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Historical perspective

Near-infrared light activated delivery platform for cancer therapy

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ABSTRACT

Cancer treatment using conventional drug delivery platforms may lead to fatal damage to normal cells. Among various intelligent delivery platforms, photoresponsive delivery platforms are becoming popular, as light can be easily focused and tuned in terms of power intensity, wavelength, and irradiation time, allowing remote and precise control over therapeutic payload release both spatially and temporally. This unprecedented controlled delivery manner is important to improve therapeutic efficacy while minimizing side effects. However, most of the existing photoactive delivery platforms require UV/visible excitation to initiate their function, which suffers from phototoxicity and low level of tissue penetration limiting their practical applications in biomedicine. With the advanced optical property of converting near infrared (NIR) excitation to localized UV/visible emission, upconversion nanoparticles (UCNPs) have emerged as a promising photoactive delivery platform that provides practical applications for remote spatially and temporally controlled release of therapeutic payload molecules using low phototoxic and high tissue penetration NIR light as the excitation source. This article reviews the state-of-the-art design, synthesis and therapeutic molecular payload encapsulation strategies of UCNP-based photoactive delivery platforms for cancer therapy. Challenges and promises for engineering of advanced delivery platforms are also highlighted.

Contents

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1. Introduction

Cancer is a major public health issue with over 1.6 million new cases and almost 600,000 deaths occurring in the United States in 2014 [1]. Significant toxicity to normal tissues and development of drug resistance in tumor cells are two major obstacles for current cancer chemotherapy. Short circulation times of most chemotherapy drugs and difficulty of localization to tumor sites further challenge current cancer therapies. Normal cell damage induced by chemotherapy can, in some cases, even be fatal. The almost universal development of multidrug resistance (MDR) by tumor cells is responsible for the majority of treatment failures in clinic. Overcoming these challenges associated with current cancer treatments has been a high priority goal of clinical and basic scientists, but remains an elusive outcome.

In recent years, nanotechnology has been successfully applied in vitro and in animal models in vivo to overcome these hurdles in cancer therapy. Nanotechnology is quickly becoming a promising innovation in cancer treatment for the future. With new advances in nanotechnology, nanoparticle based controlled drug delivery systems may find wide applications in various cancer therapies. The delivery of therapeutic payload using engineered micro/nanomaterial-based delivery systems, such as polymeric micelles [2,3], dendrimers [4,5], meso-porous silica [6,7], gold nanoparticles [8], and ion oxide nanoparticles [9,10], has attracted increasing attention. While these delivery systems are extremely valuable, they suffer from irregular release and notched distribution of payloads in physiological conditions leading to adverse reactions. Ideal delivery systems entail "zero-release" before reaching the targeted biosites and controlled release of the therapeutic payloads. With the development of various stimuli-responsive delivery platforms, greater control over the delivery and release processes in either temporal or spatial manners have been made possible. Several release strategies have been developed, including low pH [11,12], high enzyme concentration [13], redox materials within the cells [14], and the use of light as external stimulus [15]. Among these strategies, light activation offers unprecedented control over others. Light of specific wavelength allows remote, noninvasive, spatial, and temporal control over photoactive delivery platforms, enabling greater safety, specificity, and therapeutic efficacy. Despite numerous benefits, the majority of the existing photoactive delivery platforms require ultraviolet (UV) or short visible light as external excitation sources, which inevitably involve cellular phototoxicity and poor tissue penetration depth resulting in limited clinical potential.

Alternatively, upconversion nanoparticles (UCNPs) feature advanced optical properties enabling conversion of near infrared (NIR) excitation to localized UV/visible emission. High tissue penetration and low photo energy of NIR endow UCNPs with many advantages over quantum dots and organic fluorescent materials in biological applications, such as low photodamage and enhanced tissue penetration [16,17], minimal autofluorescence background [18], and improved resistance to photobleaching and blinking [19]. These intrinsic upconversion luminescence properties provide many unprecedented opportunities for UCNPs to serve as nanotransducers to substitute the undesired direct UV/visible excitation with NIR excitation. This potentiates remote, "on demand" NIR photoactivated therapeutic payload release with high spatial and temporal resolution, allowing for the design and optimization of photoactivated delivery at a desired location and specific time. Accumulating evidences show that UCNP-based photoactive delivery platforms have been engineered for NIR activated therapeutic applications, including chemotherapeutic drugs [20–22], gene therapy [23–25], photodynamic therapy [20,26,27], and photothermal therapy [20,28,29].

In the past few years, investigations on design and synthesis of UCNPs and their bioapplications, including drug delivery, theranostics, biodetection, and bioimaging, have been of increasing interest [30–43]. This rapid development of UCNPs in biological applications necessitates a thorough state-of-the-art review focusing on the most recent advances in UCNP-based NIR activated delivery platform for cancer therapy. Our review article elaborates on the following topics: In Section 2, engineering of upconversion based photoactivative delivery system is presented, with emphasis on recent advances in therapeutic molecules encapsulation strategies. For this, we first illustrate the mechanism of upconversion luminescence and the principle of dopant/host selection criteria for design of UCNPs. Two representative synthesis routes are discussed with advantages and disadvantages. Surface chemistry for aqueous solubility, bioconjugation, and targeting capabilities are then summarized. Various strategies for therapeutic molecule encapsulation are highlighted. Section 3 focuses on the application of UCNP-based NIR activated delivery platforms for cancer therapies, including chemotherapy, gene therapy, photodynamic therapy, and photothermal therapy. Section 4 summarizes limitations associated with current progress and envisions the prospective bioapplications of UCNPs by highlighting areas with exceptional promise and challenges.

2. Engineering of upconversion nanoparticle based photoactive delivery system

Applications of UCNPs as a photoactive delivery system demand precise control over synthetic strategies, including high crystallinity, monodispersed size and morphology, good solubility in aqueous solution, and suitable functional groups on the surface that allow further conjugation or targeting capabilities. The following sections will review the design principles of UCNPs, surface chemistry for aqueous solubility, and bioconjugation. Emphasis will be placed on payload encapsulation strategies.

2.1. Design of UCNPs with superior optical properties

Upconversion luminescence refers to a unique process defined by sequential absorption of two or more photons with low-energy at a long wavelength, followed by the emission of photons with higher energy at a shorter wavelength [44]. The mechanism of upconversion luminescence can be classified into three groups: excited state absorption (ESA), energy transfer upconversion (ETU), and photon avalanche (PA) [45]. Among these three processes, ETU is instantaneous and pump power independent (Fig. 1 A), and is widely used to offer efficient upconversion luminescence (~ two orders of magnitude higher than ESA) [45].

To achieve upconversion luminescence, lanthanide-doped UCNPs are mainly composed of crystalline hosts and lanthanide dopants, which incorporate into to the host lattice at low concentrations [45]. The ion that emits fluorescence is the activator, while the donator of the energy is the sensitizer. In the case of sensitized luminescence, the activator radiates upon its excitation to a higher energetic state obtained from the non-radiative transfer of the energy from sensitizer. In principle, efficient upconversion luminescence only occurs by well selected dopant-host combinations. The dopant selection criteria is based on the characteristic spaced energy levels that render photon absorption by sensitizer and subsequent energy transfer between the sensitizer and activator in the upconversion process [46]. Due to its high absorption coefficient and upconversion efficiency, Yb^{3+} is usually selected as the sensitizer [47]. Er^{3+} and Tm^{3+} are most frequently used as activators, which possess ladder-like energy levels and are well resonant with non-radiative multiphonon relaxation from Yb^{3+}, enabling efficient energy transfer from Yb^{3+} to these ions (Fig. 1 B) [45]. Fluorides usually exhibit low phonon energies (~350 cm^{-1}) and high chemical stability, and thus are widely used as host materials [48–50].

2.2. Synthesis strategies

A variety of methods, including thermal decomposition [49,51–57], hydro(solvo)thermal synthesis [58–65], co-precipitation [50,62,66–68], sol–gel process [69–73], and combustion synthesis [74–76],