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Label and label-free based surface-enhanced Raman scattering for pathogen bacteria detection: A review

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ABSTRACT

Rapid, accurate detection of pathogen bacteria is a highly topical research area for the sake of food safety and public health. Surface-enhanced Raman scattering (SERS) is being considered as a powerful and attractive technique for pathogen bacteria detection, due to its sensitivity, high speed, comparatively low cost, multiplexing ability and portability. This contribution aims to give a comprehensive overview of SERS as a technique for rapid detection of pathogen bacteria based on label and label-free strategies. A brief tutorial on SERS is given first of all. Then we summarize the recent trends and developments of label and label-free based SERS applied to detection of pathogen bacteria, including the relatively complete interpretation of SERS spectra. In addition, multifunctional SERS platforms for pathogen bacteria in matrix are discussed as well. Furthermore, an outlook of the work done and a perspective on the future directions of SERS as a reliable tool for real-time pathogen bacteria detection are given.

1. Introduction

Foodborne illnesses caused by pathogen bacteria such as *salmonella*, *Escherichia coli (E.coli), Staphylococcus* present a continuous challenge for food safety and are considered as a common, costly, global public health concern (Havelaar et al., 2015; McLinden et al., 2014; Wu et al., 2016). Centers for disease control and prevention (CDC) in the US estimates that roughly 1 in 6 Americans get sick from contaminated food or beverages and 3000 die each year, costing $15.6 billion in the US each year (Israelsen et al., 2016). To guarantee food safety and public health, rapid and portable detection techniques for pathogens are urgently needed. Traditional methods such as analytical profile index (API), requires a series of biochemical tests for cultured microbes that takes days to finish (Hoelzle et al., 2014; Jarvis and Goodacre, 2008). Such a delay is unacceptable when facing life-threatening emergencies. Current developed bio-sensing methods generally employ polymerase chain reaction (PCR) or enzyme-linked immunosorbant assay (ELISA) (Cheng et al., 2011; Tripp et al., 2008), which have shown improved robustness and rapidity (Huang et al., 2014). However, their widespread applications in point-of-care (POC) diagnosis are limited in regards to low sensitivity, specificity, speed, cost efficiency. In addition, they are usually unable to distinguish the pathogens with low concentration and live/dead bacteria. Thus, for the sake of public health, it is highly desirable to develop a detection method with reduction or elimination of preparation time, together with sensitivity, reproducibility with on-the-spot interpretation of results, cost and time effectiveness, and ease of use under most conditions (Cho, 2011; Craig et al., 2013).

Surface-enhanced Raman scattering (SERS) possesses several attractive properties, such as ultrasensitivity, high speed, comparatively low cost, and multiplexing ability and portability (Gao et al., 2013; Jiang et al., 2013; Shi et al., 2015; Yan and Vo-Dinh, 2007), which enable SERS been widely used for sensitive detection of chemical (Kurouski and Van Duyne, 2015; Wang et al., 2016d; Yang et al., 2013a) and biological agent (Driskell et al., 2005; Gao et al., 2015; Gong et al., 2015; Liu et al., 2015; Wigginton and Vikesland, 2010; Xu et al., 2015). In particularly, the identification and detection of microorganism by SERS has attracted high interest recently due to the spectroscopic fingerprint and nondestructive data acquisition in aqueous environment, since the first SERS spectrum of bacteria was reported by Holt and Cotton (1989). SERS amplifies the Raman signal of bacteria through SERS-active substrates such as a roughened noble-metal surface or noble-metal nanoparticles (NPs). Current SERS detection of pathogen bacteria is usually accomplished by two strate-

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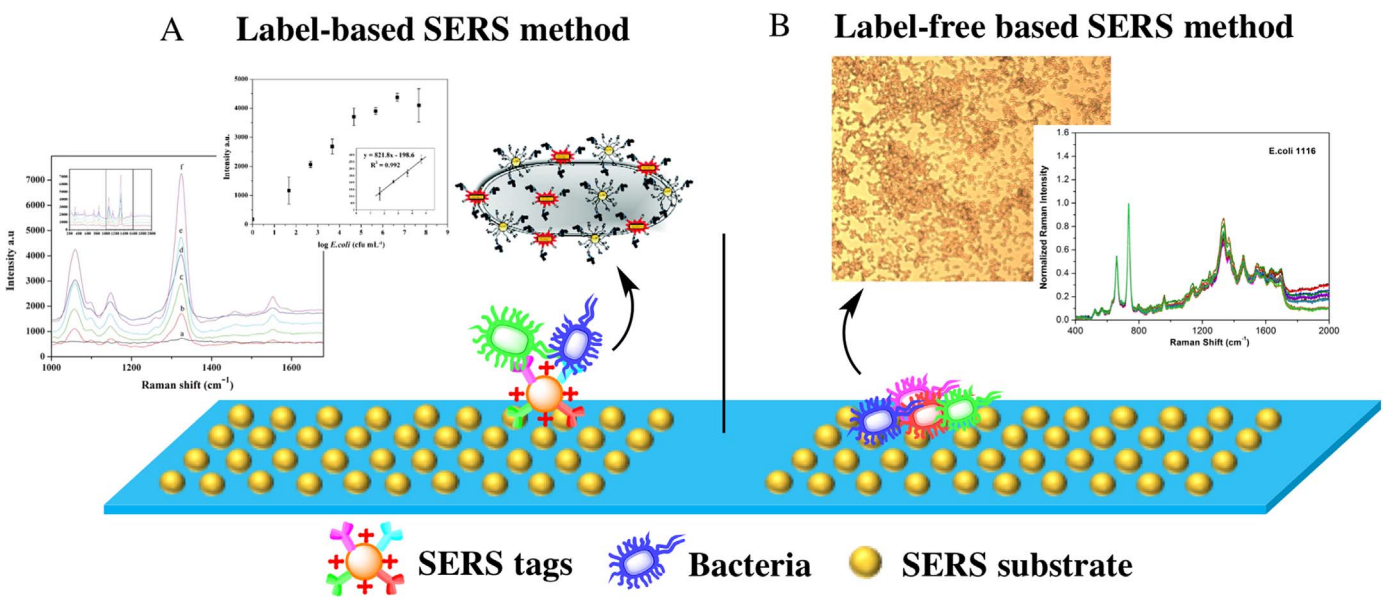

Fig. 1. Schematic illustration of label based and label-free based SERS method for bacteria detection. The insert graphs in A, B are reproduced from Ref (Guven et al., 2011) and Ref (Yang et al., 2016), respectively.

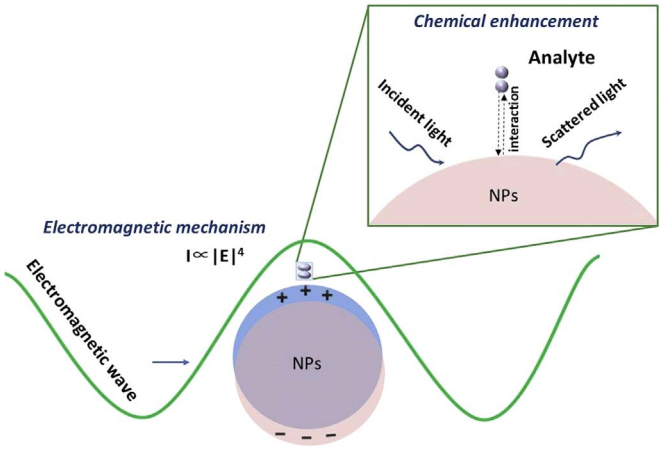

Fig. 2. Two mechanisms contributed to SERS.

gies: label based (indirect) and label-free (direct) based method, which are schematically depicted in Fig. 1.

Label based SERS method is considered as an indirect approach. SERS-active nanoprobes named SERS tags in label method are widely used as the extrinsic mode of bacteria detection (Liu et al., 2010). The employment of SERS tags enables a highly sensitive detection of bacterial cells via reporting the spectra of Raman reporter molecules in close proximity to SERS substrate. For instance, Guven et al. (2011) demonstrated a specific label based SERS method to enumerate *E. coli* in water samples with a limit of detection (LOD) of 8 cfu/mL. In comparison with label method, label-free method does not require a secondary label dye and can directly obtain the intrinsic fingerprint of bacteria, which relies on the mutual interaction of bacteria cell with the SERS substrate (Pahlow et al., 2015). With clearer interpretation of SERS spectra of bacteria (Efrima and Zeiri, 2009; Kahraman et al., 2007; Zeiri et al., 2004), *E. coli* and *S. aureus* at a LOD of as low as 10^3 cells/mL can also be successfully detected through their own Raman fingerprint (Wang et al., 2016a). In combination with Raman compatible techniques such as microfluidics or immunoassays (Cowcher et al., 2013; Zhou et al., 2015b), chemometrics method (Kaminska et al., 2016b; Witkowska et al., 2016), SERS indicates itself as an alternative potential of traditional bacterial detection methods for real world samples.

Within this review, a wealth of literature is emerging with the goal to provide an overview of the most important trends and developments of pathogen bacteria detection by label and label-free based SERS method in the last few years. This article also discussed the relatively complete interpretation of SERS spectra of bacteria with the two approaches. In addition, the novel multifunctional SERS platforms for better reproducibility and wider application of bacteria detection in real samples are discussed. Conclusively, a critical outlook summarizes the achieved results and suggests what have to be done in the future.

2. A brief tutorial on SERS

SERS observed by Fleischmann and Van Duyne group (Fleischmann et al., 1974; Jeanmaire and Vanduyne, 1977) in the 1970s, is an extension and variation of Raman scattering. Metallic NPs or nanostructured metal surfaces are used in SERS to enhance the intrinsically weak Raman signal by several orders of magnitude (typically 10^6 to 10^{14}) (Yang and Ying, 2011). The combination of excellent specificity of Raman signature with high sensitivity up to 10^{14} enables SERS for single molecule detection. The enhancement factors (EF) of SERS effect contributes to two mechanisms primarily (Fig. 2): electromagnetic mechanism (EM) and chemical enhancement (CE) (Kambhampati et al., 1999; Schatz et al., 2006).

It is believed that both a long-range EM effect and a short-range CE effect are simultaneously operative (Qian and Nie, 2008). Usually, the EF for EM is thought to be of the order of 10^6 to 10^8, whereas the chemical contribution can only be of the order of 10^2. For chemical enhancement, molecules are absorbed at certain sites of the noble metal rough surface. The electrons from the molecules are allowed to interact with the electrons from the metal surface, which lead to a similar enhancement effect to resonance Raman scattering (Doering and Nie, 2002). The SERS effect due to CE varies from substrates, adsorbed molecules, and mutual adsorption sites (Bantz et al., 2011). Compared to CE, the EM enhancement arising from optical excitation of the localized surface plasmon resonances (LSPR) (Kovacs et al., 1986) is thought to be a major contribution to SERS phenomenon. The oscillation of conduction electrons can occur in noble metal nanoparticles (NPs), sharp metal tips, or roughed metal surfaces. In this process, it leads to redistribution of the local field and a great enhancement of the EM field at a specific position around the NP (called a “hot spot”) (Haes et al., 2005). This enhancement has a strong