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Review

Nanoparticles in Nuclear Imaging

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ABSTRACT: The present review article summarizes the current state radiolabeled nanoparticles for molecular imaging applications mainly targeting cancer. Due to their enormous flexibility, and versatility the radiolabeled nanoparticles have shown their potential in the diagnosis and therapy. As the matter of fact, these radiolabeled imaging agents enable the visualization of the cellular function and the follow-up of the molecular process in living organisms. Moreover, the rapidly advancing field of nanotechnology has provided various innovative radionuclides and delivery systems, such as liposomes, magnetic agents, polymers, dendrimers, quantum dots, and carbon nanotubes to cope up with the hurdles which have been posed by various disease states.

KEY WORDS: ***Nuclear Imaging; Nanoparticles; Diagnostic imaging; Medical imaging***

INTRODUCTION

Nuclear imaging is a branch of medical imaging that uses radioisotopes for the study of the physiology and the metabolism of the body.[1] This is achieved by administrating radiopharmaceuticals to the patients and imaging the emitted radiation. The acquired information is useful not only for diagnostic purposes, such as detection of functional abnormalities or early identification of tumors, but also can be very helpful in therapy planning and follow-up. The two most common types of nuclear medicine studies are Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT).

Positron Emission Tomography (PET) is an imaging technique which detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide introduced into the body.[1] Hence, a radioisotope which undergoes positron emission decay (PET) emits a positron that encounters with an electron, producing a pair of gamma photons moving in opposite directions. These gamma photons are detected by the photomultiplier tubes or silicon avalanche photodiodes place in the opposite direction at 180°. Basically, PET imaging depends on simultaneous detection of the pair of photons and those photons which do not arrive in pairs are ignored. These photons are then detected by the scanner which can estimate the density of positron annihilations in a specific area. When enough interactions and annihilations have occurred, the density of the original molecule may be measured in that area. Typically ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{64}Cu, ^{62}Cu, ^{124}I, ^{76}Br, ^{82}Rb, ^{68}Ga, and ^{18}F can be used with ^{11}C, ^{13}N, ^{15}O, ^{18}F being the first choice. **Table 1** and **2** show various radionuclides commonly used for tumor imaging along with their production techniques, emission types and respective half life. Of the various radionuclides listed in table 1 and 2 ^{18}F nuclide is more preferred radionuclide due to the lowest energy. On the other hand, SPECT is similar to PET which utilizes radiotracers that emit a single or multiple photons which are not simultaneously detected. The photons emitted by the nucleus, after traversing the human body, are detected and registered as a projection (2D distribution) by the scintillation camera. The projections are re-arranged as sinograms for tomographic reconstructions.

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Table 1: Common β emitter Radionuclides for tumor PET imaging along with their production techniques, emission types, respective half life and biomedical application[2, 3]

Radionuclide	Emission type	Half-life	Emax (keV)	Mode of Generation	Biomedical Application
^{18}F	Positron	1.83 h	640	Cyclotron	Glucose metabolism, Hypoxic tissue, Nicotinic acetylcholine receptors
^{11}C	Positron	20.4 min	960	Cyclotron	Biosynthesis of phospholipids, Choline receptors
^{13}N	Positron	9.96 min	1190	Cyclotron	Blood flow
^{15}O	Positron	2.07 min	1720	Cyclotron	Oxygen metabolism, Blood flow, Blood volume.
^{64}Cu	Positron	762 mins	0.655	Cyclotron	Tumor detection
^{68}Ga	Positron	78.3 h	93, 184, 300, 393	Cyclotron	Tumor detection

Table 2: Common γ emitter radionuclides for SPECT imaging along with their production techniques, emission types, respective half life and biomedical application [2, 3]

Radionuclide	Emitter	Half Life (h)	Emax (KeV)	Mode of Generation	Biomedical Application
^{99m}Tc	γ	6.0	140	^{99}Mo generator	Tumor imaging
^{201}Tl	γ	73	70-80; 135;167	Cyclotron	Tumor imaging
^{67}Ga	γ	78	93.5;184.5; 296; 388	Cyclotron	Tumor imaging
^{111}In	γ	67.2 h	171, 245	Cyclotron	Imaging and radiotherapy
^{123}I	γ	13.2 h	159	Cyclotron	Thyroid
^{131}I	γ (81.2%), β	8.0 days	284, 364, 637	Cyclotron	Thyroid

Even though, SPECT is much cheaper than PET, cost of making these instrument is one of the major disadvantages of nuclear imaging. Conversely, both of these nuclear imaging does have many advantages though. First, the sensitivity of a typical PET scanner is very high and can detect between 10^{-11} mol/L to 10^{-12} mol/L concentrations. Secondly, PET images biochemical or physiologic phenomena in contrast to computed tomography (CT) which show anatomic detail. Because of this, PET offers substantial advantages over other anatomic imaging modalities.

In general, majority of the radionuclides used in PET imaging are produced by cyclotrons either on site or at a site near the scanner.[1] Once the radiolabeled isotopes are produced its replacement

can be carried out *via* isotopic substitution or non isotopic substitution. Since ^{12}C, ^{14}N and ^{16}O being part of the biomolecules their replacement with their respective isotopes is isotopic substitution, whereas the radiolabeling with ^{18}F is mainly the substitution of a hydrogen atom or hydroxyl group by a fluorine atom.[4] Not being part of biomolecules, the replacement of the ^{18}F induces only minimum steric perturbations.[5] In addition, the strong electronic property of fluorine atom modulates the lipophilicity and biological characteristics of the radiopharmaceuticals as compared to the nonfluorinated analogues as shown by Zang and Coworkers.[4, 6] The longer half-life of ^{18}F (110 min) allows complex radio synthesis, and longer *in vivo* investigation. As the matter of fact, current PET imaging techniques utilizes isotopically labeled Fluorodeoxyglucose (FDG) as the imaging agent as the malignant cells have higher rates of aerobic glycolysis than normal tissues. Thus, the malignant cell utilizes more glucose to meet its energy needs. Fortunately, while Fluorodeoxyglucose (FDG) is not an ideal imaging agent as some tumors show poor FDG metabolism than some benign processes, it works very well in most malignant tumors of clinical importance.[7-9] Hence, FDG uptake reflects the culmination of complex and incompletely understood biological processes that affect glycolysis in a specific tumor. Infact, use of ^{19}F labled FDG have shown the its high potential with PET for detection and staging of the breast cancer.[10,11] Although there are no ideal radiopharmaceuticals, the following characteristics should direct the proper choice of an adequate compound: its concentration in the target organ or tissue should be higher than in non-target regions; the binding to the radionuclide should be strong enough for allowing the completion of the study; the radiation dose delivered to the patients should be as low as reasonably possible without degrading the diagnostic quality of the images; their preparation should be simple, convenient, fast and cost-effective; and they should interfere as least as possible with the normal physiological conditions of the patients. More often, the drug delivery carriers in diagnostics and therapeutics offers a major challenge on terms of the low drug bioavailability within cancer cells and the high toxicities to normal organs[12,13]. Moreover, to maximize the therapeutic index and to minimize the toxicity of radionuclides used in imaging, it is very important to increase the selectivity of radionuclides to the site of action especially on the tumors cells. These challenges have been addressed by the development of novel nanoparticulated system including iron-oxide nanoparticles, gold nanoparticles, liposomes, emulsions, dendrimers, and nanotubes.[14] In addition, to maximize the therapeutic index and to minimize the toxicity of radionuclides used in imaging these novel systems are developed so that they range in particle size between 10-500 nm, seldom exceeding 700 nm.[15] Thus, this review article focuses on radiolabeled nanoparticulated systems which have shown the future in the field of cancer diagnosis and therapeutics assisted via nuclear imaging.

NANOPARTICLES IN NUCLEAR IMAGING

Nanoparticles are long known to be ideal candidates for targeted drug delivery and imaging. Hence various approaches have been put forth for the modification of the nanoparticles to include various radionuclides rendering them available for nuclear imaging. The nano size of these particles allows various communications with biomolecules on the cell surfaces and within the cells in way that can be decoded and designated to various biochemical and physiochemical properties of these cells.[14,15] In an effort to utilize nanoparticles at their maximum potential, more specific targeting systems are designed to recognize the targeted cells such as cancer cells. This can be achieved by conjugating the nanoparticle with an appropriate ligand which has a specific binding activity with respect to the target cells. In addition, nanoparticles provide a platform to attach multiple copies of therapeutic substance on it and hence increase the concentration of therapeutic and diagnostic substances at the pathological site. Once targeted (active or passive), these nanocarriers can be designed in a way to facilitate them to act as imaging probes.[16] Hence, these so called "molecular imaging probes" can non-invasively provide valuable information about differentiate abnormalities in various body structures and organs to determine the extent of disease, and evaluate the effectiveness of treatment.[14] Thus in short, molecular imaging enables the visualization of the cellular function and the follow-up of the molecular process in living organisms without perturbing them.[17] These advances in the field of nanotechnology have opened endless opportunities for molecular diagnostics and therapy.[18] However, synthesizing these nanocarriers with stealth characteristics with improved in vivo targeting capabilities are the major challenges of applying nanoparticles to delivery of drugs or radionuclides.[19-21] Fortunately, these affairs has been well tackled by the rapidly advancing field of cancer nanotechnology by providing various innovative radionuclides and delivery systems, such as liposomes, magnetic agents, polymers, dendrimers, quantum dots, and carbon nanotubes.[13,22-38] These novel systems have enormously helped to rally the transport of radionuclides to tumor sites [2,12,13,19,20,39]. In effect, the development of polymeric nanoparticulate systems encompassing long lived radionuclide such

as ^{3}H, ^{14}C, ^{125}I is long known.[20,40-42] These radionuclides still remain resource for researchers studying new materials. As the matter of fact, it is estimated that approximately 240 nano-enabled products entered pharmaceutical research pipelines in 2006.[21,43] These nanocarrier systems could provide the delivery platforms needed for improving the delivery of radionuclides to tumor sites by targeted delivery of drugs to the tumor site thus reducing their toxic side-effects.[44-49]

Various approaches are used for labeling radionuclides are the surface labeling of the nanoparticle after encapsulation or encapsulating a radiolabeling nanoparticle. However, the nanoparticles conjugated with bifunctional chelators and targeting ligands are particularly useful because their higher surface area which allows a higher number of targeting residues and radionuclides per particle. This relays higher affinity and specific activity of the molecules towards the target cells.[20] Thus, the surface labeling the nanoparticle has shown a wide of interest to the molecules that may be directly coupled *via* a suitable coupling strategy. Generally, linker should be readily labelable with the radionuclide, the label should be sufficiently stable under *in vivo* conditions without any non-specific interactions in the organism.[50]

Various radionuclides with functional characteristic has been designed and tagged onto a nanoparticle. In fact, *Hallahan et al* developed ^{131}I labeled albumin nanaoparticles targeted on the integrin receptors for the imaging of the tumor blood vessles.[51] They used the peptide that included the amino acid sequence RGDGSSV. This peptide binds to integrins within the tumor microvasculature. It was demonstrated that the radiopharmaceuticals were localized to irradiated tumors by use of $\alpha_{2b}\beta_3$ ligands conjugated to nanoparticles and liposomes. In a similar approach *Hu et al* presented perfluorocarbon nanoparticles labelled with iodine conjugated to intergrin seeking peptide sequence.[51,52] In both studies tumor active targeting, intra-tumoral radioactivity uptake reached high levels up to 90% of total body radioactivity.[2, 52]

Likewise, Plotkin and Coworkers developed O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) based amino acid tracer for targeting the nanoparticles to be imaged by PET. Results showed that PET imaging increased the estimation of the gross tumor volume by 22-28% and are highly valuable for defining the target volume for the nano cancer therapy.[53] Other methods of labeling a nanoparticle involve the conjugation of methalchelate to nanoparticle. *Rossin et al* evaluated the use of PET to noninvasively image the lung uptake and distribution of NPs coated with an anti-ICAM antibody and radiolabelled ^{64}Cu-DOTA (DOTA is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid).[54] Results showed that even after 24 hours of injection the lungs of mice injected with radiolabeled anti-ICAM NPs were clearly imaged by microPET.[54] Similarly, in an attempt to improve the blood circulation time, Fukukawa and coworkers have reported synthesis of novel core-shell star copolymers having a poly(ethylene glycol) outer shell, a hydrophilic inner shell of *N*,*N*-dimethylacrylamide bearing reactive functional groups, and a central hydrophobic core *N*-acryloxysuccinimide. Functionalization of these polymeric nanoparticles with a DOTA-ligand capable of chelating radioactive ^{64}Cu nuclei enabled in vivo positron emission tomography (PET) imaging. The particle size of these nanoparticles ranged from 3-70 nm as calculated by DLS. Further, the results indicated that nanoparticles with increasing PEG shell show increased blood circulation and suggesting application as *in vivo* carriers for imaging, targeting, and therapeutic groups.[55]

Similar to these conjugated radiolabeled doping of radiolabel into nanoparticles or the use of doped radiolabeled nanoparticles is seen as another way of optimizing lead molecules on to the target cells. Doped nanoparticles often provide enormous advantages by reducing the direct impact of radionuclide onto the benign tissue. Thus, even with these advances in the synthesis of nanoparticle, the inability to detect small macroscopic disease (<0.5 cm) and the lower sensitivity of for accurate staging are some of the disadvantages of nuclear imaging.[56,57] The most impeding factors to the PET studies is that the images obtained with PET are of substantially lower resolution than, for example, those of MRI. To add, PET is generally poor at delineating anatomic details. This lack of detail results in poor localization of lesions and poor demarcation of lesion borders. Moreover, lesions are often complex, with some portions more metabolically active than others.[58] The operating cost and the side effects from radiation have always been a major issue.

CONCLUSION

Radiopharmaceuticals are long being explored as agents for the delimitation of disease, whereas, the advent of nanoparticles has accelerated this motion and has emerged as the front runner to aid its diagnosis and treatment. Despite the fact, enormous research has been done towards developing novel nanoparticulated imaging systems, the role of nanoparticle in diagnosis is far from over. Moreover, in coming years they will continue to be modified, derivatized and functionalized for its advanced application in the field of radiopharmaceuticals due to great deal of efforts from the scientist all over the world.

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