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Luminescent nanocarriers for simultaneous drug or gene delivery and imaging tracking

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ABSTRACT

Drug or gene delivery based on nanostructure is promising for treatments of cancers to solve a variety of issues associated with traditional therapeutic agents from poor bioavailability to systemic toxicity. For real-time monitoring of the delivery process, imaging-guided therapy has attracted growing interest in biomedical applications. Luminescent nanostructures serve as an essential tool for illuminating the pathway of drug or gene delivery in biomedical systems. Considering their crucial role in medical applications, we summarize recent progress of luminescent nanostructures as drug- or gene-delivery nanocarriers with simultaneous imaging tracking. We also discuss the design principles and the critical issues faced by multifunctional nanostructure engineering, which might provide guidance for further development in this field.

Contents

Abbreviations: AAm, Acrylamide; AMIN, 1-allyl-3-methylimidazolium chloride; CPT, Camptothecine; CT, Computed tomography; DCL, Down-conversion luminescence; DOX, Doxorubicin; Ex, Excitation wavelength; GFP, Green fluorescence protein; LSPR, Localized surface plasma resonance; MAA, Methacrylic acid; miRNA, MicroRNA; MRI, Magnetic resonance imaging; MSNP, Mesoporous silica nanoparticles; NC, Nanocomposite; NGO, Nano-graphene oxide; NIPAM, *N*-isopropylacrylamide; NIR, Near infrared; OAm, Oleylamine; PAA, Poly-allyl alcohol; PAH, Poly-allylamine hydrochloride; PCL, Poly-ε-caprolactone; pDNA, Plasmid DNA; PEG, Polyethylene glycol; PEI, Polyethyleneimine; PET, Positron emission computed tomography; PLGA, Polylactic-co-glycolic acid; PSI, Polysuccinimide; PSI_{OAm}, PSI functionalized with oleylamine; PTI, Photothermal imaging; PTX, paclitaxel; QD, Quantum dot; siRNA, Short interfering RNA; SNT, Silicon nanotube; St, Styrene; UCL, Upconversion luminescence; UCNP, Upconversion nanoparticle.

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1. Introduction

As devastating malignant diseases, cancers, such as breast cancer, lung cancer, colon and rectal cancer, are the leading cause of death and account for large economic costs in the world. However, there are many problems in conventional chemotherapy, such as drugs being rapidly metabolized or excreted from the body, non-specific distributions and poor water solubility of small molecular drugs [1,2]. Inspired by the impressive development of nanotechnology, nanoscale systems for drug or gene delivery recently attracted much attention [3]. The nanostructures offer suitable platforms with appropriate sites or cavities for drug loading and installing stimuli-responsive moieties, affording safe and efficient drug or gene delivery in a controlled fashion – so-called "smart" delivery vehicles. Intensive study in this field has promoted biomedical applications, such as monitoring the targeted delivery process, tracking *in vivo* distribution of drugs or genes, and understanding the mechanism of how drugs or vectors enter a cell. Nevertheless, most of the drugs are non-fluorescent, except for doxorubicin (DOX), and functional genes are non-fluorescent or cannot express any fluorescent proteins. It is therefore appealing to develop nanocarriers with multiple functions by incorporating external signal reporters. To date, signal reporters based on luminescence, magnetic resonance imaging (MRI), ultrasound, positron-emission tomography (PET) and computed tomography (CT) have been reported [4]; luminescence imaging was shown to be a promising tool for imaging-guided drug or gene delivery in terms of the broad choices of luminescent nanomaterials, good sensitivity and high spatial resolution.

Luminescent nanomaterials, including quantum dots (QDs) [5,6], lanthanide-doped nanocrystals [7–11], carbon nanomaterials [12] and noble-metal nanoclusters [13–18] have been widely utilized for sensing, imaging and drug or gene delivery [19–21]. QDs, with unique tunable optical properties, have frequently been utilized for designing multifunctional drug- or gene-delivery nanovectors [22–24]. Lanthanide-doped nanocrystals, due to their upconversion luminescence (UCL) properties [16,20,25–27], have become popular candidates especially in *in vivo* tracking studies. Carbon nanomaterials have extra benefits when employed as imaging agents, such as being cost effective and of low cytotoxicity. Furthermore, QDs with near-infrared (NIR) emission [28,29] and UC nanoparticles (UCNPs) are two extensively explored inorganic luminescent nanomaterials with high chemical stability, excellent tissue-penetration depth and optical features (low autofluorescence) [20]. Based on such excellent properties, luminescence imaging allows real-time monitoring of the delivery process, the fate of drugs or genes and the location of their action sites, and quantifying the process of drug or gene release (i.e., drug concentrations during the journey of delivery).

It is therefore highly desirable to develop a novel, versatile strategy for the fabrication of nanocarriers with good water-stability, appropriate size, good biocompatibility and wide applicability for different kinds of drugs, especially for providing real-time tracking of drug or gene delivery. Herein, we first briefly discuss the general prerequisites for fabricating smart nanovectors for simultaneous drug or gene delivery and real-time luminescence tracking. Then, based on the types of the luminescent nanostructure, we summarize different drug- or gene-delivery nanocarriers (Table 1). Finally, we discuss current challenges in this field.

2. Design principles for luminescent nanocarrier-based drug or gene delivery

2.1. Typical properties of nanocarriers

To construct an effective, successful controlled drug- or gene-delivery system (smart nanocarriers) with novel luminescence tracking, there are five basic requirements:

1 luminescent nanomaterials for biomedical imaging tracking should be biocompatible and have no or negligible toxicity;
2 high photostability;
3 modest size, surface chemistry (charge, density and distribution of surface ligands), hydrophilicity and hydrophobicity are important factors for delivering drugs or genes (Fig. 1);
4 controllable drug or gene release;
5 high drug- or gene-loading capacity.

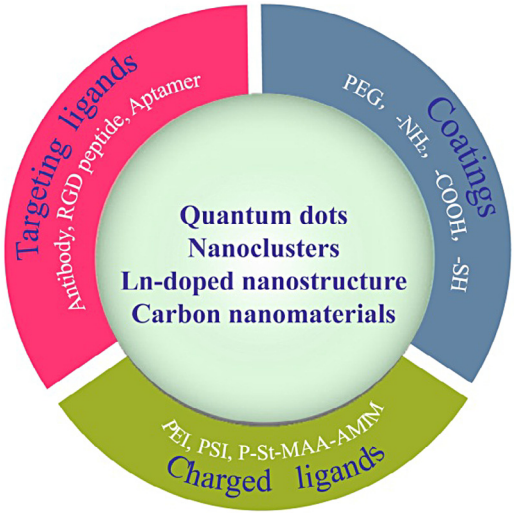

Fig. 1. Summary of different types of luminescent nanostructures and different surface ligands.

Table 1
Representative drug- or gene-tracking systems by luminescent nanostructures

Types of nanocarriers	Parameters (Size, cytotoxicity, Ex/Em)	Released drug / targeting locations	Ref.
CdSe QDs	~13 nm, high/medium, Ex/Em = 400–500/ 545 and 620 nm	siRNA; MDA-MB-231 cells	[23]
ZnS:Mn^{2+} QD NCs	~100 nm, medium, Ex/Em = 342/580 nm	pDNA; HepG2 cells	[22]
AS1411-MSQDs (CdSeTe@ZnS-SiO_2)	~136 nm, Ex/Em = 300–500/580 nm	DOX; HeLa cells	[30]
$Ag_2S@PSI_{OAm}$	<100 nm, low, Ex/Em=808/1000–1400 nm	PTX/CPT; HeLa cells and nude mice	[31]
Silicon QDs	2~3 nm, low, Ex/Em = 488/510–530 nm	*ABCB1* siRNA,Caco-2 cells	[32]
Gold nanoclusters	~ 1 nm, low, Ex/Em = 400/ ~ 680 nm	Insulin, C57BL/6J mice	[33]
$NaYF_4:Yb^{3+}/Tm^{3+}@NaYF_4:Yb^{3+}@mSiO_2$	54 nm, low, Ex/Em = 980/350, 450, 800 nm	DOX; L929 fibroblast, 293T, U87 MG, and murine 4T1 cells	[34]
$NaYF_4:Yb^{3+}/Er^{3+}@SiO_2@P$(NIPAM-*co* -MAA)	150 nm, low, Ex/Em = 980/523, 541, 653 nm	DOX; SKOV3 ovarian cancer cells	[35]
carbon dots	<10 nm, NG, ex from 340 nm to 500 nm	pDNA; COS-7 cells and HepG2 cells	[36]