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Research review paper

Raman tags: Novel optical probes for intracellular sensing and imaging

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ABSTRACT

Optical labels are needed for probing specific target molecules in complex biological systems. As a newly emerging category of tags for molecular imaging in live cells, the Raman label attracts much attention because of the rich information obtained from targeted and untargeted molecules by detecting molecular vibrations. Here, we list three types of Raman probes based on different mechanisms: Surface Enhanced Raman Scattering (SERS) probes, bioorthogonal Raman probes, and Resonance Raman (RR) probes. We review how these Raman probes work for detecting and imaging proteins, nucleic acids, lipids, and other biomolecules in vitro, within cells, or in vivo. We also summarize recent noteworthy studies, expound on the construction of every type of Raman probe and operating principle, sum up in tables typically targeting molecules for specific binding, and provide merits, drawbacks, and future prospects for the three Raman probes.

Contents

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1. Introduction

Because they are non-intrusive, optical methods and tools are attractive in cell biology for probing living cells and monitoring intracellular processes. Optical labels are valuable tools for studying specific targets in complex biological systems. Extensively used fluorescence labels provide high sensitivity, but they permit investigation only of the targeted object, and the information they provide is limited (Huang & Marti, 2012; Yamakoshi et al., 2012). Moreover, common fluorescent tags are relatively bulky and often considerably alter biological activity when used to tag small biomolecules. In addition, fluorescent tags are not usually suitable for multiplex detection of more than three targets because of their broad spectrum (Huang & Marti, 2012). Therefore, developing optical labels with enhanced information content, minimal perturbation, high sensitivity, and specificity is a critical subject in current biophotonics research. Developing more advanced optical methods and tools for probing living cells and monitoring intracellular processes is attracting growing interest in cell biology.

One emerging strategy is the Raman tag, which permits quantitative, qualitative, and multiple analyses of molecules, both labeled and unlabeled. The Raman spectrum's high information content can provide scientists with essential information to answer fundamental questions concerning intracellular pharmacokinetics, such as drug location, drug concentration in subcellular regions, intracellular kinetics, and the nature of the interaction between drugs and their pharmacological targets. The sharp, molecularly specific spectra obtained from endogenous biomolecules and exogenous reporters make it possible to specifically identify individual components from a mixture, consequently making the Raman probe an ideal method for the detection and imaging of multiple analytes. The development of the confocal Raman microscope and improvement of Raman detection systems have resulted in more proposed Raman imaging or detection applications in biochemistry.

The Raman signals of the molecules, which work as a Raman probe, should have unparalleled strong Raman intensity or a unique Raman shift, which enables recognition of the targeted molecule in a complex cell environment. Raman reporters may be grouped into three categories: the SERS probe, the bioorthogonal Raman probe, and the RR probe. The SERS probe is an ideal method for multiple target detection owing to its high levels of sensitivity and narrow spectral widths of Raman peaks. However, SERS tags cannot identify gradient information for distribution of biomolecules in cells because nanoparticles (NPs) are much larger than most biomolecules. The bioorthogonal Raman probe improves intracellular bioimaging because of its ultra-small size and relatively strong Raman signals in the cellular silent region (Yamakoshi et al., 2012; Lin et al., 2012; Yamashita et al., 2015; Song et al., 2014; Hong et al., 2014; Wei et al., 2014; Yamakoshi et al., 2011). The RR probes have sizes similar to the fluorescent tags because most RR probes require light absorption in the visible range, but it is still much smaller than the SERS probe. Furthermore, the RR probes demonstrate 10^2– 10^6 enhancement of Raman intensity, which permits rapid Raman imaging with rich gradient information for intracellular components (Weeks et al., 2012; Carey, 1998; Niebling et al., 2011; Carey & Schneider, 1978; Kumar et al., 1978; Li et al., 2015). Among Raman probes, SERS probes are the most developed because absorbing the reporter molecule onto a roughened metal surface, thus producing enhancement factors of 10^4–10^8, could significantly enhance the Raman signal of a reporter molecule. Several excellent reviews have covered the basic materials (Sharma et al., 2012), multiplex optical sensing (Rodriguez-Lorenzo et al., 2012; Laing et al., 2016), and application for biosensing and bioimaging (Vo-Dinh et al., 2010; Vo-Dinh et al., 2015; Wang et al., 2013a; Ando & Fujita, 2013; Bantz et al., 2011). In this review, we will focus on the construction, characteristics, and application of these three Raman probes for intracellular sensing or imaging and also discussed advantages, limitations, and future directions of these three probes. We attempt to outline clearly various Raman probes for chemists, physicists, and biologists and to push the development and application of Raman probes in the biochemical field.

2. SERS Raman probes

Because the proximity of Raman active signature molecules and metal NPs produces an extremely strong Raman signal, SERS probes are currently the most attractive Raman probes. They are capable of marking specific molecules, and Raman microscopy can indirectly map the target molecules in biological samples. As one excellent review has covered SERS tag development before 2013 (Wang et al., 2013b), we will only briefly summarize it here and focus on recent processes.

2.1. History and current development

Martin Fleischmann et al. first observed SERS in 1974 (Fleischmann et al., 1974). Two groups proposed electromagnetic effect (Jeanmaire & Van Duyne, 1977) and charge-transfer effect (Albrecht & Creighton, 1977) to explain Raman signal enhancement. After that, SERS was overwhelmingly used for high-sensitivity detection in various fields, especially in chemistry and biology. The most commonly used experimental method is to directly connect the analyte to a SERS substrate (Banholzer et al., 2008a), then conduct qualitative and quantitative analysis by studying the analyte's SERS spectrum.

In the past few decades, the development of nano-manufacturing technology has promoted exploration of SERS-based probes. Like the fluorescent probe design, the design of most SERS probes is based on immune-labeling. Tarcha et al. (Rohr et al., 1989) first reported SERS-based immunoassay in 1989. Since then, SERS tags have been extensively studied because of their high detection sensitivity (Sha et al., 2007; Cui et al., 2006; Grubisha et al., 2003), narrow spectral bandwidth for multiplex detection (Wang et al., 2012a; Zavaleta et al., 2009a; Cao et al., 2002), immunity to photo-bleaching (Zavaleta et al., 2009a), and ability to perform detection in biological matrices (Zavaleta et al., 2009a; Lutz et al., 2008).

2.2. SERS probe construction

A representative SERS probe consists of four parts: nano-structured substrates, Raman reporter, targeting molecule, and protection shell. The Raman reporter is conjugated on the surface of the nano-structured substrate, where the excitation of the localized surface plasmons significantly enhances the Raman signals of proximate Raman reporters. The targeting molecule is a biorecognition element, which may be an antibody or other molecule designed to bind a specific target molecule with good biostability and biocompatibility. The protection shell is essential for both improving biocompatibility and reducing the nonspecific binding of tags. Therefore, a multistep preparation is required, each step of which is vital for monitoring physical and chemical properties of the final SERS tags.

2.2.1. Nano-structured substrates

In general, Au and Ag are most often popular SERS substrates because they are air-stable and have localized surface plasmon resonances that cover most of the visible wavelength ranges where most Raman measurements occur. Different particle shapes (Fales et al., 2011; Yang et al., 2010; Rodriguez-Lorenzo et al., 2009; Moreton et al., 2015) and new plasmonic materials (Boltasseva & Atwater, 2011; Wang et al., 2014) have recently been explored for moving the excitation wavelength to near-infrared (NIR) or mid-infrared, where light has its maximum depth of penetration in biological samples. This is particularly significant for in vivo detection because the long-wavelength excitation also minimizes auto-fluorescence of cell or tissue, and then increases the signal-to-noise ratio. Among these new substrates, nanoshells are the most attractive structures for longer wavelength (Bedics et al., 2015).

According to surface plasmon resonance (SPR) theory, SERS intensity enhancement occurs only when the laser excitation is in resonance with the plasmon frequency of NPs. Thus, selecting a particular NP