sensitivity, stability, functional diversity, and application expansion, providing new insights for the advancement of SERS technology. To achieve large-scale fabrication of high-performance SERS substrates, Gao et al. [32] designed an Ag/Si/Ag structure based on micro–nano porous particles. This architecture exhibits a dual-capture effect, enabling efficient trapping and aggregation of both light and gaseous molecules. This structure can further excite cascade optical field modes between plasmonic nanopores and nanoparticles, resulting in a richer local electric field distribution pattern. The “hot spots” within this structure can be modulated at arbitrary positions of the dielectric pores, improving the spatial matching between analytes and local electric fields. Chen et al. [33] fabricated a hybrid substrate combining $Ti_3C_2T_x$ MXene with a patterned array of Au–Ag core–shell nanocubes(Figure 2). This substrate was applied for exosome

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detection using SERS, exhibiting remarkable SERS activity and nonspecific exosome-capturing capability, thereby achieving ultrasensitive detection of exosomes.

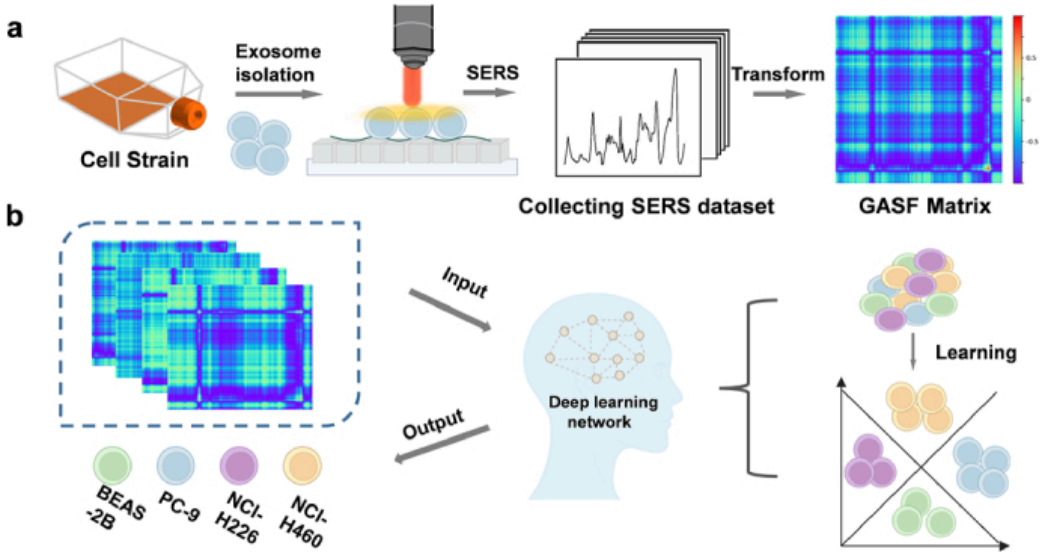

Figure 2. Schematic representation of deep learning-based spectral analysis of exosomes for lung cancer differential diagnosis. (a) SERS detection of exosomes secreted by different NSCLC cell lines using MGS substrate. (b) Classification of NSCLC subtypes based on the obtained SERS spectra using a deep learning-enabled GASF approach. .Adapted from reference [33]

3. SERS detection strategies

To achieve highly sensitive and specific detection, it is essential to combine appropriate SERS substrates with suitable detection strategies. The choice of substrate affects signal amplification and the overall sensitivity of the detection process, while the applied detection strategy significantly influences analytical performance, particularly in complex biological environments such as those encountered in lung cancer diagnosis. Accordingly, researchers have developed various SERS-based detection strategies, including label-free and labeled approaches, as well as AI-assisted methods to enhance detection accuracy and efficiency.

3.1. Label-free detection

Label-free SERS avoids external reporters, instead boosting the native Raman emission of analytes via the enhancing substrate. The signal originates from characteristic peaks generated by molecular vibrational or rotational energy level transitions [34]. This detection method preserves the natural biochemical information of the target molecules, requires no design of specific probes, is simple to operate, and facilitates the exploration of unknown biomarkers. Lu et al. [35] utilized label-free SERS profiling of plasma to distinguish early-stage lung cancer individuals from healthy donors. The plasma was diluted and adjusted to a mildly acidic pH, then combined with AgNPs for SERS analysis. This method proved to be simple and efficient. Cai et al. [36] introduced a label-free SERS serum fingerprinting approach for clinical samples. Using slippery liquid-infused porous SERS, this method enabled rapid identification of lung cancer and demonstrated strong potential for non-invasive diagnosis.

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3.2. Labeled detection

In labeled SERS, tailored tags recognizing specific analytes are employed, indirectly enhancing the Raman signatures corresponding to the targets [37]. This approach provides remarkable signal amplification efficiency and high specificity, as the recognition elements can precisely bind to target molecules while minimizing matrix interference during detection. Mao et al. [38] immobilized DNA hairpin 1, dual-labeled with thiol and biotin groups, together with two Raman reporter molecules on gold nanocages to form SERS tags. Integrating CHA, they established a SERS-based lateral-flow strip for simultaneous, rapid, and sensitive detection of two NSCLC-linked microRNAs within one test zone. Lu et al. [39] introduced a straightforward immuno-SERS platform, employing 5-methylcytosine-antibody-conjugated magnetic probes for capturing methylated DNA. They used magnetic probes modified with 5-methylcytosine antibodies to enrich methylated DNA sequences and employed core–shell nanoparticles carrying probe DNA as SERS nanolabels for multiplex detection, enabling sensitive and convenient detection of DNA methylation biomarkers associated with lung cancer. Xu et al. [40] designed a dual-signal SERS probe loaded with 4-mercaptobenzonitrile and 6-carboxy-X-rhodamine, quantifying circSATB2 via ROX intensity while using 4-mercaptobenzonitrile for signal normalization. In this SERS biosensor, the intensity of the ROX signal was used to determine the concentration of the target circSATB2, while 4-mercaptobenzonitrile served as an internal standard to calibrate the 6-carboxy-X-rhodamine signal, enabling highly sensitive and reliable detection of circular RNA targets.

3.3. AI-assisted detection

Recent progress in large-scale AI models has introduced significant innovations to conventional analytical methodologies. Machine-learning and deep-learning algorithms enable comprehensive interrogation of lung-cancer-associated Raman datasets acquired via SERS.Such methods address long-standing limitations of SERS—namely spectral complexity, background noise, and reproducibility—greatly enhancing its reliability for lung-cancer early detection, subtyping, and treatment follow-up [41-46].

Lu et al. [47] adopted an AI-augmented SERS framework, training a deep-learning model on Raman spectra of exosomes derived from lung-cancer and normal cell lines.(Figure.3) A CNN was trained to capture exosome signatures from spectral data, followed by an SVM classifier, enabling label-free plasma exosome profiling and highlighting their utility as early lung-cancer biomarkers. Xie et al. [48] employed AI-based analysis of SERS spectra derived from exhaled breath collected on plasmonic metal–organic framework nanoparticle films, achieving precise and superior noninvasive diagnosis of multiple cancer types. A CNN was trained to capture exosome signatures from spectral data, followed by an SVM classifier, enabling label-free plasma exosome profiling and highlighting their utility as early lung-cancer biomarkers. Shi et al. [49] merged Raman spectroscopy with ML to create a non-invasive lung-cancer test. Spectra were acquired from pre-surgical, post-surgical, and healthy volunteers, processed via PCA, and classified using CNN and ResNet architectures, allowing stratification of patient cohorts and identification of high-risk postoperative cases.

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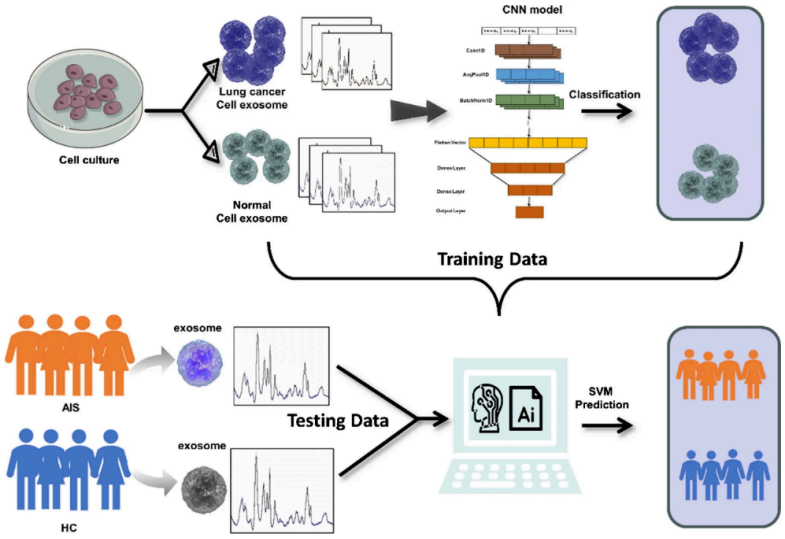

Figure 3. Schematic representation of deep learning-based cellular exosome classification and lung cancer diagnosis using SERS signal patterns of exosome. Adapted from reference [47]

4. Conclusion and perspectives

This review systematically summarizes the design of SERS enhancement substrates and the specific applications of various detection strategies in the analysis of lung cancer biomarkers. Currently, SERS technology, with its ultrahigh sensitivity and unique molecular fingerprinting capability, shows tremendous potential in early screening, precise diagnosis, and therapeutic monitoring of lung cancer. Despite its promising outlook, several challenges remain for the clinical translation of SERS technology: (1) standardization and stability of SERS substrates; (2) interference resistance and specificity in complex biological matrices; and (3) quantification and reproducibility of detection results. To address these challenges, and in light of both the development trends of SERS technology and the clinical requirements for lung cancer diagnosis and treatment, future research should focus on the following key directions: (1) Develop standardized protocols that finely tune nanostructure dimensions and shapes, guaranteeing consistent and reproducible substrate performance; (2) Optimize sample preparation protocols tailored to various lung cancer sample types (e.g., serum, saliva) by considering biomarker concentration levels and molecular states, and design adaptive pretreatment strategies such as target enrichment, matrix removal, or microfluidic integration; (3) Design functionalized SERS probes with specific recognition sites (e.g., antibody or aptamer modifications) to minimize nonspecific binding with impurities in samples, thereby improving detection precision and anti-interference capability; (4) Integrate AI-driven models to decode SERS signatures, allowing swift multi-biomarker quantification and interpretation in complex specimens, thereby delivering smarter, faster, and more accurate solutions for lung-cancer early detection, precise diagnostics, and therapy monitoring.

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