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Review

Fluorescent nanoprobes for sensing and imaging of metal ions: Recent advances and future perspectives

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ABSTRACT

Recent advances in nanoscale science and engineering have generated nanomaterials with unique optical properties. Over the past decade, numerous fluorescent nanoprobes have been developed for highly sensitive and selective sensing and imaging of metal ions, both *in vitro* and *in vivo*. In this review, we provide an overview of the recent development of the design and optical properties of the different classes of fluorescent nanoprobes based on noble metal nanomaterials, upconversion nanoparticles, semiconductor quantum dots, and carbon-based nanomaterials. We further detail their application in the detection and quantification of metal ions for environmental monitoring, food safety, medical diagnostics, as well as their use in biomedical imaging in living cells and animals.

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Introduction

Metal ions play fundamental roles in biology by serving as essential cofactors in processes such as energy metabolism and storage, signal transduction, and nucleic acid processing [1–7]. However, some essential metal ions, including Fe^{2+}, Cu^{2+}, Mn^{2+}, and Co^{2+}, can also be toxic at high doses [8]. Therefore, metal ion's import, trafficking, availability, and export must be tightly regulated at the cellular level. In addition, other heavy metal ions, such as Hg^{2+}, Cd^{2+}, Pb^{2+}, and As^{3+}, are acutely toxic to humans and aquatic species even at low concentrations, and bioaccumulation of these metal ions can cause serious health problems [9]. Therefore, developing sensitive and selective methods to detect and quantify metal ions for environmental monitoring, food safety, and medical diagnostics and imaging is of considerable importance.

Traditional analytical techniques for metal ion detection, such as atomic absorption or emission spectroscopy (AAS/AES) [10], inductively coupled plasma mass spectrometry (ICP-MS) [11], anodic stripping voltammetry [12], and capillary electrophoresis [13], typically require expensive instrumentation and/or complicated sample preparation, making it difficult for on-site and real-time detection. In light of these drawbacks, there is increasing interest in developing new sensing techniques for the detection of metal ions that have higher sensitivity and selectivity, shorter response times, and lower costs [14]. Among the current sensor approaches, fluorescence detection [3,15–21] is the most common analytical tool used in the detection of metal ions due to its capabilities for high sensitivity, selectivity, reproducibility, and rapid, real-time monitoring. The critical element that achieves this goal is the fluorescent probe which offers a real-time, noninvasive way to image metal ions in their native environments with high spatial and temporal resolution [3]. Because of these capabilities, fluorescent probes have contributed greatly to insights into production, localization, trafficking, and biological roles of metal ions in complex living systems [3,19].

Organic dyes, such as rhodamine, fluorescein, and cyanine, are the most commonly used fluorescent probes [22–24], but their low absorption coefficients and weak signal reduce the sensitivity and response of metal ions [5,25–27]. In addition, most organic fluorophores undergo irreversible photobleaching during prolonged illumination, which makes them incapable of continuous observation and long-term imaging for studies of living cells [28]. Furthermore, some organic dyes, such as fluorescein isothiocyanate (FITC), are strongly phototoxic, and could produce reactive oxygen species (ROS) in the excitation process. These drawbacks have stimulated the development of alternative fluorescent probes for metal ions with brighter luminescence, higher photostability, and better biocompatibility, through advances in the fields of nanoscale science and engineering. The typical construction of fluorescent nanoprobes starts with synthesis of the nanoprobes using top-down or bottom-up approaches, followed by designed surface modifications. The precisely-controlled preparation of size, shape, chemical composition, and surface chemistry of the nanoprobes is critical to obtain unique optical properties and high performance in sensing and imaging applications.

Recent advances in nanobiotechnologies are expanding the availability of nanomaterials varying in size and structure [29–32], offering many exciting opportunities for discovering new fluorescent nanoprobes [33–39]. A variety of nanoprobes have already been prepared, evaluated, and applied in fluorescent sensing and imaging of various metal ions, including metal nanomaterials [40–42], lanthanide-doped upconversion nanoparticles (UCNPs) [43–47], semiconductor quantum dots (QDs) [48,49], and carbon-based nanomaterials [50–54]. These fluorescent nanoprobes can overcome several limitations of conventional organic dyes, such as poor hydrophilicity and photostability, low quantum yield and detection sensitivity, insufficient stability in biological systems, and weak multiplexing capability [55,56]. In addition, surface functionalization of these nanomaterials offers selective delivery of the nanoprobes to specific cells or even to subcellular organelles to realize effective intracellular imaging.

Several excellent review papers have been published to highlight the potential of fluorescent nanoprobes for analyzing metal ions in environmental and biological samples [57–62]. However, most of the reviews focused on either environmental sensing or biological imaging. In an effort to fill this gap, we herein review the literature of the last five years covering recent advances of different fluorescent nanoprobes in both sensing and imaging systems for metal ions. The representative literature reports utilizing fluorescent nanoprobes for metal ion sensing are summarized in Table 1. Current challenges and future prospects of fluorescent nanoprobes for fundamental studies and clinical applications will also be discussed.

Noble metal nanomaterials-based fluorescent nanoprobes for sensing and imaging of metal ions

Noble metal nanomaterials, such as gold and silver, have frequently been used in the construction of fluorescent nanoprobes for metal ions during the past decade because of their unique optical properties [63–65]. These metal nanomaterials can be categorized into two types based on the size and optical properties: colloid metal nanoparticles (NPs) and metal nanoclusters (NCs). Colloid metal NPs generally refer to materials with diameters more than 10 nm and less than a few 100 nm. Typically, these NPs produce localized surface plasmon resonance (LSPR) and strong light scattering [66–69], however, they usually have poor intrinsic fluorescent quantum yields (QYs) that are not suitable for direct fluorescent sensing of metal ions. Nevertheless, with the ability to quench molecular excited states, colloid metal NPs could function as effective photoluminescence (PL) quenchers in designing fluorescence-based sensors. On the other hand, metal NCs are defined as small metal clusters (*e.g.*, Au, Ag, Cu, and Pt) with size ranges from sub-nanometer to 10 nm in diameter. Specific features of such metal NCs include high fluorescence, excellent photophysical and chemical stability, good biocompatibility, controllable sizes and tunable emissions, and rich surface chemistry for functionalization [70]. Because of these useful features, fluorescent probes using metal NCs have contributed to the development of many innovative analytical methods for biosensing and bioimaging *in vitro* and *in vivo*.

Colloid metal nanoparticles

Detection of metal ions in environmental and biological samples

Colloid metal NPs with unique optical properties have been widely used for the detection of metal ions in environmental and biological samples [71]. Among these, gold nanoparticles (AuNPs), including nanospheres and nanorods, are especially attractive because of their convenient synthesis, biocompatibility, and novel optical properties. The synthesis of AuNPs can date back to Michael Faraday's work in 1857, in which the gold hydrosols were prepared by reduction of an aqueous solution of chloroaurate with phosphorus dissolved in carbon disulfide. Since then, numerous methods have been developed to synthesize and functionalize AuNPs, and these methods have been extensively reviewed in the past [72–74]. Although AuNPs display rather weak fluorescence, they can be used in fluorescent sensors as a "super-quencher" for almost all dyes, because the quenching effect of AuNPs is generally several orders of magnitude higher than that of an organic quencher. Therefore, a critical parameter for fluorescent sensing using AuNPs is the change