Journal of Luminescence ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Journal of Luminescence

journal homepage: www.elsevier.com/locate/jlumin

Luminescent nanoprobes for thermal bio-sensing: Towards controlled photo-thermal therapies

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ARTICLE INFO

Article history:
Received 13 October 2014
Received in revised form
15 March 2015
Accepted 31 March 2015

Keywords:
Photo-thermal therapies
Neodymium
Nanoparticle

ABSTRACT

Photo-thermal therapies, based on the light-induced local heating of cancer tumors and tissues, are nowadays attracting an increasing attention due to their effectiveness, universality, and low cost. In order to avoid undesirable collateral damage in the healthy tissues surrounding the tumors, photo-thermal therapies should be achieved while monitoring tumor's temperature in such a way that thermal therapy could be stopped before reaching the damage limit. Measuring tumor temperature is not an easy task at all and novel strategies should be adopted. In this work it is demonstrated how luminescent nanoparticles, in particular Neodymium doped LaF_3 nanoparticles, could be used as multi-functional agents capable of simultaneous heating and thermal sensing. Advantages and disadvantages of such nanoparticles are discussed and the future perspectives are briefly raised.

1. Introduction

1.1. Nanoparticles and nanomedicine

"The battle against cancer is fought on many fronts" [1]. This is the basic premise on which many interdisciplinary research groups are nowadays working, i.e., on the research and development of new nanomaterials that, in a near future, would be used to achieve effective and minimally invasive therapies for a disease whose social effect is indisputable. For instance, it is estimated that in 2030 a total of 2.2 million cases of colorectal cancer will be diagnosed. However, the most recent technological advances have improved the diagnosis and therapy of cancer, the society and health systems continuously require innovative tools that would contribute to the improvement of the quality of life of patients as well as of the treatment success. Successful cancer cure lies in achieving early detection and implementation of an effective and selective treatment. The methods of diagnosis and treatment of existing cancer are, in some cases, highly invasive (if biopsy and surgery) and, in other cases, cause serious side effects due to their low selectivity (case of chemotherapy and radiotherapy). It is necessary to find new techniques that allow detection and therapy advance and enhance detection of incipient tumors as this would unequivocally lead to an increment of the treatment success rate in certain tumors for which conventional therapies are not effective. Nanotechnology offers new and interesting alternatives in biomedical applications opening a new discipline that is popularly known as "Nanomedicine" [2]. Within this, the development of nano-tools against cancer is to selectively target nanostructured detection and removal of cancerous tissue systems. This represents a novel approach in the fight against cancer therapeutic action leading to the origin of the disease: the cell.

Nanomedicine proposed for the detection and treatment of cancer, the use of nanoparticles (NPs) biocompatible smaller than 100 nm, with different physical, chemical and biological features. These NPs have attracted great interest due to the wide variety of its applications [3]. Its small size allows them to cross biological barriers, join or internalize into cells and distribute throughout the body through the blood stream [4]. Progress of inorganic chemistry has allowed the synthesis of biocompatible NPs with pre-tailored physical and chemical properties during synthesis procedure. In addition, the incredible advance of surface chemistry has also lead to an almost full control over the surface properties of NPs so that it is nowadays possible to decorate their surface with antibodies that interact with membrane receptors leading to a highly selective targeting of specific cancer cells [5]. Nowadays NPs are being used as both diagnosis and treatment agents.

1.2. Nanoparticles for diagnosis

In general, the NPs applicable to the cancer diagnosis can be classified into two groups: Luminescent NPs (LNPs) and magnetic NPs (MNPs). Their working principles, advantages, and disadvantages are explained below.

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http://dx.doi.org/10.1016/j.jlumin.2015.03.037
0022-2313/© 2015 Published by Elsevier B.V.

The LNPs are NPs presenting luminescence after being optically excited (by lamps or lasers) and generally have high fluorescence efficiency. When they are functionalized may accumulate in tumors such that its luminescence allows their optical/fluorescence location [6]. Today, there is a tremendous numerous number of research groups working on the design and synthesis of LNPs for cancer diagnosis. These can be classified in different groups: (i) rare earth ion doped dielectric nanocrystals (RENPs) [7], (ii) semiconductor nanocrystals (quantum dots, QDs) [8], (iii) carbon nanotubes (CNTs) [9], (iv) gold nanoparticles (GNPs) [10], and (v) luminescent organic nanoparticles (LONPs) [11]. Each group has their own advantages and disadvantages although RENPs are attracting much attention because of their unique combination of outstanding properties such as low toxicity, high spectral stability, narrow luminescence lines, high photo-stability and so on. Despite the good results obtained by using LNPs, the development of LNPs for diagnosis trials is currently limited by the low penetration length of optical radiation into tissues, preventing the detection of non-superficial tumors. Most LNPs present their emissions in the visible range, where human tissues are highly opaque. Achieve high penetration lengths requires the use of LNPs whose emission occurs in the so-called biological windows that are spectral ranges in which optical radiation is weakly attenuated (700–950, 1000–1400 and 1570–1750 nm, for the first, second, and third biological windows, respectively) [12,13]. Many different LNPs working in these spectral ranges have been already successfully used for deep tissue in vivo imaging. Among them, Neodymium doped nanocrystals result of special interest as they show different fluorescence bands in the 800–1500 nm range that can be used for high contrast, autofluorescence free in vivo imaging [14,15]. Infrared emitting LNPs, therefore, emerge as highly interesting systems but, before clinical application, a critical study on the possible adverse effects that infrared radiation can have on healthy tumors and tissues needs to be performed.

In the case of MNPs, their potential use for cancer detection and diagnosis is based on their magnetic properties and how they induce magnetic resonance contrast [16]. There are many successful examples on the use of MNPs for the detection of cancerous tissues in vivo studies that have led to its commercial use as contrast agents. When comparing to LNPs, MNPs have a clear and outstanding advantage that is the much superior penetration depth into tissues. Based on this “unlimited” penetration depth, it is indeed possible the generation of real three dimensional magnetic images that would allow for accurate tumor location and study. However, there are still a number of constraints to be solved, such as altering the magnetic properties of MNPs due to aggregation that occurs upon internalization into cells and tissues.

Cancer diagnosis (tumor detection) is not only possible based on particle targeting and induced accumulation at cancerous tissues and cells by surface design. Recent works have demonstrated that NPs can be also used as luminescent nano-thermometers (LNTs) for early tumor detection based on the discovery of thermal singularities inside tissues [17,18]. LNPs are NPs whose luminescent properties are strongly temperature dependent in the biophysical range (30–60 °C). They allow for non-contact remote local temperature sensing from simple analysis of their luminescent properties. Since the tumors have a temperature different from that of healthy tissue, the ability to measure small changes in temperature with high resolution constitutes a novel method of detection and, therefore, a diagnosis alternative. LNTs have been successfully demonstrated at the cellular level (in vitro) as well as in small organism (such as C-elegants) [19,20]. Despite the good results obtained so far, LNTs have not been yet used for in vivo (small animal) thermal sensing. This is an exciting challenge that still needs to be faced. Obviously, if a LNT is to be used for in vivo application, it should operate in any of the above mentioned biological windows such that it could provide sub-tissue thermal information.

1.3. Nanoparticles for thermal treatments

In 540 B.C., Parmenides stated “give me the power to produce fever and I will cure all diseases”. Today, this statement still serves as a guide for treatment of numerous diseases by the application of heat (thermotherapy). In the nineteenth century, a higher cure rate was demonstrated in patients with cancer who had experienced febrile. Recently, animal studies have shown the complete elimination of tumors under moderate heating and increasing efficiency of the traditional treatments (chemotherapy and radiation) when they were applied after thermotherapy cycle [21]. These achieving are based on the processes at the cellular level that are activated when the temperature rises above 40 °C (hyperthermia). Such processes may induce cell damage from transient to onset of irreversible cell damage that can lead to cellular death [22].

Conventional thermotherapy techniques (such as microwave, infrared, and ultrasound) are not selective, since they produce temperature increments in both healthy and unhealthy tissues. Increasing the efficiency and selectivity of hyperthermic treatments require the use of Heating NPs (HNPs capable of generating heat in the presence of external stimuli). The surface bio-functionalization of HNPs would allow preferential accumulation at tumors, so that the heat exposure would be completely selective. Today there are two types of HNPs: those activated with optical radiation (optical HNPs, hereafter LHNPs) and those activated with alternating magnetic fields (magnetic HNPs, MHNPs) [22]. Their main characteristics are explained next.

The LHNPs are LNPs that show large light-to-heat conversion efficiencies, i.e., they produce a relevant increment in the local temperature when are excited by optical radiation. Among the different LHNPs, GNPs, QDs, CNTs, and graphene based NPs have been demonstrated to be specially efficient. Additionally, it has been demonstrated recently that certain RENPs could also present large light-to-heat conversion efficiencies [23,24]. Both RENPs and QDs are of special interest since, due to their intense fluorescence, they would allow for simultaneous imaging and photo-thermal therapy. This is of crucial importance as this dual functional character enables simultaneous location, study, and treatment of the tumor. The design and synthesis of new QDs, RENPs or composite materials that show simultaneously high efficiency light-heat conversion and fluorescence bands in biological windows, is a challenging area receiving much attention nowadays.

The MHNPs are magnetic NPs that in the presence of a high frequency (~kHz) alternating magnetic field dissipate heat in their environment [16,25–27]. This occurs because the magnetic susceptibility of MNPs under high frequencies becomes complex and a delay between the external magnetic field and the magnetic moment of the MNPs appears. This process leads to heat losses associated with different relaxation mechanisms that depend on the size, crystallinity, concentration, and field conditions. As main drawback, it should be noted in recent works that the MHNPs thermal efficiency could suffer a strong reduction when incorporated into cells due to agglomeration of MHNPs that occurs because the reduced size of the vesicles in which they are allocated when trespassing the cell membrane [28]. The agglomeration problem seems to minimally affect LHNPs and, therefore, they emerge as specially promising for efficient thermotherapies.

1.4. The need for control in thermal therapies

When tumor cells or cancerous tissues undergone a thermal treatment, the bio-modifications appearing on them are strongly

Please cite this article as: D. Jaque, C. Jacinto, J. Lumin. (2015), http://dx.doi.org/10.1016/j.jlumin.2015.03.037