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Recent Advances in Magnetic Upconversion Nanocomposites for Bioapplications

Yadan Ding, Xia Hong, Yichun Liu and Hong Zhang

Abstract: The combination of magnetism and upconversion luminescent property into one single nanostructure is fascinating for biological fields, such as multimodal bioimaging, targeted drug delivery, and imaging-guided therapy. In this review, we will provide the state-of-the-art advances on magnetic upconversion nanocomposites towards their bioapplications. Their structure design, synthesis methods, surface engineering and applications in bioimaging, drug delivery, therapy as well as biodetection will be covered.

Keywords: Magnetic optical nanocomposite, upconversion luminescence, structure design, synthesis, surface modification, bioimaging, drug delivery, therapy.

1. INTRODUCTION

Magnetic optical nanocomposites integrating magnetic and optical properties may have a significant potential for bioapplications, e.g., magnetic separation, magnetic resonance imaging (MRI), magnetic hyperthermia, optical bioimaging and optical labeling [1-9]. The magnetic component of the nanocomposite is usually superparamagnetic iron oxide-based nanoparticles, whereas the optical part is diverse from organic dyes, quantum dots (QDs) to lanthanide doped nanoparticles [10-18]. Especially, lanthanide-doped upconversion nanoparticles (UCNPs) have attracted considerable attention ascribed to their unique luminescent properties, such as large anti-Stokes shift, narrow emission bandwidths, tunable emission wavelengths, and absence of photobleaching and photobleaching [19-22]. Importantly, the near-infrared (NIR) excitation light has a deeper tissue penetration depth than ultraviolet (UV) and visible light necessary for the excitation of organic dyes, QDs, etc. [23-27]. Thus, magnetic upconversion nanocomposites are regarded as one of the ideal nanoplatforms for background-free bioimaging, magnetic targeted drug delivery, imaging-guided phototherapy, etc.

Despite the robust application potential of the nanocomposites and the continuous growth of research interest, relevant reviews are scarce. The one published 5 years ago covered synthesis and bioapplications in multimodal imaging and magnetic targeted drug delivery [9]. In recent years the synthesis strategy has improved and application has expanded to photothermal and photo/sono-dynamic therapy, biodetection, etc. It is therefore very demanding to update the latest advance in this field.

This review will update relevant progress on the design principles, synthesis, surface engineering and bioapplications of magnetic upconversion nanocomposites.

2. RATIONAL DESIGN OF MAGNETIC UPCONVERSION NANOCOMPOSITES

In order to be used in biological fields, the magnetic upconversion nanocomposites must have sufficient upconversion luminescence (UCL), strong magnetism, proper size and good biocompatibility. These requirements can be fulfilled by rational structure design, developed synthesis techniques and surface engineering.

2.1. Design Principle

The combination of UCL and magnetism provides intriguing dual-functionalities, however, the interplay of these functional components has to be considered. The emission quenching effect of magnetic nanoparticles (MNPs) has been widely recognized for fluorescent dyes and QDs [1, 28-30]. Although the quenching effect of MNPs to UCL was found to be much weaker than Au, and a layer of MNPs could act as a buffer to alleviate gold-induced UCL quenching [31], the reduction of UCL intensities in the presence of MNPs has also been frequently identified [32-38]. The quenching effect is generally attributed to the broad absorption of the MNPs (extending from UV to NIR region), which can attenuate both the excitation and emission light of the upconversion component. Accordingly, the shorter wavelength emission (e.g., green emission) is quenched more seriously than the longer wavelength emission (e.g., red emission) [32, 36]. Besides, the close proximity of the MNPs and the UCNPs in magnetic upconversion nanocomposites is also widely regarded as a major reason for UCL quenching. As far as the quenching mechanism is concerned, nonradiative energy transfer (ET) has been taken into consideration although not distinctly pointed out in most cases [39]. The ET efficiency depends on both the spectral overlap between the absorption of the acceptor and the emission of the donor as well as the donor-acceptor distance. It becomes much less efficient when the donor-acceptor distance is enlarged, which is often used as the basis for suppressing UCL quenching in most cases. In magnetic upconversion nanocomposite systems, reabsorption and nonradiative ET are very likely to coexist, similar to our previously reported ET nanoplatforms composed of NaYF₄-Yb, Er@NaYF₄ UCNPs and a photosensitizing molecule

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rose bengal [40]. Challenor et al. [36] found that the thermal effect of Fe$_3$O$_4$ nanoparticles also had a significant impact on the UCL properties of solid-state NaYF$_4$: Yb, Er nanoparticles, however, this phenomenon was rarely noticed by other groups. It is probably due to the different measurement conditions, such as the power density of the excitation light and the concentration of the samples.

![Core@shell structure](image1)  ![Coencapsulation structure](image2)  ![Janus structure](image3)  ![Spacer inserted structure](image4)

**Fig. (1).** Typical structures of magnetic upconversion nanocomposites.

Until now, various structures have been designed for constructing magnetic upconversion nanocomposites. Fig. 1 provides the schematic structures of some typical ones. The first one is a typical core-shell structure with one component inside and the other component outside. The second one is the coencapsulation structure with both the magnetic and upconversion components wrapped within SiO$_2$, polymer, etc. The third one is the Janus structure with two non-centrosymmetric hemispheres comprising the two components separately. The last one is a spacer inserted structure with the two components separated by, typically, SiO$_2$. In the core-shell structure, either the magnetic or the upconversion component can be wrapped inside. However, it is preferred to coat the magnetic core with upconversion shell for the sake of UCL. In the coencapsulation structure, the magnetic and upconversion components are wrapped together. Although it is difficult to determine whether the two components are distributed uniformly or the upconversion component is in direct contact with the magnetic component, the UCL was found to be quenched significantly [35]. In the Janus structure, the magnetic and upconversion components are incorporated into two separate hemispheres, thus improving UCL by reducing light attenuation and ET efficiency. Spacer inserted structure is the most popular for the alleviation of UCL quenching. The lengthened distance between the upconversion and magnetic components facilitates the decrease in the reabsorption rate and especially ET efficiency.

As iron oxide-based MNPs can always reduce the upconversion luminescence to some extent, alternatives have also been reported recently. Chen et al. [41] introduced a 4-carboxyl-tetramethyllumiperidine 1-oxyl (TEMPO) nitroxide radical as a contrast agent for MRI. The TEMPO radical was doped into silica, and coated onto NaYF$_4$: Yb, Er@NaYF$_4$ UCNPs to construct multifunctional nanoprobes for UCL/MRI dual-modal imaging. Although the UCL intensity decreased by ~65% after transferring NaYF$_4$: Yb, Er@NaYF$_4$ UCNPs to cyclohexane to water, which can be ascribed to H$_2$O solvent effect, the UCNP@TEMPO@SiO$_2$ nanocomposites exhibited similar UCL intensity compared with UCNP@SiO$_2$. It indicates negligible quenching effect of the TEMPO radicals to UCL. Nanoscale Fe-MIL-101-NH$_2$ metal-organic framework (MOF) was also incorporated with NaYF$_4$: Yb, Er UCNPs by Li et al. [42] to construct core-shell structured nanoprobes for UCL/MRI bimodal bioimaging.

Apart from efficient UCL, strong magnetism of the nanocomposites is also preferred. As the incorporation of nonmagnetic components, such as NaYF$_4$-based UCNPs and SiO$_2$, would reduce the magnetism significantly, magnetic nanoparticle clusters consisting of numerous MNPs were introduced to prepare magnetic upconversion nanocomposites [43-47]. The resultant nanocomponents generally possess higher magnetism (saturation magnetization Ms >10 emu/g), however, the size of the nanocomponents increased dramatically (generally, larger than 200 nm). It might induce unsatisfactory colloidal stability, reticuloendothelial system clearance, etc. [48-51]. Zeng et al. [52] synthesized core-shell Fe$_3$O$_4$@NaYF$_4$: Yb, Er nanocomposites with oleylamine (OM) capped Fe$_3$O$_4$ nanoparticles (~10 nm) acting as the seeds. The obtained Fe$_3$O$_4$@NaYF$_4$: Yb, Er nanocomposites exhibited an average size of ~30 nm and Ms of 16.6 emu/g. However, further modification of the OM capped nanocomposites with biocompatible molecules, e.g. polyethylene glycol (PEG), is a prerequisite for broad biapplications. Recently, we have designed and fabricated water-dispersible multimagnetic beads-embedded Fe$_3$O$_4$@NaYF$_4$: Yb, Er nanocomposites [53]. The average size of the nanocomposites is ~33.8 nm, much smaller than those with magnetic nanoparticle clusters as the core. Simultaneously, the Ms of the nanocomposites is ~17.8 emu/g, higher than those following single magnetic nanoparticle embedded approach. The nanocomposites exhibited a great potential in magnetic field-assisted sensitive UCL bioimaging.

2.2. Synthesis

The magnetic upconversion nanocomposites can be synthesized by multiple methods, such as seed-mediated growth, amorphous layer-intermediated synthesis, co-encapsulation, ligand coupling, electrospinning, etc.

Seed-mediated growth method involves the growth of one component with its reaction precursors on the surface of the other preformed component [32, 48, 52, 54-61]. Xia and coworkers [32] obtained NaYF$_4$: Yb, Tm@Fe$_3$O$_4$ nanocomposites by thermalysis of Fe(acac)$_3$ in the presence of oleic acid (OA) capped NaYF$_4$: Yb, Tm seeds. The ~30 nm core-shell structured nanocomposites exhibited excellent water dispersibility after being modified with dopamine hydrochloride. By using OM capped Fe$_3$O$_4$ nanoparticles as the seeds, Fe$_3$O$_4$@NaYF$_4$: Yb, Er nanocomposites with an ultrasmall size of 14.5 nm were prepared via thermal deposition of lanthanide trifluoroacetates [58]. Luo and coworkers [61] synthesized Fe$_3$O$_4$@Mn$^{2+}$-doped NaYF$_4$@Mn$^{2+}$-doped NaYF$_4$: Yb, Er core-inert shell-active shell structured nanocomposites with OA capped Fe$_3$O$_4$ nanoparticles as the seeds. The shell was formed by the hydrothermal reaction of MnCl$_2$, lanthanide nitrates and NaF in the presence of OA and appropriate solvents. Mn$^{2+}$ doping was found to play an important role in the formation of the core-shell structure by inducing hexagonal to cubic phase transformation of NaYF$_4$, which improved the lattice match degree of NaYF$_4$ with FeOx. Chen et al. [48] transferred OA capped Fe$_3$O$_4$ nanoparticles to water phase by breaking the double bond of OA with NaO$_2$ to produce carboxyl group, and deposited the precursor of upconversion nanoporphosphor (Gd$_3$(COO)$_3$)$_2$H$_2$O: Yb, Er/Tm) on the surface of Fe$_3$O$_4$ by precipitating lanthanide ions with urea. Then, negatively charged sodium alginate and positively charged polyethyleneimine (PEI) were alternatively adsorbed on the surface by electrostatic interaction to prevent aggregation during the conversion of Gd$_3$(COO)$_3$)$_2$H$_2$O: Yb, Er/Tm to NaGdF$_4$: Yb, Er/Tm in the auto clave. The amine groups in PEI can also be used for further functionalization with PEG diacid. Except for the generally produced core-shell structured magnetic upconversion nanocomposites, dumbbell-like MnFe$_2$O$_4$-NaYF$_4$: Yb, Er Janus nanoparticles have also been fabricated recently by Wu et al. [60]. MnFe$_2$O$_4$ nanoparticles with a diameter of 11 nm were firstly prepared to act as the seeds, and then epitaxial growth of Yb, Er doped NaYF$_4$ with trifluoroacetate lanthanide precursors produced MnFe$_2$O$_4$@NaYF$_4$: Yb, Er nanocomposites. The dumbbell structure is a little bigger...
Amorphous layer-intermediated synthesis can alleviate the negative effects resulting from crystal mismatch between two components. An amorphous layer, such as SiO$_2$ and polymer, is introduced as the buffer to mediate the growth of the second component [44, 53, 62, 63]. SiO$_2$ is used most frequently due to its excellent water dispersibility, good biocompatibility, facile surface modification, favorable optical transparency, mature silanization chemistry, etc. [64-67] Zhu and coworkers [43] firstly coated citrate groups-capped Fe$_3$O$_4$ cores (~180 nm) with SiO$_2$ (thickness: ~35 nm) by Stöber method, and then precipitated a lanthanide carbonate layer (Lu,Yb,Er/Tm(OH)$_2$CO$_3$) on the surface with lanthanide chlorides and urea. After the calcination process and treatment with HF and NaF, Fe$_3$O$_4$/NaLuF$_4$: Yb, Er/Tm nanocomposites with an average size of ~330 nm were obtained. Gai et al. [68] prepared nonporous silica coated Fe$_3$O$_4$ (Fe$_3$O$_4$/aSiO$_2$) with Stöber method first, followed by mesoporous silica layer (average pore size: 2.2 nm) using cetyltrimethylammonium bromide (CTAB) as the organic template. Finally, NaYF$_4$: Yb, Er nanocrystals were deposited on the surface of the CTAB-removed bilayer silica coated Fe$_3$O$_4$ (Fe$_3$O$_4$/nSiO$_2$/mSiO$_2$) using lanthanide chlorides, NaF, etc. Zhang and coworkers [62] transferred oleate-capped Fe$_3$O$_4$ nanocrystals (~20 nm) to water phase by SiO$_2$ coating by reverse microemulsion. The Fe$_3$O$_4$/SiO$_2$ nanospheres were then coated with Y/Yb, Er(OH)$_2$CO$_3$, and underwent thermal treatment and ion exchange in the presence of HF and NaF. Fe$_3$O$_4$/SiO$_2$/NaYF$_4$: Yb, Er nanorattles with a diameter of ~115±20 nm were obtained. They are composed of a magnetic core (~20±10 nm), a silica middle layer (~10±5 nm), an intervening hollow space, and a NaYF$_4$: Yb, Er shell (~20±5 nm). Zhang et al. [44] synthesized Fe$_3$O$_4$/LaF$_3$: Yb, Er nanocomposites with polyacrylic acid (PAA) modified Fe$_3$O$_4$ nanoparticle clusters as the core. The uncoordinated carboxyl groups of PAA not only rendered Fe$_3$O$_4$ nanoparticle clusters water dispersibility, but also anchored rare earth ions through coordination interaction. LaF$_3$: Yb, Er shell was then formed on the surface of Fe$_3$O$_4$ following co-precipitation reaction. The size of the nanocomposites could be controlled from 190 nm to 220 nm depending on the reaction time and the amount of the shell precursors. Branched PEG, a well-known polyelectrolyte with high coordinating capacity with various nanomaterials, was used to transfer OA capped Fe$_3$O$_4$ nanoparticles to polar ethylene glycol by ligand exchange and direct the growth of Yb, Er codoped NaYF$_4$ [53]. By carefully adjusting the relative amount of Fe$_3$O$_4$ nanoparticles, Fe$_3$O$_4$/NaYF$_4$: Yb, Er nanocomposites with multiple magnetic beads embedded were obtained.

Co-encapsulation method was also used to construct magnetic upconversion nanocomposites. Different from the seed-mediated growth approach, this method is not restricted by the crystal mismatch between these functional components. Until now, organic polymer and inorganic oxides (e.g., SiO$_2$ and TiO$_2$) have been explored to encapsulate preformed MNP s and UCNPs [35, 46, 69-73]. A typical example of polymer encapsulation was presented by Xu et al. [69], who encapsulated hydrophobic UCNPs and MNPs with an amphiphilic block polymer, poly (strene-block-allyl alcohol) (PS$_{16}$-b-PAA$_{10}$), by a microemulsion method. Fluorescent dye and an antitumor drug can be loaded within the nanocomposites for additional functionalities. Recently, Yu et al. [70] encapsulated NaYF$_4$: Yb, Er UCNPs, Fe$_3$O$_4$ functionalized zirconium bis-(monohydrogen orthophosphate) monohydrate (α-ZrP) and genitamic sulfate (GS) with chitosan (CHI). The Fe$_3$O$_4$ nanoparticles and GS were intercalated into the interlayer of α-ZrP, while the NaYF$_4$: Yb, Er UCNPs were adsorbed on the surface of α-ZrP. The encapsulation with CHI not only improved the stability and bio-compatibility of the layered multifunctional nanosystems, but also prolonged the drug release time. Inorganic encapsulation of MNPs and UCNPs was firstly explored by Liu et al. [73] with SiO$_2$, where magnetic upconversion nanocomposites with NaYF$_4$: Yb, Er UCNPs (~10 nm) and Fe$_3$O$_4$ nanoparticles (~16 nm) encapsulated in SiO$_2$ were obtained by using a simple reverse-microemulsion method. Recently, TiO$_2$ encapsulation was developed to construct magnetic upconversion nanocomposites [46, 71]. For example, Shen et al. [71] synthesized dual-core-shell (Fe$_3$O$_4$/NaYF$_4$: Yb, Er/α-TiO$_2$) multifunctional nanocomposites. Trisodium citrate modified Fe$_3$O$_4$ nanoparticles (~150 nm) were firstly assembled with PEI modified NaYF$_4$: Yb, Er UCNPs (~50 nm) by electrostatic attraction, and then TiO$_2$ was coated on the complex by a thin sol-gel layer (average pore size: 2.2 nm) to water phase by SiO$_2$ coating through condensation of tetrabutyl titanate (TBOT). The TiO$_2$ shell not only encapsulated the MNPs and UCNPs to form stable magnetic upconversion nanocomposites, but also acted as a sonosensitizer for sonodynamic therapy of deeply located tumor.

Ligand coupling strategy incorporates MNPs and UCNPs through coordination, electrostatic attraction, covalent interaction, etc. [34, 45, 74-76] Surface ligands served as the bridges to link MNPs and UCNPs, eliminating the requirement of lattice matching of the two components. Shen et al. [77] synthesized NaYF$_4$: Yb, Er@Fe$_3$O$_4$ hetero-NPs using coordination-based coupling method. 1,10-decanedicarboxylic acid (DDA) or 11-mercaptoundecanoic acid (MUA) firstly inserted into the OA ligand on the surface of as-prepared NaYF$_4$: Yb, Er UCNPs by ligand exchange. Then the overhanging coordinating groups of DDA or MUA on UCNPs captured Fe$_3$O$_4$ nanoparticles by multivalent binding-like coordination interaction. Multiple Fe$_3$O$_4$ nanoparticles were anchored onto the surface of NaYF$_4$: Yb, Er UCNPs. Cheng et al. [31] adsorbed dopamine (DA) modified MNPs (~5 nm) onto the surface of PAA modified NaYF$_4$: Yb, Er UCNPs (~160 nm) by electrostatic interaction, and then core@shell nanoparticles were obtained by a thin shell of gold. The multifunctional nanocomposites can be used for multimodal imaging, therapies, cell isolation and detection [18, 31, 78, 79]. Zhao et al. [45] coupled amino-modified Fe$_3$O$_4$/SiO$_2$ and carboxyl-modified NaYF$_4$: Yb, Er by covalent interaction under the assistance of crosslinking agents N-ethyl-N’-[3-(dimethylamino) propyl]carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS). After further modification with MnO$_2$ nanosheets, the nanocomposites could act as bioimaging agents and magnetic targeted drug carriers.

Electrosprinning is a versatile and straightforward technique to construct one-dimensional micro-/nanоструктуры. It has been used by Dong’s group to prepare magnetic upconversion multifunctional nanofibers and nanoribbons with various structures in the past few years [80-83]. Fe$_3$O$_4$/NaYF$_4$: Yb, Er/polyvinylpyrrolidone (PVP) composite nanofibers were obtained when mixing Fe$_3$O$_4$ nanoparticles and NaYF$_4$: Yb, Er UCNPs together with PVP to prepare the electrosprinning solution [80]. To improve UCL, nanostructures with UCNPs isolated from Fe$_3$O$_4$ nanoparticles were also developed. By using an electrosprinning setup equipped with a homemade coaxial multi-spinneret, core-shell nanofibers with Fe$_3$O$_4$/PVP as the core and NaYF$_4$: Yb, Er/PVP as the shell were fabricated, where the electrosprinning solutions containing Fe$_3$O$_4$ or NaYF$_4$: Yb, Er were prepared separately and injected into coaxial inner and outer plastic syringes, respectively [80]. When the electrosprinning solutions containing Fe$_3$O$_4$ or NaYF$_4$: Yb, Er were loaded into two separate syringes, and ejected from specially designed spinnerets simultaneously, Janus nanofibers and nanoribbons with Fe$_3$O$_4$ and NaYF$_4$: Yb, Er distributed in two half sides were obtained [81, 82]. Recently, quadrifunctional [polyamine (PANI)/Fe$_3$O$_4$/polyacrylonitrile (PANi)]/[B$_2$WO$_6$:Yb, Er/PANI] bilayered composite fibrous membrane with electricity-magnetism at one layer and UCL-photoradiolysis at the other layer were prepared [83]. It was realized
by using a layer-by-layer electrospinning process, i.e., ejecting one electrospinning solution after the other one was completely consumed. The electrospinning method is simple, however, the large size of the obtained one-dimensional nanocomposites has hindered their practical applications in biomedical fields.

Due to the extraordinary physical and chemical properties of graphene, Yan et al. [84] fabricated a new class of multifunctional nanocomposites by incorporating brittle Fe$_3$O$_4$ nanocrystals (~200 nm) and NaYF$_4$: Yb, Er UCNPs (~50 nm) within graphene oxide (GO) matrix. The nacre-like structured nanocomposites were obtained by co-assembly of positively charged nanocrystals with negatively charged GO nanosheets and subsequent vacuum filtration. The ~23 μm-thick graphene nanocomposite films exhibited favorable UCL and magnetism as well as enhanced mechanical properties. By adsorbing Fe$^{3+}$ in Fe(acac)$_3$ and Zn$^{2+}$ in Zn(acac)$_2$ onto negatively charged GO nanosheets by an electrostatic force after the hydrothermal process, GO@ZnFe$_2$O$_4$ was prepared [85]. Nitrosonium tetrafluoroborate (NOBF$_4$) modified NaGdF$_4$: Yb, Tm UCNPs were further anchored by physical adsorption. Ultrasmall ZnFe$_2$O$_4$ nanoparticles (3-5 nm) and monodisperse UCNPs (less than 10 nm) were found to be loaded successfully on GO nanosheets.

Recently, Engel et al. [17] developed a modular system for constructing stimuli-responsive multifunctional nanoparticle aggregates using supramolecular host-guest chemistry. UCNPs, MNPs and Au nanoparticles were firstly modified with β-cyclooctetrin (β-CD, the host), and then divalent guest molecule, arylazopyrazole (E-AAP), was used to interconnect these nanoparticles by entering the immobilized β-CD to form aggregates. After (NIR converted) UV light irradiation, E-AAP can be isomerized to Z-AAP, which does not fit into β-CD cavities. The nanoparticles were thus dispersed. Reversibly, the Z-isomer of AAP can be converted to E-isomer under green light irradiation, which renders dynamic and reversible self-assembly of these nanoparticles. The size, shape and properties of the multifunctional nanoparticle aggregates can be adjusted by varying the nanoparticle ratio, the AAP linker concentration, the irradiation time of green light, etc.

In order to provide guidance for researchers to choose suitable synthesis method of magnetic upconversion nanocomposites towards their bioapplications, we have summarized some important features, e.g., size, Ms and dispersibility, of magnetic upconversion nanocomposites obtained by various methods in the literature. UCL intensity is not listed due to its dependency on specific measurement conditions.

2.3. Surface Engineering

In order to apply the magnetic upconversion nanocomposites in biomedical and biomedical fields, good aqueous dispersibility and biocompatibility are always required. To this end, surface modification with SiO$_2$, poly(allylamine) (PAAm), ozone, and particularly, poly(ethylene glycol) (PEG) and its derivatives, have been adopted. SiO$_2$ can not only act as a binder or a glue to incorporate IONPs with UCNPs, but also render magnetic upconversion nanocomposites biocompatible and easily functionalized with various biomolecules [87]. PAAm was used by Wu et al. [60] to endow OM capped MnFe$_2$O$_4$-NaYF$_4$: Yb, Er Janus nanoparticles with hydrophilicity by ligand exchange, and the amino group of PAAm was further used for covalent conjugation with folic acid (FA). Shen et al. [77] used ligand ozonolysis treatment to transfer hydrophilic NaYF$_4$: Yb, Er@Fe$_3$O$_4$ nanocomposites to water phase by producing carboxyl groups from broken double bonds of OA ligands. As a popular class of polymer in biological applications, PEG and its numerous derivatives have not only been widely applied to improve the solubility and biocompatibility of the hydrophilic magnetic upconversion nanocomposites [34, 42, 75, 85], but also been designed to transfer the hydrophobic magnetic upconversion nanocomposites to water phase [52, 57, 59, 61]. For example, Cui et al. [57] prepared OM capped Co$_{0.16}$Fe$_{2}$$_{8}$_{4}$_{6}$O$_{12}$@NaYF$_{4}$: Yb, Tm and Fe$_{3}$O$_{4}$@NaYF$_{4}$: Yb, Er nanocomposites by a two-step thermolysis method, and then transferred them to water phase by ligand exchange with bisphosphonate polyethylene glycol conjugates (BP-PEG). The PEGylation could stabilize the nanocomposites against aggregation in aqueous solution and also affect the circulation time and reticuloendothelial clearance of the nanocomposites.

3. BIOAPPLICATIONS OF MAGNETIC UPCONVERSION NANOCOMPOSITES

Compared with organic dyes and QDs, lanthanide-doped UCNPs are particularly attractive in bioimaging due to the resistance of photobleaching and background autofluorescence interference and the deep tissue penetration depth of the NIR excitation light [88, 89]. The incorporation of MNPs brings in additional functionalities, e.g., MRI and magnetic targeted drug delivery. Some new therapeutic techniques, such as photodynamic therapy (PDT) and photothermal therapy (PTT), have also been explored with magnetic upconversion nanocomposites. With the multifunctional nanocomposites as luminescent tags, biodetection can also be realized. Importantly, these applications can be combined into one single nanoplatforms, for example, imaging-guided drug delivery and therapies. In this section, we will review the applications of magnetic upconversion nanocomposites in bioimaging, drug delivery, therapies and biodetection. To get an insight of researchers’ interest in these bioapplications of magnetic upconversion nanocomposites, we scanned over 60 publications on magnetic upconversion nanocomposites from 2004 to estimate the proportions of these applications (Fig. 2). It can be seen clearly that bioimaging gets the most attention, drug delivery and therapies hold similar percentages, while biodetection is paid relatively less attention than the others.

Fig. (2). The proportion of different bioapplications of magnetic upconversion nanocomposites from literature published since 2004.

3.1. Bioimaging

Bioimaging is the most popular application of magnetic upconversion nanocomposites due to the intriguing UCL properties and MRI capability [32, 42-44, 48, 57]. Chen et al. [48] incubated MCF-7 breast cancer cells with PEGylated Fe$_3$O$_4$@NaGdF$_4$: Yb, Er nanocomposites, and observed bright UCL under 980 nm excitation. When they injected Fe$_3$O$_4$@NaGdF$_4$: Yb, Tm nanocomposites into the chicken breast at 1 cm depth, background-free deep tissue UCL imaging was realized. The nanocomposites could also act as T$_1$- and T$_2$-weighted MRI contrast agents due to the presence of Fe$_3$O$_4$ core and NaGdF$_4$ shell. Xia et al. [32] injected NaYF$_4$: Yb, Tm@Fe$_3$O$_4$ nanocomposites into the right forepaw of a nude mouse, and realized T$_2$-weighted MRI and NIRM-to-NIR UCL dual-modal imaging of the lymphatic system in vivo. MRI, UCL and computed tomography (CT) tri-modal imaging of tumor-bearing mice have also been achieved by using multifunctional nanocomposites composed of Fe$_3$O$_4$ and Yb, Er/Tm doped NaLuF$_4$ [43]. With
Table 1. The properties of magnetic upconversion nanocomposites prepared with various methods according to the literature.

<table>
<thead>
<tr>
<th>Synthesis Method</th>
<th>Material</th>
<th>Size/nm</th>
<th>Ms/emu·g⁻¹</th>
<th>Water Dispersibility</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seed-mediated synthesis</td>
<td>Fe₃O₄@NaYF₄:Yb, Er@NaYF₄: Yb, Er</td>
<td>~32</td>
<td>1.1</td>
<td>No</td>
<td>[56]</td>
</tr>
<tr>
<td>Seed-mediated synthesis</td>
<td>Fe₃O₄@NaYF₄:Yb, Er</td>
<td>~50</td>
<td>16.60</td>
<td>No</td>
<td>[52]</td>
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<tr>
<td>Seed-mediated synthesis</td>
<td>Fe₃O₄@NaYF₄:Yb, Er/Tm</td>
<td>65/68</td>
<td>7.0</td>
<td>Yes</td>
<td>[48]</td>
</tr>
<tr>
<td>Seed-mediated synthesis</td>
<td>Fe₃O₄@NaYF₄:Yb, Er</td>
<td>~14.5</td>
<td>8.45</td>
<td>No</td>
<td>[58]</td>
</tr>
<tr>
<td>Seed-mediated synthesis</td>
<td>Fe₃O₄@NaYF₄:Yb, Er, Mn³⁺</td>
<td>24-36</td>
<td>6.2</td>
<td>No</td>
<td>[59]</td>
</tr>
<tr>
<td>Seed-mediated synthesis</td>
<td>Fe₃O₄@NaYF₄: Mn³⁺@NaYF₄: Yb, Er, Mn³⁺</td>
<td>~20</td>
<td>3.85</td>
<td>No</td>
<td>[61]</td>
</tr>
<tr>
<td>Amorphous layer-intermediated synthesis</td>
<td>Fe₃O₄@sSiO₂@mSiO₂@NaYF₄: Yb, Er/Tm</td>
<td>~80</td>
<td>38.0</td>
<td>Yes</td>
<td>[68]</td>
</tr>
<tr>
<td>Amorphous layer-intermediated synthesis</td>
<td>Fe₃O₄@sSiO₂@Y₂O₃:Yb, Er</td>
<td>75.63±3.77</td>
<td>7.22</td>
<td>Yes</td>
<td>[39]</td>
</tr>
<tr>
<td>Amorphous layer-intermediated synthesis</td>
<td>Fe₃O₄@sSiO₂@NaLuF₄: Yb, Er/Tm</td>
<td>~330</td>
<td>15</td>
<td>Yes</td>
<td>[43]</td>
</tr>
<tr>
<td>Amorphous layer-intermediated synthesis</td>
<td>Fe₃O₄@sSiO₂@NaYF₄: Yb, Er</td>
<td>~115±20</td>
<td>1.28</td>
<td>Yes</td>
<td>[62]</td>
</tr>
<tr>
<td>Amorphous layer-intermediated synthesis</td>
<td>Fe₃O₄@PAA@LaF₃: Yb, Er</td>
<td>190-220</td>
<td>20-29</td>
<td>Yes</td>
<td>[44]</td>
</tr>
<tr>
<td>Amorphous layer-intermediated synthesis</td>
<td>Fe₃O₄@PEI@NaYF₄: Yb, Er</td>
<td>~33.8</td>
<td>17.8</td>
<td>Yes</td>
<td>[53]</td>
</tr>
<tr>
<td>Co-encapsulation method</td>
<td>Fe₃O₄@NaYF₄:Yb, Er@SiO₂</td>
<td>~60</td>
<td>1.64</td>
<td>Yes</td>
<td>[73]</td>
</tr>
<tr>
<td>Co-encapsulation method</td>
<td>NaYF₄:Yb, Er/Tm-Fe₃O₄@SiO₂</td>
<td>~150</td>
<td>5.6</td>
<td>Yes</td>
<td>[86]</td>
</tr>
<tr>
<td>Co-encapsulation method</td>
<td>Fe₃O₄@NaYF₄: Yb, Tm@TiO₂</td>
<td>~310</td>
<td>12.23</td>
<td>-</td>
<td>[46]</td>
</tr>
<tr>
<td>Co-encapsulation method</td>
<td>NaYF₄: Yb, Er-IONP@PS₂-c-PAA₉₀</td>
<td>~250</td>
<td>40</td>
<td>Yes</td>
<td>[69]</td>
</tr>
<tr>
<td>Co-encapsulation method</td>
<td>NaYF₄: Yb, Er-α-ZrP@Fe₃O₄@GS@CHI</td>
<td>~1700×625 (diameter×thickness)</td>
<td>2.1</td>
<td>Yes</td>
<td>[70]</td>
</tr>
<tr>
<td>Ligand coupling strategy</td>
<td>NaYF₄: Yb, Er@Fe₃O₄</td>
<td>~250/140</td>
<td>9.25/7.05</td>
<td>No</td>
<td>[77]</td>
</tr>
<tr>
<td>Ligand coupling strategy</td>
<td>NaYF₄: Yb, Er@SiO₂@Fe₃O₄</td>
<td>100-150</td>
<td>2.85</td>
<td>Yes</td>
<td>[74]</td>
</tr>
<tr>
<td>Ligand coupling strategy</td>
<td>NaYF₄: Yb, Er@Fe₃O₄</td>
<td>~170</td>
<td>~45</td>
<td>Yes</td>
<td>[31]</td>
</tr>
<tr>
<td>Ligand coupling strategy</td>
<td>NaGdF₄: Yb, Tm@NaGdF₄@ZnFe₃O₄</td>
<td>~100</td>
<td>~1.4</td>
<td>Yes</td>
<td>[8]</td>
</tr>
<tr>
<td>Ligand coupling strategy</td>
<td>NaYF₄: Yb, Er@mSiO₂@Fe₃O₄</td>
<td>~70-100</td>
<td>~2.7</td>
<td>Yes</td>
<td>[34]</td>
</tr>
<tr>
<td>Electrospinning</td>
<td>[Fe₃O₄/PVP]@[NaYF₄: Yb, Er/PVP] nanofiber</td>
<td>~260 (diameter)</td>
<td>~30</td>
<td>No</td>
<td>[80]</td>
</tr>
<tr>
<td>Electrospinning</td>
<td>[Fe₃O₄/PMM]@[NaYF₄: Yb, Er/PMM] nanoribbon</td>
<td>~10000×1000 (width×thickness)</td>
<td>~30</td>
<td>No</td>
<td>[82]</td>
</tr>
</tbody>
</table>

¹⁸F-labeled Fe₃O₄@NaYF₄:Yb, Tm or Co₃O₄Fe₃O₄@NaYF₄: Yb, Er providing magnetic, upconversion luminescent and radionuclide capabilities, MRI, UCL and positron emission tomography (PET) tri-modal imaging was realized by Cui et al. [57] Single photon emission computed tomography (SPECT) could also be incorporated by introducing ¹⁵³Cu or ⁹⁹mTc.

3.2. Drug Delivery

Magnetic upconversion nanocomposites are promising for drug delivery due to their magnetic manipulation capacity [45, 63, 68-71, 90]. Gai et al. [68] loaded ibuprofen (IBU) into mesoporous Fe₃O₄@mSiO₂@mSiO₂@NaYF₄: Yb, Er/Tm nanocomposites, and studied the IBU release process in simulated body fluid (SBF). It was found that amino modification of the nanocomposites could delay the release of IBU markedly, and the UCL intensity increased with the increasingly released amount of the drug. Zhao et al. [45] loaded Congo red, a model anionic drug, onto MnO₂ nanosheet-modified Fe₃O₄@SiO₂@NaYF₄: Yb, Er by electrostatic interaction. The MnO₂ nanosheets served as not only drug carriers, but also UCL quenchers. The drug can be released by glutathione (GSH)
induced reduction reaction of MnO₂. Simultaneously, increased UCL intensity can be used for monitoring GSH levels. Peng et al. [90] loaded etoposide (VP16) on glycol-functionalized Fe₃O₄@TiO₂: Yb, Er nanocomposites through hydrogen bonding. The release of the drug could be triggered by microwave induced local heating. The drug loading and release mechanisms were also studied by using microradiometry. In vivo studies with magnetic upconversion nanocomposites as drug carriers have also been explored by several groups [34, 62, 71]. Zhang et al. [62] loaded anti-tumor drug doxorubicin (DOX) into the interior hollow space of Fe₃O₄@SiO₂@NaYF₄: Yb, Er nanorattles by using the mesoporous shell as the gateway to the loading cavity. After injecting the DOX-loaded nanorattles to the tail veins of tumor-bearing nude mice, magnetic targeting enhanced accumulation of the nanocarrier in tumors was demonstrated by stronger UCL compared with non-targeted cases (enhanced permeability and retention (EPR) effect) induced accumulation. Accordingly, the enhanced therapeutic efficacy was observed for targeted delivered nanocarriers after PH-sensitive DOX release in the cancerous tissues. With hyaluronic acid (HA) modified Fe₃O₄@NaYF₄: Yb, Er@TiO₂ nanocomposites as drug carriers for DOX, synergetic chemotherapy and sonodynamic therapy (sonosensitizer: TiO₂) effect was also observed in tumor-bearing mice by Shen et al. [71].

3.3. Therapies

Rather than just drug carriers, the magnetic upconversion nanocomposites can also contribute to therapy directly. For instance, it is popular to use the NIR-excitable upconversion component as UV-vis source to trigger PDT or PTT efficacy. Until now, therapy has held a large proportion in the applications of magnetic upconversion nanocomposites, and multiple therapeutic modalities have been explored, such as PDT, PTT, stem cell therapy, and Fenton reaction induced therapy [8, 31, 72, 75, 79, 91]. Zeng et al. [91] loaded FA-functionalized Fe₃O₄@NaYF₄: Yb, Er with photosensitizer (tetra-sulfonic phthalocyanine aluminium), and realized FA-targeted MRI and visualized PDT with tumor-bearing nude mice under NIR irradiation. UCL, MRI, photoacoustic tomography (PAT) multimodal imaging-guided photothermal ablation of the tumor were also demonstrated with HA and Prussian blue nanoparticles decorated NaYF₄: Yb, Er@SiO₂@Fe₃O₄ nanocomposites [75]. Both magnetic field and HA contributed to the targeting process of the multifunctional nanocomposites to the tumor. Cheng et al. [79] labeled mouse mesenchymal stem cells (mMSCs) with PEGylated NaYF₄: Yb, Er@Fe₃O₄@Au nanocomposites, and then tracked the labeled mMSCs by UCL and MRI after injecting them into wound-bearing mice with a magnet placed nearby the wound site. Remarkable stem cell therapeutic efficacy was observed in the wound site resulting from magnetically induced translocation of the labeled stem cells. Bi et al. [8] used platinum (IV) prodrugs (Pt(IV)) as a bridge for coupling NaGdF₄: Yb, Tm@NaGdF₄: Yb UCNPs and ZnFe₂O₄ MNPs. Multimodal imaging (UCL, CT, MRI and PAT) guided synergetic therapy (chemotherapy, PDT and Fenton reaction) was demonstrated. The reduction of the Pt(IV) prodrugs to high virulent Pt(II) by gluthathione after entering the cancer cells could reduce the side effects of cisplatin such as cytotoxicity and drug resistance.

3.4. Biodetection

The application of magnetic upconversion nanocomposites in biodetection has also been explored in the past few years [18, 92, 93]. The unique UCL properties under NIR excitation endow the biodetection with high sensitivity, and the magnetism facilitates the separation and purification processes greatly. Zhang et al. [92] incorporated UCNPs and MNPs into polystyrene microspheres, and then modified the multifunctional microspheres with rabbit-anti-mouse antibodies for sandwich-structured immunoassay. The coded signal of UCNPs can only be excited under NIR excitation, while the reporter signal of fluorescein labeling rabbit-anti-mouse antibodies can only be excited with blue light. It avoids optical interference between the coded and reporter signals, in stark contrast with microspheres encoded with QDs or organic dyes. This unique advantage allowed for detection of mouse IgG with the detection limit of 0.01 ng/mL. Benefiting from tunable and narrow emission bands of UCNPs, double-antibody sandwich immunoassay was also realized.

Wang et al. [18] developed a sensitive and convenient method for simultaneous isolation and detection of circulating tumor cells (CTCs) using multifunctional magnetic upconversion nanocomposites. Anti-EpCAM antibody-functionalized NaYF₄: Yb, Er@Fe₃O₄@Au nanocomposites were used to specifically recognize the tumor cells in the sample solution flowing through a micro-fluidic device containing silicon nanowire (SiNW) arrays. The cancer cells were then captured by a magnet placed right below the microfluidic chamber. The magnetic field induced capture of CTCs on microfluidic SiNW array not only exhibited high capture efficiency (~90%), but also allowed for the convenient release of the captured CTCs for further analysis and re-culturing. Due to the autofluorescence-free nature of UCL imaging, highly sensitive detection of small numbers of CTCs could be achieved. This detection technique was also used for real clinical samples, and obtained consistent results with clinical outcomes for lung cancer patients.

CONCLUSION

This review has discussed the design principle of magnetic upconversion nanocomposites, and updated their recent advances in the synthesis, surface modification and bioapplications. Despite the great progress over the past decade, some key issues remain to be addressed. For example, the exact effect mechanism of MNPs on UCL should be clarified so as to provide guidance for enhancing the UCL intensity efficiently. It is still challenging to prepare monodisperse magnetic upconversion nanocomposites with efficient UCL, strong magnetism, readily controllable size and excellent aqueous dispersibility. On top of that, the uniformity of relevant properties of every nanocomposite deserves more attention and study.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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