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Review

Luminescent biodetection based on lanthanide-doped inorganic nanoprobes

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ABSTRACT

Sensitive and selective biodetection is essential for many applications in biology and medicine, including protein purification, DNA immunoassay, early cancer diagnosis and therapeutics. Lanthanide-doped inorganic nanoprobes, emerging as an alternative to conventional molecular luminescent probes by overcoming their current limitations, have attracted a reviving interest for a variety of bioapplications due to their distinct optical properties. In this review, we focus on the most recent progress on the development of lanthanide-doped luminescent nano-bioprobes and their biodetection of model analytes, nucleic acids, ions, and disease markers both *in vivo* and *in vitro*. In particular, we highlight the typical bioconjugation strategies and detection techniques for different target analytes. Finally, some most important emerging trends and future efforts toward this rapidly growing field are also proposed.

Abbreviations: ATF, amino-terminal fragment; BSA, bovine serum albumin; CT, computed tomography; DCC, dicyclohexylcarbodiimide; DIEA, N,N-diisopropylethylamine; DMF, 2,5-dimethylformamide; DS, downshifting; ELISA, enzyme-linked immunosorbent assay; FIR, fluorescence intensity ratio; FITC, fluorescein isothiocyanate; FRET, Förster resonance energy transfer; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBTU, o-benzotriazole-N,N,N′,N′-tetra-methyluronium hexafluorophosphate; hCG, human chorionic gonadotropin; hCy, heptamethine cyanine; HOBT, 1-hydroxybenzotriazole; Ln^{3+}, lanthanide; LRET, luminescence resonance energy transfer; LOD, limit of detection; NCs, nanocrystals; MRI, magnetic resonance imaging; NIR, near-infrared; PBA, 3-phenoxybenzoic acid; PDT, photodynamic therapy; PET, positron emission tomography; PL, photoluminescence; PMPD, poly-m-phenylenediamine; QDs, quantum dots; RhBITC, rhodamine B isothiocyanate; suPAR, soluble urokinase plasminogen activator receptor; TEM, transmission electron microscopy; TR, time-resolved; UC, upconversion; uPA, urokinase plasminogen activator; U.S. EPA, United States Environmental Protection Agency; UV, ultraviolet.

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1. Introduction

The last few decades have witnessed the emergence and rapid development of nanoscience and nanotechnology including nano-chemistry, nano-physics, nanomedicine and nano-biomaterials, which allows for the exploration of facile, inexpensive and sensitive biological analytical techniques by employing nano-bioprobes [1–3]. To date, the most common types of luminescent bioprobes are organic dyes, lanthanide chelates, and semiconductor quantum dots (QDs) [4–9]. However, the use of these conventional bioprobes in biodetection always suffers from several disadvantages, for instance, high autofluorescence background and considerable photodamage associated with ultraviolet (UV) excitation, large emission bandwidth, low photochemical stability, short luminescent lifetime, and/or long-term toxicity [10]. In comparison with these traditional counterparts, lanthanide (Ln^{3+})-doped luminescent inorganic nanocrystals (NCs) possess high chemical stability and superior optical features such as long-lived luminescence (from several to tens of milliseconds), large antenna-generated Stokes or anti-Stokes shifts, narrow emission bands, and excellent photostability. Therefore, Ln^{3+}-doped nanomaterials are regarded as a new generation of bioprobes that can circumvent the above limitations of conventional bioprobes [11–13]. Particularly, near-infrared-to-visible upconversion (UC) NCs have been proposed as an ideal probe for biological labeling and imaging, due to their remarkable light penetration depth, weak autofluorescence, and low radiation damage.

The optical properties of lanthanide-doped NCs depend critically on the hosts in which the lanthanide ions reside, and thus it is important to seek for suitable host matrices to achieve desirable luminescence of Ln^{3+}. Up to now, oxides [14–16], vanadates [17,18], oxysulfides [19,20], phosphates [21,22] and fluorides [23–27] have been extensively synthesized and proved to be the ideal host candidates for producing highly efficient photoluminescence (PL) of Ln^{3+} ions. Besides the controlled synthesis of these Ln^{3+}-doped NCs, great efforts have been dedicated to the surface modification and bioconjugation, in order to render these Ln^{3+}-doped NCs water-soluble and biocompatible for specific targeting in biodetection. In clinical bioassays, the application of such Ln^{3+}-doped probes may be compromised by the undesirable background noise induced by the excitation light. To avoid the autofluorescence and improve the sensitivity of luminescent detection, some novel Ln^{3+}-based assay techniques have emerged. For instance, time-resolved PL (TRPL) assay was recently introduced as a good candidate for the quantitative biodetection [28], where the short-lived background noise from biological samples can be completely eliminated by gating and sampling the long-lived luminescence of Ln^{3+} (such as Eu^{3+} and Tb^{3+}). UC PL technique by employing the UC luminescence of Ln^{3+} provides another effective strategy to remove the unwanted background noise [29]. In the UC PL detection, phosphors are excited in the near-infrared (NIR) region, thus weak or no autofluorescence is produced from biocompounds.

The Ln^{3+}-based assay techniques have been utilized in a variety of sensitive bioassays, in which model analytes (such as avidin–biotin and IgG antibody–antigen) have been most frequently tested [30–32]. Subsequently, based on lanthanide-doped nanoprobes and bioconjugation strategies developed for the detection of model analytes, some practical biosensing systems can be established for the assays of nucleic acids and ions, which play key roles in biological functions [33,34]. Eventually, our goal for the development of new bioprobes and detection techniques is aimed at early disease therapeutics and diagnostics (the so-called theranostics). The unique optical properties of Ln^{3+}-doped nanoprobes combined with the well-established assay methods enable the design of highly sensitive biomarker platform [35,36].

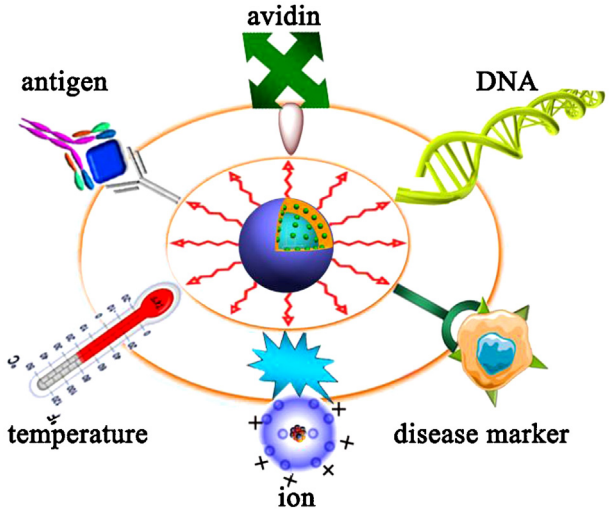

Fig. 1. Typical luminescent biodetection of antigen, avidin, DNA, disease marker, ion and temperature based on Ln^{3+}-doped nanoprobes *via* conjugation with specific biomolecules or complexes.

In the past few years, some reviews on the topic of luminescent bioprobes have been documented, but most of them are focused on conventional molecular bioprobes or QDs [37–44]. Recently, Ln^{3+}-doped luminescent NCs have gained reviving interest because of their potential applications in bioimaging, drug delivery, photodynamic therapy (PDT), as well as disease theranostics. Controlled synthesis, optical spectroscopy, surface modification of Ln^{3+}-doped NCs along with their early-stage applications have been summarized in several critical and tutorial reviews [45–56]. Rather than being exhaustive, this review is aimed at highlighting the most representative applications of Ln^{3+}-doped inorganic nano-bioprobes in heterogeneous or homogeneous luminescent biodetection, with an emphasis on *in vitro* and *in vivo* bioassays of model analytes, nucleic acids, ions and disease markers, *etc.* (Fig. 1). The most important emerging trends and future efforts in the development of lanthanide-doped luminescent nanoprobes are proposed at the end of this review.

2. Lanthanide doped luminescent nanoprobes

The lanthanide elements refer to a series of consecutive chemical elements from lanthanum (La, atomic number 57) to lutetium (Lu, atomic number 71), which have similar electronic configurations for their trivalent ions ($[Xe]4f^N$) with unfilled electron shell $4f^N$ ($N = 0–14$). Due to the unique and abundant energy level structures arising from these $4f^N$ inner shell configurations, Ln^{3+} ions can exhibit sharp and multicolor emissions spanning a broad spectral range from UV (Gd^{3+}) to visible (*e.g.*, Eu^{3+}, Tb^{3+}, and Dy^{3+}) and to near-infrared (*e.g.*, Ho^{3+}, Nd^{3+}, Er^{3+} and Tm^{3+}) [57]. The emissions of Ln^{3+} in inorganic host lattice vary with the concentration and combination of doped ions as well as their local site symmetry in the lattice. Besides, the phonon energy and crystal-field strength of the host lattice also influence the transitions within Ln^{3+} ions [58]. Therefore, by proper selection of the dopant Ln^{3+} ions and the host matrices, multicolor emissions can be realized in Ln^{3+}-doped luminescent materials. Generally, the emissions of Ln^{3+}-doped NCs can be classified into two categories based on the relative frequencies of the excited and emitted light: downshifting (DS) and UC [59]. DS luminescence refers to the phenomenon where one high-energy photon is transformed into one or more lower energy photons (Stokes emission). Theoretically, DS luminescence is expected for most Ln^{3+} ions due to the abundant energy level structures of Ln^{3+} ions [55]. However, strong and practically