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Nanoparticle-based theragnostics: integrating diagnostic and therapeutic potentials in nanomedicine

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1. Introduction of theragnostics in nanomedicine

Theragnostics is a strategy that integrates therapeutics with diagnostics to develop new personalized treatments with enhanced efficacy and safety. One key component of theragnostics is diagnostic imaging with high sensitivity and molecular specificity. The advent of molecular imaging has brought revolutionary changes to conventional imaging by enabling characterization of biological processes at the cellular and molecular levels spatially and temporally [1]. Depending on the molecular imaging modality and contrast agent used, theragnostics could be achieved by applying imaging throughout treatment planning, drug and dosage selection, and therapeutic response monitoring.

Nanotechnology has led the advances in theragnostics, as a result of the development of a variety of fine particulate materials with size dimensions in the range of 1–200 nm, and the discovery of their unique physicochemical properties that are not found in their bulk counterparts. These properties include quantum confinement in semiconductor nanoparticles (also known as quantum dots), superparamagnetism in certain oxide nanoparticles, and surface-enhanced Raman scattering (SERS) in metallic nanoparticles, among others. These unique physical properties have substantially expanded the potential of molecular imaging, and led to the development of highly sensitive, and cost-effective novel molecular imaging agents. These new imaging agents can be broadly categorized as optical (fluorescent, SERS, photoacoustic, etc.), magnetic, radioactive (positron or γ-ray emitting), X-ray opaque (nanoparticles with high electron density) and ultrasound-sensitive (nanobubbles) agents.

Nanoparticles used in medicine are typically coated with a polymer that bears ample functional groups providing flexibility to integrate multiple functionalities. With this flexibility, nanoparticles can serve as diagnostic tools, or therapeutic carriers, or both. In fact, the rapid emerging of theragnostics in nanomedicine is largely dependent upon this flexibility. Various biomolecules have been conjugated on nanoparticles through surface functional groups for intended function, such as targeting ligand for cell specific binding, drugs for chemotherapy, genes for cell transfection, or combination of them. With size dimensions at the nanoscale, these particles can navigate through microvasculature and across various biological barriers to reach target tissue. The size, surface charge, and hydrophobicity of nanoparticles can be controlled to minimize renal and hepatic clearance [2], and thus extend their blood circulation time and reduce potential immunogenicity. Most of theragnostic nanoparticles, such as liposomes, micelles, and nanocomposites, have

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complex nanostructures that consist of building blocks with diverse chemical compositions [3-6].

2. Theragnostic nanoparticles for imaging and drug delivery

Most of theragnostic nanoparticles are built upon four basic components: signal emitter, therapeutic payload, payload carrier, and targeting ligand. The signal emitter possesses certain unique optical, magnetic, or radioactive property, and can emit physical signals spontaneously or upon excitation by an external source. The signal can be detected by an external receiver and reconstructed to form images. The therapeutic payload can be chemotherapeutic drugs, or nucleic acids, such as DNA and siRNA. The payload carrier is generally a matrix commonly comprised of polymeric materials with multiple functional groups on which signal emitters or therapeutic payloads can be conjugated. The targeting ligand on the nanoparticle is selected to bind to and form a complex with a specific disease marker on the target cell, facilitating transport of theragnostic nanoparticle to the site of interest and enabling specific interactions with the target cell or tissue. The signal emitter and therapeutic payload of theragnostic nanoparticles can be either embedded in the carrier or conjugated on its surface, while the targeting ligand is always covalently attached to the surface of the carrier, which allows the direct interaction with the target cell or tissue.

A diverse set of non-invasive imaging modalities are employed to visualize the distribution of theragnostic nanoparticles in real time. The commonly-used imaging modalities include: magnetic resonance imaging (MRI), X-ray computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), and ultrasound (US). Several new promising imaging modalities, such as fluorescence-mediated tomography (FMT), photoacoustic tomography (PAT), are being developed [1]. Each of these diagnostic modalities has its advantages and disadvantages. For example, MRI and CT have high spatial resolution and are able to provide detailed anatomical information, but they are lack of sensitivity. Alternatively, PET and SPECT are highly sensitive, but they have limited resolutions and could not provide anatomical information. To overcome the limitations of individual imaging modalities, multi-modality imaging techniques have been developed, including PET-CT, MRI-optical, and MRI-PET. Theragnostic nanoparticles can be constructed to serve as a multi-modality contrast agent, making these imaging techniques readily available to clinicians.

For in vivo imaging, high background noise of normal tissue can present a significant challenge for the practical use of nanoparticle theragnostic imaging agents. Therefore, different chemical or biological signal amplification strategies are utilized to circumvent the high background noise. These mainly involve developing agents that can respond to local chemical or biological stimuli at disease sites [1], such as acidic pH, hypoxia, elevated temperature or ligand binding, to trigger a sharp increase or decrease of local signal intensities. These stimuli induce physical or chemical changes of signal emitters, such as surface coordination state, electron density, chemical structure, discrete-aggregate state, and therefore alter the amplitude or composition of the emitted signal. Popular strategies include relaxivity changes (magnetic switch) [7], quenching (pairing-unpairing of deactivator and fluorophores) [8], chemical exchange saturation transfer (CEST) [9], and Förster resonance energy transfer (FRET) [10,11]. Since nanoparticles can be engineered to develop a relatively complex structure, one theragnostic nanoparticle can also contain several signal emitters with different signaling mechanisms, offering multi-modality imaging that synergizes the advantages of individual imaging modalities and expanding applicability of the carrier. Common multi-modality nanoparticle imaging agents include MRI-optical, MRI-PET, and optical-PET agents [5,12-14]. For example, iron oxide superparamagnetic nanoparticles can be conjugated with a fluorophore to enable both MR and biophotonic

imaging [12]. With this dual-imaging capability, MRI scans can be used to identify tumor localization and for post-operation monitoring, while biophotonic imaging, with the resolution at the cellular level, can be used intraoperatively to identify tumor boundaries for precise resection.

The signal emitter, as well as the therapeutic payload of a theragnostic nanoparticle can be either encapsulated by or conjugated onto a payload carrier. A variety of polymers, including both synthetic and natural polymers, have been employed to serve as payload carriers. Polymers can be immobilized on nanoparticles via covalent and non-covalent interactions in situ during synthesis of nanoparticle cores [12] or via surface modification post-synthesis of nanoparticle cores [15]. Covalent bonding is commonly established through silane [16], carboxyl [15], or amine [17] linkages. Non-covalent bonding typically includes electrostatic, hydrophobic, and hydrogen interactions [12,18]. These polymer coatings contain either enormous amount of pedant functional groups, or large blocks of hydrophobic segments, and therapeutic molecules can be readily loaded through either covalent linkages or non-covalent interactions. In case of covalent linkage, activated therapeutic molecules react with pendant functional groups on the carrier polymer, and form linkages such as amide, ester, thioether, disulfide, hydrazone, or enzyme-specific polypeptide spacers [19,20]. Non-covalent interactions include hydrophobic interaction (commonly for loading hydrophobic drugs), and ionic interaction (commonly for loading nucleic acid) [19].

Clinical applications require carrier polymers to be biodegradable and eventually be eliminated from the body. Therefore, polymer backbones often contain multiple amide, ester or glycosidic bonds, and are cleavable hydrolytically or enzymatically once the carrier reaches the intended site. Cleavable linkages and degradable backbones allow therapeutic payload to be released at the target site in a controllable fashion. The payload release can be triggered either by a change in environmental condition, such as pH, ionic strength, temperature, or hydrolytic and enzymatic degradation, or by an external stimulus, such as radiofrequency electromagnetic wave or light excitation. Polymers that have been approved for clinical applications or currently under clinical trials include poly(ethylene glycol) (PEG), dextran, carboxydextran, β-cyclodextrin (βCD), poly (DL-lactide-co-glycolide) (PLGA), and poly(L-lysine) (PLL).

One of the most important applications of theragnostic nanoparticles is targeted imaging and therapeutic delivery, which includes passive and active targeting. The passive targeting has been demonstrated with nanoparticles with a size range of 10–500 nm via a mechanism known as the enhance permeability and retention (EPR), in which the nanoparticles extravasate out of leaky vasculatures and accumulate in tumors [21,22]. In active targeting, nanoparticles are conjugated with ligands with high affinity to tumor cells. These target-specific nanoparticles could increase their accumulation in disease tissue while reducing unwanted uptake by healthy tissue, thus minimizing side effects. Targeting can also help achieving higher efficiency and reduce the overall dosage and administration frequency. Some targeting ligands can also facilitate ligand-mediated endocytosis, and thus greatly improve the cellular uptake of therapeutic payloads. A wide variety of targeting ligands have been used to guide nanoparticles toward the site of interest, including small organic molecules, oligosaccharides, aptamers, peptides, antibodies and other proteins, with molecular weights ranging from a few hundred to tens of thousands of Daltons. Targeting ligands are covalently assembled on the surface of nanoparticles. The binding sites of targeting ligands need to be readily accessible for ligand-receptor interaction. Therefore, it is quite difficult to assemble antibodies or other large-molecule ligands on nanoparticle surface in correct orientation, while small-molecule ligands often require long linker molecules to avoid steric hindrance by nanoparticle coating. On the contrary, short peptides or aptamers

can be engineered to allow precise modification and assembly on the nanoparticle surface to achieve maximum preservation of ligand activity. Iron oxide nanoparticles conjugated with chlorotoxin, a peptide that has strong affinity to the vast majority of brain tumors, demonstrated accumulation in tumors more than 6 times higher than non-targeted control nanoparticles 48 hours after systemic injection in genetically engineered mice with brain tumors and prolonged retention in tumors for up to 5 days post-injection [12]. Magnetopolymeric nanohybrids conjugated with an antibody specific to human epidermal growth factor receptor (HER 2) demonstrated specific tumor targeting (>3 times in R2 change) and effective tumor growth inhibition (~3 times in reduction of tumor growth rate) as compared with the control nanoparticle conjugated with an irrelevant antibody [23]. Multiple targeting ligands can be linked to a single nanoparticle to achieve multivalency effect, resulting in higher affinity to the target than the monomeric targeting ligand itself. This has been recently demonstrated *in vitro* [24]. However, since surface-immobilized targeting ligand could change the physicochemical properties of nanoparticles, a higher ligand density would not always translate to a higher accumulation in target tissue [25]. Therefore, the ligand density of each nanoparticle system for each intended application has to be optimized on a case-by-case basis.

3. Theragnostic nanoparticles for monitoring treatment efficacy

Currently it requires weeks to months for clinicians to evaluate treatment efficacy and then adjust treatment plan accordingly. This lag causes loss of opportunities of treating diseases effectively, especially for rapid progressing diseases like cancer. Nanotheragnostic approach to monitor treatment efficacy is to track therapeutic response in a precise, non-invasive, and timely manner, therefore expedite therapeutic decisions while improve patients' quality-of-life. Theragnostic nanoparticles could be employed to characterize the event of therapeutic payload release and treatment response in both qualitative and quantitative ways in a matter of days after treatment.

The ability to obtain the accurate dosage and distribution information of the administrated therapeutics is essential for projecting expected response of the treatment. The payload release is often accompanied with the dissociation of carrier nanoparticles, resulting in rapid diffusion of therapeutic molecules and changes in physicochemical properties of the surrounding microenvironment such as pH, solute concentration, redox-potential, or magnetic relaxivity. In order to capture and quantify these changes, the imaging components of theragnostic nanoparticles should be designed to respond to those changes with a readily detectable manner in either property or intensity of emitted signal. Therefore, by combining above-mentioned amplification techniques with a nanoparticle-based imaging contrast agent (e.g., MRI or CT), one could create theragnostic nanoparticles that are capable of monitoring and quantifying payload release. For established modalities, such as MRI, CT and ultrasound, the changes in physical properties of contrast agents due to payload release are shown as the change of signal intensity and image contrast. Researchers have been using MRI technique to track payload release by measuring the change of longitudinal (T_1), transverse (T_2) relaxivity and CEST chemical shift at the region of interest [26-28]. A straightforward approach is to track the released of T_1 contrast agent from the nanoparticle carrier, as the increase of T_1 contrast indicates the dissolution of carrier [27]. Another approach is to use CEST technique to amplify MRI signal and track drug release due to the dissolution of temperature-sensitive drug-carrying liposomes [26]. This is achieved by measuring the proton-exchange rate of water molecules around CEST agents before and after the release of CEST agents entrapped in a liposomal carrier. The rapid exchange of water molecules across the phospholipid membranes can be utilized to achieve chemical exchange of magnetically labeled water molecules by entrapped CEST agents. After the dissolution of the liposomal carrier, the entrapped water mixes with bulk water, and the

exchange of water no longer exists, causing the loss of CEST signal. By measuring the change of the CEST chemical shift, the dissolution of the liposomal drug carrier and release of drug can be detected and measured [26]. Another important modality for tracking therapeutic release is fluorescent based imaging modality with the aid of FRET or quenching [29]. In the case of using FRET technique to monitor drug release, two types of fluorophores are incorporated into the core of drug-carrying nanoparticles, such as liposome, micelle and polymeric nanoparticles. Those fluorophores served as energy donors and acceptors in FRET interaction. Since FRET interactions are the distance-dependent interactions between the donor-acceptor pair of fluorophores, FRET occurs only in intact nanoparticle carriers with intimate contact of donor-acceptor pairs. Once the nanoparticle carriers become disintegrated, these fluorophores are discharged from the carrier, and diffuse throughout. Since now the distance between donors and acceptors are farther enough, a decrease in FRET signal would be captured by fluorescence imaging, which visualizes the event of drug release. Non-invasive, real-time monitoring of released MR or PET/SPECT contrast agents can be readily applied in clinical practice while the monitoring of the release of optical contrast agents is highly beneficial to basic research because of its high sensitivity, rapid acquisition of *in vivo* optical tomography, and easy use in histological evaluation [30]. The biological response to a treatment is assessed to evaluate the outcome of the treatment and serves as a guide for possible adjustment of the treatment plan. The biological responses can be measured either at the macroscopic level, such as inflammation, angiogenesis, tumor invasion and metathesis, or at the cellular level, such as the degree of hypoxia, the gene expression level, receptor density, apoptosis or cell death. Small molecule PET imaging agents, such as 9-(4-[^{18}F]fluoro-3-hydroxymethylbutyl) guanine (^{18}FHBG) [31], have demonstrated the capability to reveal the molecular event of gene expression. However, the smaller molecular weight of these agents can lead to rapid renal clearance, and the lack of chemical flexibility and limit their potential for therapeutic applications. Since PET nuclides have short half-life, multiple administrations are required for monitoring any treatments that last for a long period of time. Nevertheless, the earlier research on these imaging agents has provided insight into the molecular imaging, and their limitations have encouraged the development of novel multifunctional nanoparticle-based systems that integrate the capabilities of diagnostic imaging, drug delivery, and post-treatment monitoring. In addition, these nanoparticle-based agents can be designed to possess a prolonged blood half-life that would potentially survive the entire therapeutic process. For example, magnetic theragnostics nanoparticles have been used to assess treatment response such as if they can kill malignant cells, or suppress or replace aberrant disease-causing genes by monitoring the changes in the tumor size and boundary of metastatic lesions before and after treatments [6,32,33]. Iron oxide nanoparticles-based dual MR/fluorescent probes have been employed to monitor the level of tumor-specific antigen after chemotherapy of breast cancer-bearing mice [34]. In this design, the nanoparticles are conjugated with glutamic acid-proline-proline-threonine (EPPT) peptide that specifically targets the tumor-specific antigen, and are also labeled with fluorescent dye for biophotonic imaging. After treatment with a chemotherapeutic drug doxorubicin, the change of the tumor size, along with the decreased expression of tumor-specific antigen, can be visualized by MRI and fluorescent imaging.

4. Conclusions and future perspectives

Nanoparticle-based agents have shown tremendous promise in the development of theragnostics. Nanoparticles possess unique physicochemical properties that allow integration of multiple functionalities in a single design, which is the foundation that makes theragnostics possible in nanomedicine. Due to their large surface area to volume ratio, nanoparticles can serve as high-capacity carriers for therapeutic drugs and genes, and offer targeted delivery and controlled release of these therapeutics to diseased sites. These

favorable attributes of nanoparticles allow in situ imaging of therapeutic payload release, and real-time monitoring of treatment response.

Despite the significant progress made in development nanoparticle-based imaging and therapeutic agents and the great promise that has been shown in developing theragnostic nanoparticles, nanoparticles do not come without limitations. Due to their higher molecular weights as compared to small-molecule drugs, nanoparticles have a tissue penetration depth smaller than small-molecule drugs or molecular imaging agents. Importantly, more functionalities present in a single nanoparticle design are achieved at the cost of increased complexity. The complex structure required for multiple functionalities presents great technical challenges on manufacturing these theragnostic nanoparticles, such as colloidal stability, reproducibility and cost control. These challenges increase the difficulty of chemical synthesis and product purification, as well as the monodispersity of end products, and lead to storage and shelf-life issues.

To meet the requirements for nanotheragnostic agents, nanoparticles must be developed with high stability in extreme conditions such as high salt concentrations and wide pH and temperature ranges and retain minimum active interaction with serum proteins, which would allow the nanoparticles to conjugate alternative or additional biomolecules without substantially alternating its colloidal stability. Furthermore, the biocompatibility and toxicity of theragnostic nanoparticles need to be thoroughly evaluated as addition of each component material would potentially alter the pharmacokinetic profiles of the nanoparticle. It also requires to further identify new molecular targets that are fully correlated with diseases and discover new targeting ligands with high specificity, small molecular footprint, and good stability. Future improvement will also need to focus on development of innovative strategies to allow efficient tissue penetration of nanoparticles and offer controlled delivery of therapeutics to a particular type of tissue or subcellular compartments, such to mitochondria, nucleus or cytosol.

Equally important is to develop nanoparticles with higher therapeutic loading capacity and tunable payload releasing profile. This can be achieved, in part, by exploration of novel polymer coatings that can provide abundant functional groups to maximize therapeutic loading, and by development of conjugation methods that are environment-sensitive for payload release. Personalized health care requires the composition of the theragnostic nanoparticle varies for different patients and at different stages of treatments. Therefore, a flexible and adaptive nanoparticle platform is highly desirable that allows interchangeable therapeutics. Future nanoparticle-based theragnostics will offer new hope in a cost-effective way to combat deadly and debilitating diseases, such as cancer, cardiovascular and neurodegenerative diseases.

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