The Development of Contrast Agents for Photoacoustic Molecular Imaging

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ABSTRACT: Au Photoacoustic molecular imaging (PAI) is a novel biomedical imaging technique that utilize ultrasonic signal as an information carrier. PAI provides optical absorption and dielectric properties relevanted physiology and pathology at the cellular and molecular level through the use of exogenous contrast agents. These contrast agents can generate strong photoacoustic (PA) signal and provide contrast enhancement. In addition, they can be conjugated with molecular probes for targeted early detection and treatment of cancers. Here we review the new exogenous contrast agents in recent years from five types, including dyes, plasmonic nanostructure, various new class nanoparticles and multimodality contrast agents. At last we conduct a further outlook of the application prospects in the field of biomedicine.

1 INSTRUCTIONS

In recent years, PAI as a noninvasive imaging mode has been developing rapidly; it utilizes ultrasonic signal as an information carrier. Compared with the traditional medical imaging technology, PAI is more promising. The basic principle of the PAI include the following points: (1) the tissue absorbs light energy after being irradiated by visible light or near-infrared light; (2) the absorber produces adiabatic expansion that induces PA signals; (3) the transducers detect the signals; (4) a data acquisition card stores up information for image reconstruction analysis. PAI has a close relationship with optical properties, thermal properties and acoustic properties of biological tissue. Thus, the imaging mode can obtain high contrast and resolution images to combined excellent selectivity of optical imaging and high penetration of ultrasonic imaging. So far, PAI has developed into a variety of imaging methods. For instance, PAI applied to spectral research has formed the photoacoustic spectroscopy (PAS); PAI combined with CT formed the photoacoustic tomography technology (PAT); Photoacoustic microscopy (PAM) imaging is a new microscopic imaging technology based on PAS and acoustic microscope [1-2].

PAI is usually used hemoglobin, melanin, lipid and water as endogenous contrast agents. When detection depth is limited or an endogenous contrast is not available, an exogenous contrast agent may be added. There are various contrast agents of principles, materials, shapes, and sizes suitable for different imaging modalities. Selection of contrast agents for imaging is particularly important, ideal contrast agents could significantly increase contrasts, effectively improve imaging depth or accuracy, and provide molecular specific information. Based on ligand-receptor mechanism, molecular imaging contrast agent was synthesized by molecular probe (proteins, nucleic acids, peptides, etc.) with biochemical methods. Then combination molecular probe and target molecules make contrast agents gathered at the targeted location after injection it into the organism. Through binding distribution of contrast agent can obtain the target molecules distribution in vivo and achieve the goal of molecular imaging in subsequence [1]. To sum up, the further research of contrast agent is very meaningful to light the development of molecular imaging, also helpful to the diagnosis and treatment of cancer. This article will briefly summarize photoacoustic molecular imaging contrast agents.

2 CONTRAST AGENTS FOR PHOTOACOUSTIC MOLECULAR IMAGING

2.1 Dyes

Dyes and other related materials used for PAI have long-standing history, of which the most common is indocyanine-green (ICG). ICG is an FDA approved fluorescent contrast agent that can be used for
human, its absorption peak at 780 nm, belongs to the near infrared region. At present, one of the key PAI research is near-infrared PAI, which laid foundation to the wide application of ICG. However, single ICG molecule has inevitable drawbacks: poor stability, bad water solubility, short half-life, etc. ICG can be loaded into the nanoparticles systems, so that overcome these shortcomings, and introduction some new functions (such as magnetic targeting, MRI, ultrasonic imaging) for preparing multifunctional nano system, so that it can be better applied to biomedicine.

Wang, et al., designed and developed folate receptor targeted, ICG dye doped poly (D, L-lactide-co-glycolide) lipid nanoparticles (FA-ICG-PLGA-lipid NPs) for molecular photoacoustic imaging of tumor. The fabricated FA-ICG-PLGA-lipid NPs exhibited good aqueous stability, a high folate-receptor targeting efficiency, and remarkable optical absorption in near-infrared wavelengths, providing excellent PA signals in vitro. After intravenous administration of FA-ICG-PLGA-lipid NPs, mice bearing MCF-7 breast carcinomas showed significantly enhanced PA signals in vivo in the tumor regions, compared with those using non-targeted ICG-PLGA-lipid NPs [3].

Kanazaki et al., prepared a human serum albumin (HSA) conjugated with ICG as a PA contrast agent allowing enhanced permeability and retention effect for sensitive tumor imaging. They concluded that HSA-ICG clearly visualized the allografted tumors with high tumor-to-background ratios having high quantitative and spatial resolution for the sensitive PAI of tumors. HSA-ICG could be useful as a favorable contrast agent for PA tumor imaging for the management of cancer [4].

Basic PA characteristics of IC7-1-Bu were compared with ICG in an aqueous solution. Temma et al., evaluated the tumor accumulation profile of IC7-1-Bu and ICG by in vivo fluorescence imaging. Unlike ICG, IC7-1-Bu showed high tumor fluorescence after intravenous injection. In vivo PAI provided a tumor to background PA signal ratio of approximately 2.5 after intravenous injection of IC7-1-Bu. These results indicate that IC7-1-Bu is a promising PAI contrast agent for cancer imaging without conjugation of targeting moieties [5].

2.2 Plasmonic nanostructure

Noble metal nanoparticles have been widely used as PA contrast agents due to their surface plasmon resonance (SPR) effect. A linear optical property (extinction, absorption and scattering) of noble metal nanoparticles was influenced by particle size, shape, material. The light absorption of general noble metal nanoparticles is bigger than traditional dyeing molecular several magnitude orders [6]. Furthermore, noble metal nanoparticles surface can be modified by polyethylene glycol (PEG), which can enhance the circulation time in vivo, reduce the cytotoxicity. Thus nanoparticle can be more stable, reducing its polymerization [7]. There are a lot of noble metal nanoparticles as PA contrast agents; they mainly have two materials, gold and silver. At present the gold nanoparticles basically have the following several shape: Au nanospheres, Au nanoshells, Au nanorods, Au nanoclusters, Au nanostars, Au nanobeacons(see in Figure 1).

Jokerst et al., showed GNRs@SiO2 nanoparticles by a layer of silicon dioxide on the surface of the gold nanorods. The particle size is about 42 nm, its absorption peak at 676 nm. There are some red shift relative to no silica shell GNRs (665 nm), and it has better biocompatibility and PAI effect [8].

Unlike nanosphere clusters, which have been well studied, nanoplate clusters have unique properties due to the different possible orientations of interaction between the individual plates, resulting in a significant broadening of the absorption spectra. The polymer-coated silver nanoplate clusters show a lower toxicity compared to the uncoated nanoparticles. Ray et al., present a new optical contrast agent based on silver nanoplate clusters embedded inside of a polymer nano matrix. They used these nanoparticles as PA contrast agents in vivo to enhance the contrast of the vasculature structures in a rat ear model, and then observed a contrast enhancement of over 90% following the nanoparticle injection [9].

2.3 Various new class nanoparticles

Besides noble metal nanoparticles, there are others based on different principles, most of these material with low toxicity, small size, good PA response characteristic. They are mainly including quantum dot (QD), nanodiamond, semiconductor copper sulfide nanoparticles (CuS NPs) and graphene nanosheets (GO nanosheets). A highly radiation-damaged or irradiated nanodiamond (INDs) is a new type of nanomaterial developed recently as a potential PA contrast agent for deep-tissue imaging.
Fang, et al., found that compared with gold nanorods of similar dimensions (10 nm × 67 nm), the INDs have a substantially smaller (by > 4 or-ders of magnitude) molar extinction coefficient per particle. However, the deficit is readily compensated by the much higher thermal stability, stronger hydrophilic interaction with water. Cell viability assays at the IND concentration of up to 100 μm/mL showed that the nanomaterial is non-cytotoxic and potentially useful for long-term PA bioimaging applications [10].

Ramirez-Perez et al., studied the cellular health of two different nanoparticle-labeled (AuNPs and R6G-NPOs) cell lines one hour after being subjected to a single laser pulse in vitro. A significant finding is the R6G-NPOs proved capable of non-destructive PA signal generation in both cell types [11].

Zha et al., showed a polypyrrole nanoparticles (PPy NPs) with low toxicity. Monodisperse PPy NPs are 46 nm in di-ameter with strong absorption in the near-infrared (NIR) range, which allowed visualization of PPy NP-containing agar gel embedded in chicken breast muscle at a depth of 4.3 cm. Their results indicated that PPy NPs are promising contrast agents for PAT with good biocompatibility, high spatial resolution and enhanced sensitivity [12].

2.4 Multimodality contrast agents

At present, molecular imaging technology has developed a variety of modalities, including ultrasound imaging (UI), MRI, PAI, fluorescence imaging (FI), etc. However, mono-modality imaging cannot obtain all the information needed in biomedical imaging technologies. The preponderance complementarity of various imaging modes, multimodal imaging, will greatly improve medical high-tech. Each imaging mode need to respective contrast agents, multimodal imaging requires modal contrast agents to assist imaging. Here are several multimodal contrast agents. Kothapalli, et al., showed that combinations of microbubbles (MBs) and superparamagnetic iron oxide nanoparticles (SPIIONS) are used to fabricate dual contrast agents for ultrasound and MRI, and then they can observed the significant change before and after injection contrast agents [13].

Besides, Molecular imaging technology has enabled the development of a new generation of imaging probes. These sophisticated probes can visualize biological processes or enable early diagnosis of diseases in vivo. Feng et al., designed PEG-Glu-GNPs for used as an imaging nanoprobe to act an effective contrast agent for both CT and PET scans. Compared to conventional CT images and PET scans, PEG-Glu-GNPs significantly improve image quality at the cellular and molecular level, which can significantly aid the early detection of cancer or cancer metastases [14]. At last, Inorganic nanoparticles have been introduced into biological systems as useful probes for in vitro diagnosis and in vivo imaging, due to their relatively small size, exceptional physical and chemical properties. Guo et al., demonstrated that a new kind of colorantable Gd-Zn-Cu-In-S/ZnS (GZCIS/ZnS) quantum dots (QDs) with stable crystal structure could be a dual-modal contrast agent to simultaneously produce strong MR contrast enhancement as well as fluorescence emission for in vivo imaging [15].

3 CONCLUSION

Along with the development of the biomedical and interventional therapy deepening, the application of contrast agents may be more and more extensive. PAI is a set of optical imaging and acoustic imaging for the integrated imaging mode, its good application and development prospects will greatly promote the rapid development of PA contrast agents. At present, studies about contrast agents mainly in two aspects: (1).improving the existing PAI materials, such as chemical modification on the material and combined to other functional materials form new multi-functional system, etc. (2).constantly developing new effective PA contrast agents in overcoming the conventional contrast agents drawback, at the same time which can achieve higher efficiency of PAI. For this reason, the current study of PAI contrast agents is moving toward no poison, low cost, functionalization and new direction, and this type of contrast agents will be the future research hot spot.

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REFERENCES


