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Near-infrared upconversion nanoparticles for bio-applications

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ABSTRACT

Upconversion nanoparticles (UCNs) attract intensive attentions in biomedical applications. They have shown great potential in bioimaging, biomolecule detection, drug delivery, photodynamic therapy and cellular molecules interactions. Due to the anti-Stokes optical property and NIR excitation, UCNs overcome the drawbacks encountered in conventional luminescent biomarkers. High signal to noise ratio, low cytotoxicity and stable high throughput results are obtained using UCNs as luminescent labels or light triggers in biomedical applications. In this review article, the reason for choosing UCNs as biomedical agents, the progress of the UCNs development and case studies of their biomedical applications will be discussed.

1. Introduction

Fluorophores have been used for non-invasive detection of biological molecules and monitoring of real-time biological processes for several decades [1]. As a non-destructive method, fluorescence technique produce fast, sensitive and reproducible signal, and high resolution in samples with intrinsic color (e.g. blood). The optical bio-imaging with fluorophores has become the state of the art with impacts on fundamental biomedical research and clinical practice. There are two main categories of fluorophores exploited for this purpose: one type converts short wavelength light to longer ones (downconversion), and another type converts longer wavelength to shorter (upconversion). This review focuses on the later one. Downconversion was studied earlier than upconversion. Organic dyes and quantum dots fall in this category. Most of organic fluorophores suffer from a common problem-photobleaching [2–4]. The track of the targets will be lost after the fluorescence bleaching, which lead to failure of the tasks. Quantum dots, feature with large molar extinction coefficient [5], higher quantum yield, narrow emission bandwidth [6], size-dependent tunable emission [7], composition tunable emission and higher photostability, seem to be a fantastic alternative to organic dyes [6,8,9]. Unfortunately, quantum dots are usually composed with elements exhibiting intrinsic toxicity, such as Cd, Se etc. [10]. Their potential toxicity poses risks to health and environment, which became a concern and arouse debate to apply them in biological study [11,12]. Furthermore, both the organic fluorophores and quantum dots suffer from low signal-to-noise ratio. Downconversion luminescent materials are generally excited by UV and visible light, so the autofluorescence [13,14] from the biological sample (such as mitochondria and lysosomes) is always present in the signal and thus decreases the sensitivity of the detection, leading to low signal-to-noise ratio. Moreover, the incident excitation light causes photodamage to living organisms. The second type, fluorescent upconversion nanoparticles (UCNs) overcomes most of the drawbacks of downconversion materials. UCNs exhibit anti-Stokes emission by emitting detectable photons of higher energy in the UV to a visible range upon near-infrared (NIR) irradiation. Coincidently, optical window in biological tissue falls in the NIR region [15], in which most biological molecules showing the lowest absorption of light. Therefore, the penetration depth of NIR is much deeper than UV or visible light, which enables deeper imaging or detection. As well the NIR light is much less toxic to biological system compared to UV light. Composed with inorganic crystals doped with lanthanide elements, the toxicity is much lower than quantum dots. UCNs' fluorescence originated from the energy transfer between different energy levels of lanthanide [16], so the upconversion fluorescence is much stable than organic dyes. Due to the aggregated sub-energy level of lanthanide, the emission bandwidth is very sharp and fluorescence lifetime is relatively long, up to several milliseconds [17]. The emission of the upconversion can be finely tuned by doping different lanthanide elements. The above mentioned superior properties over conventional downconversion labels render UCNs an ideal luminescent label for biological applications. In this review, we focus on the second type of fluorescent material-upconversion nanoparticles (UCNs). The development of UCNs and their applications in biomedical area will be discussed.

2. Luminescent upconversion process

Development of upconversion nanoparticles (UCNs) is one of the hottest topics in recent years. The research interests on them aroused from their unique optical property—it converts low energy photons

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of long wavelength light to high energy photons to emit shorter wavelength light. Take Yb^{3+}/Er^{3+} and Yb^{3+}/Tm^{3+} absorber/emitter pair doped UCNs as an example; it will be more clearly to understand the upconversion procedure. In this process, Yb^{3+} absorbs energy near 980 nm as it has broad cross-section in this region [18–20]. As shown in Fig. 1, The absorber Yb^{3+} ions absorb NIR light, and then through lattice vibrations of the nanocrystalline matrix, the energy transfers to the emitter Er^{3+} or Tm^{3+} ions due to the energy overlap of the transition dipoles of the two elements [21,22]. Due to the complex energy level configuration of Er and Tm, the energy relaxes to different energy levels before it is released to ground state. Subsequently, wide span emissions ranging from UV, visible to NIR, corresponding to different energy levels, are generated when the energy is released to ground state.

3. Host matrix for upconversion

It is essential to choose a proper matrix for upconversion process as it totally depends on the energy transfer between absorber and emitter within a suitable proximity. Different matrix provides different distance between the atoms in which the emitter and absorber are randomly and equally distributed. But the size or atom distance is not the only criteria for choosing the latticed. Considered in getting more effective luminescence, another requirement for the lattice is low lattice photon energy, which reduces non-radiative energy loss. The dynamics of the excited state of the rare earth ions and interactions between them, so the upconversion emissions were different in different crystal lattices even though with the same dopants [23,24]. Therefore, to search a proper crystal lattice is very essential to achieve high upconversion efficiency. So far, a lot of lattices have been explored to serve as the host matrix for upconversion process.

The host used to incorporate the lanthanide absorbers and emitters can be classified into two main categories—amorphous and crystal. Amorphous material, most of them are glass, can host the lanthanide ions in the casting procedure. Germanate chalcohalide glass composed of GeO_2–PbO–Nb_2O_5 glass [25,26] with different halide (Cl, Br, I) modifiers and Pr^{3+} dopant concentrations have been studied as an upconversion host. Calcium sodium aluminosilicate glass doped with Er^{3+} was also studied as an upconversion host material at room temperature and at 77 K [27]. Upconversion luminescence was also studied in Ho^{3+} doped ZnO–TeO_2 glass [28], Er^{3+} doped SiO_2–PbF_2–ErF_3 transparent glass ceramics [29] and amorphous $Tm_{0.1}La_{0.9}P_5O_{14}$ [30]. The requirements for the crystal lattice to be used for upconversion matrix are much higher than the amorphous material. It requires similar size lattice points and distance between them as well as similar charges. A series of crystals had been explored as upconversion host. One big category is oxide, such as Y_2O_3 [31–33], ZrO_2 [34–36], and TiO_2 [37]. Bright white upconversion emission was also observed from Yb^{3+}, Er^{3+}, and Tm^{3+} codoped Gd_2O_3 nanotubes [38–40]. Perovskite oxides were also employed as host, such as Pr^{3+} doped $Bi_4Ge_3O_{12}$ [41], Er^{3+} doped $YAlO_3$ [42], $GdAlO_3$ [43], Ti^{2+} and Er^{3+} co-doped $LiNbO_3$ [44], Yb^{3+} and Tm^{3+} co-doped $GdAlO_3$ [43], Ho^{3+} doped $LiTaO_3$ [45] and $BaTiO_3$:Er^{3+} [37,46,47].

Other crystals composed with both oxygen and lanthanide ions were also used as host materials for upconversion processes, such as $LiGd(MoO_4)_2$, $Y_3Sc_2Ga_3O_{12}$, $Gd_3Ga_5O_{12}$ [43], TmP_5O_{14} and $Tm_{0.1}La_{0.9}P_5O_{14}$ [30], $LuPO_4$:Yb^{3+},Tm^{3+} [48], $La_2(MoO_4)_3$:Yb^{3+},Tm^{3+} [49], $Tm^{3+}/Yb^{3+}/Er^{3+}$ codoped $Lu_3Ga_5O_{12}$ [50,51], La_2O_2S [52] and $YbPO_4$:Er^{3+} [48,53] were also reported for upconversion. Halide compounds crystals were also reported for upconversion study. For example, Gd^{3+} doped $Cs_2NaGdCl_6$ [54], Er^{3+} doped $RbGd_2Br_7$ [55], Tm^{3+} doped $Cs_3Yb_2Cl_9$ [56] and $BaLu_2F_8$ doped with Er^{3+} [57]. Transition metal ions (Zr^{4+} and Ti^{4+} [58,59], Re^{4+} and Mo^{3+} [60]) have similar ionic size to lanthanide ions, they were also reported to be used to generate NIR to visible upconversion luminescence.

Capobianco's group made a lot of efforts to make upconversion nanoparticles with relatively new crystal lattice. For example, CaS: Eu^{2+}/Dy^{3+} emit strong red light upon NIR excitation [61]. They also found that $GdVO_4$ doped with Er^{3+} and Yb^{3+} have two strong emissions peaks near 525 and 550 nm while a relatively weak red peak centered at 660 nm [62]. Similarly, the similar host lattice doped with different ions $GdVO_4$:$Tm^{3+}/Yb^{3+}/Ho^{3+}/Li^{+}$ could harvest white emission in total [63]. Recently, they studied Na_xScF_{3+x} crystal–monoclinic phase Na_3ScF_6 and hexagonal phase Na_3ScF_6 nanocrystals [64], as an upconversion material. Among all the crystal host, LaF_3 [65–68] and $NaYF_4$ [69–72] (including Li^{+} substitution $LiYF_4$ [73,74]) are the most studied.

Even though some host matrixes have similar size lattice points to hold the lanthanide ions, dopants easily cause defects such as interstitial anion and cation vacancies in the crystal. Considering neutrality in the crystal, the dopant concentrations have to be stringently limited. Thus, the luminescence is not high in these materials. Fluorides bear lower phonon energies (350 cm^{-1}) than oxides (500 cm^{-1}) and lower than heavy halides (300 cm^{-1}) [16]; it is more stable than halides. Lattice with low phonon energy suffers less nonradiative energy loss in upconverted energy states. Theoretically, halides are more suitable to be used for host matrix [75]. Practically, it was found that the hexagonal phase Yb^{3+}/Er^{3+} (or Yb^{3+}/Tm^{3+}) codoped $NaYF_4$ nanocrystal was the most efficient infrared-to-visible upconversion luminescent materials [76–78]. For biological purpose, the toxicity of the host lattice is a key consideration point, which adds more limitations to choose the host.

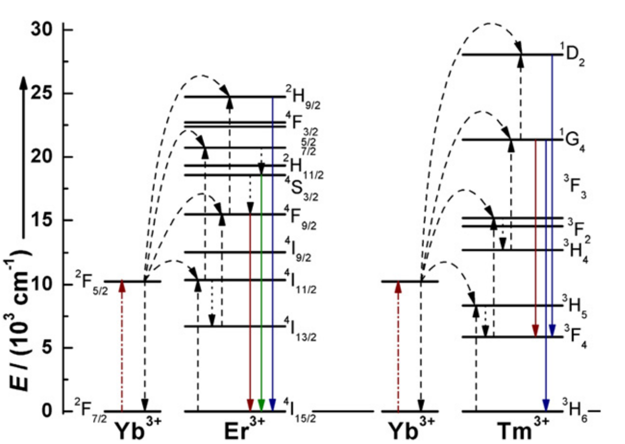

Fig. 1. Energy diagram of Yb^{3+}, Er^{3+} and Tm^{3+} and the energy transfer between them. The dashed–dotted, dashed, dotted, and full arrows represent photon excitation, energy transfer, multiphonon relaxation, and emission processes, respectively. Only visible and NIR emissions are shown here [16].

4. Efforts on improving upconversion efficiency

As a promising material used for biomedical applications, considerable efforts have been draw to improve the luminescent efficiency of UCNs. The upconversion was firstly studied in bulk material [79–81], and then researchers tried to make it into nanoscale with top-down or bottom-up methods. The small host leads to serious luminescence decrease due to the existence of a relative larger surface (larger surface to volume ratio). Especially for the upconversion process, the luminescence yield is affected in orders by any decreasing factors due to it is a multi-photon process: each photon process will be influenced by the same factor. To get repeatable and stable result, uniform size is highly required. Top-down methods cannot get as highly uniform sized nanoparticles as bottom-up methods, so intensive attention was on the latter. Hydrothermal synthesis is a typical bottom-up method for obtaining upconversion nanoparticles, but the size distribution of the nanoparticles was not satisfied [23,82]. After Zhang and Li developed a thermal decomposition method to obtain uniform sized $NaYF_4$ nanocrystals with oleic acid as a shape control agent [70,71,83], uniform 30–50 nm-UCNs with ± 3 nm sized can be easily obtained and the