Review Article
The Mutual Beneficial Effect between Medical Imaging and Nanomedicine

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The reports on medical imaging and nanomedicine are getting more and more prevalent. Many nanoparticles entering into the body act as contrast agents, or probes in medical imaging, which are parts of nanomedicines. The application extent and the quality of imaging have been improved by nanotechnique. On one hand, nanomedicines advance the sensitivity and specificity of molecular imaging. On the other hand, the biodistribution of nanomedicine can also be studied in vivo by medical imaging, which is necessary in the toxicological research. The toxicity of nanomedicine is a concern which may slow down the application of nanomedical. The quantitative description of the kinetic process is significant. Based on metabolic study on radioactivity tracer, a scheme of pharmacokinetic research of nanomedicine is proposed. In this review, we will discuss the potential advantage of medical imaging in toxicology of nanomedicine, as well as the advancement of medical imaging prompted by nanomedicine.

1. Introduction

Medical imaging is an important technology in clinical and medical research, which enables the observation of human and animals in vivo. The development of medical imaging contributes a lot to diagnosis and therapy. However, researchers are not satisfied with single anatomical image. To detect physiological function and biological process, functional imaging, molecular imaging, and multimodality imaging are invented and have developed prosperously [1–3]. Most molecular imaging today depends on synthesized probe with special property [4]. For nuclear medicine, for example, the probe is also expressed as radioactive tracer or tracer [5, 6] for positron emission tomography (PET). For fluorescence molecular tomography the probe is a fluorescence agent [7].

In terms of traditional imaging, some agents are used to increase the contrast of images [8, 9]. Contrast agent can enhance their applications and even upgrade them to cellular and molecular level.

Nanotechnology has a remarkable great contribution to the development of medical imaging. Nanomedicine is a scientific specialty of nanotechnology, which has great potentials to develop the diagnostic and therapeutic approaches [10–12]. Nanomedicine has drawn broad interests in medical imaging, as well as the targeted therapy [13]. Modified by nanotechnique, some probes and contrast agents become more efficient [14], and then they can be called nanomedicine [15]. Some kinds of nanoparticle, just as metal nanoparticles, become nanomedicine used as contrast agent of medical imaging [16, 17]. With the application of nanomedicine, medical imaging will have a broader prospect in application.

Nevertheless, the nanomedicine, used in medical imaging, must eliminate the potential risks in safety issues. Most nanomaterials have been discovered to affect cell behavior [18, 19] and even to damage the physiological system [20, 21]. The discussion of the biocompatibility and toxicity of nanomaterial is of a great importance in biological and medical research. The toxicology of nanomaterials is usually studied on cellular scale or smaller size, while the pharmacokinetics is also necessary to understand its potential toxicity [22]. As pharmacokinetics of tracer is studied by
means of nuclear medicine [23, 24], the dynamic distribution of nanomedicine could also be studied by medical imaging [25]. Thus, medical imaging could advance the research of nanomedicine, especially in the field of toxicology.

This paper aims at discussing the interaction between medical imaging and nanomedicine. Nanomedicine extents the application of medical imaging, and medical imaging enhances toxicological research at system scale. In this review, we will first discuss some imaging techniques, which are commonly used in clinic, and the imaging agents, including traditional agent and nanomedicine. Then a discussion will be shared about the toxicological research of nanomedicine. In the end, a feasible means combined with medical imaging and nanomedicine will be proposed for the quantification study of nanomedicine toxicity.

2. The Development of Imaging Affected by Nanomedicine

The development of medical imaging is built on multiple techniques. In the past decade, it has been promoted especially by nanotechnique [15]. Every imaging technique has its limitation as well as the superiority, nanomedicine is used as probe, or contrast agent, to extend the application of imaging and to improve the quality of images [26–28].

CT, which is based on X-ray attenuation, can recognize inner structure by the different attenuation coefficients of tissues. Though CT is a high-resolution imaging, it is limited in soft-tissue imaging. To increase the contrast of images, metal salts, metal particles, and some iodinated compounds have been used as contrast agents in X-ray-based imaging [29]. High osmolality, short circulation time, and toxicity of heavy metal bulk may lead to some adverse reactions at the same time. Nanotechnique overcomes some of these problems. Conjugated with nanoparticle, iodinated compounds prolong the circulation time [30], and nonionic water-soluble iodinated contrast agents have lower osmolality [31]. Heavy metal nanoparticle has shown its efficiency as contrast agent in CT imaging [32–34].

MRI is based on nuclear magnetic resonance and the relaxation of proton spins in a magnetic field. It has a high resolution for soft tissue and is highly functional for brain and nervous system scan. While For the tiny difference between lesion and normal tissue, MRI is not as sensitive or specific as ideal molecular imaging. Nanocontrast agents can help MRI become a more efficient molecular imaging [27]. Gadolinium chelates are commonly used contrast agents to enhance the signal of MRI [35]. Gadolinium-loaded single-walled carbon nanotubes are super paramagnetic, 40 times more than traditional agent [36]. Iron oxide nanoparticles (hundreds of nanometers) are super paramagnetic, which have been used to diagnose liver diseases [37, 38]. Ultrasmall iron oxide nanoparticles (less than 50 nanometers) are applied to detect macrophage [39]. The application of MRI becomes more and more extensive with the progressive research on magnetic nanomedicine [40, 41].

Nuclear medicine molecular imaging, as PET and SPECT, relies on radiotracers, which are also called probes. Fluorodeoxyglucose (18FDG) is the most commonly used radio-pharmaceutical in PET imaging [42]. As the analog of glucose, FDG can be used to detect cancer, which has a high glucose metabolic rate [43, 44]. FDG is not always sensitive to all lesions. 11C-acetate is more suitable for the detection of liver cancer [45]. For specific diagnosis, the probe of proper target is the key of medical imaging [46, 47]. Combined with nanoparticles, the radiotracers become more and more multiform; for example, radionuclides can be labeled on proteins, antibodies, and peptides. The radiolabeled single-walled carbon nanotubes can be used in PET imaging, and the efficiency can be increased by peptide coating [48]. The sensitivity and specificity of nuclear medicine imaging will increase with the application of nanomedicine.

Besides upper imaging technique, nanotechniques advance other medical imaging. The combination of nanoparticle and fluorescent probe greatly enhances imaging [49]. Quantum dot, which is referred to as semiconductor nanocrystals, can be used in fluorescence image, even to image the vasculature near tumor probe [50, 51]. To visualize microvascular, nano/microcapsules have been designed as a contrast agent for ultrasonic imaging [52].

Nanomedicine may be the most suitable probe or contrast agent for multimodality imaging because of the convenience of integrating multiple properties [53, 54]. In PET/MRI imaging, radiolabeled iron oxide nanoparticles are not only the tracers for PET but also the contrast agents for MRI [55]. With the ability of multifunction load [56], nanomedicine may boost the fusion of multiple imaging techniques and even the combination of the process of diagnosis, therapy, evaluation, and disease prevention [57]. There are so many mechanisms for creating imaging agent in nanoscale, which will progressively develop the sensitive and specific imaging technique.

3. The Study on Toxicity of Nanomedicine Could Be Supported by Imaging

Many nanomedicines are not only for imaging but also for therapy [58–60]. Nanomedicine can deliver therapeutic agents into targeted specific tissues and cells [61]. For example, gold nanoparticles are the potential for the therapy of various diseases such as cancer and Alzheimer [34, 62, 63]. Unlike the nanobimaterials applied in vitro [64, 65], nanomedicines face more risks along with the opportunities. Biocompatibility and toxicological research are significant for the materials which will be applied in human body [66, 67]. It has been reported that some nanoparticles produce inflammation and tissue damages and other adverse health effects in body [68–70]. Toxicology study is the essential safety assessment of nanomedicine [71].

In the study of toxicity, in vivo experiments are absolutely necessary for the understanding of nanotoxicity in the physiological system. The examination of serum biochemical parameters, urine parameters, and histopathology can reveal the injury of viscera and have been used as methods to
study toxicity of nanomaterials [72–74]. In the study of the nanotoxicity, biodistribution and elimination are of a great importance [61]. Nanoparticles can translocate in human body, even if they are inhaled, and the position where they settle down may decide the level of damage [75]. Central nervous system is the potential susceptible target for some nanoparticles, in which the potential lesion induced by nanoparticles will be hazardous [69, 76]. In traditional biodistribution experiments, small animals were sacrificed after administration, and the organs, liver, spleen, lung, heart, and kidney, were excised to detect the biodistribution of nanoparticles [77, 78]. In the biodistribution experiment of Fe$_2$O$_3$ nanoparticles [79], isotope was labeled to be detected by high purity germanium detector after organs excised. The radiolabeled nanoparticle can also be detected by whole body gamma camera image [25]. In other words, medical imaging can be used as a tool to study toxicity of nanomedicines. PET/CT has been used to study the tissue biodistribution and pharmacokinetics of DOTA-functionalized single-walled carbon nanotubes [80] and nano graphene [81]. MRI has been used to track mesoporous silica nanomedicine for three months [82]. The distribution of nanomedicine in various organs could be derived by medical imaging.

Pharmacokinetic model is a quantification method to describe the dynamic fate of a drug after administration, which is usually required for new drug design. Though
the dynamic distributions of nanomedicine have been discussed in some literatures [25, 81, 82], yet few pharmacokinetic models have been established. Zhu et al. used one-compartment model to describe the kinetic of ferric oxide nanoparticles in human body quantificationally [79]. In this model, the rate of absorption and elimination was included, but the different distribution of nanomedicine cannot be represented. In another application of molecular imaging, kinetic models of tracer are established to describe the metabolism of glucose [83]. By dynamic PET imaging, the kinetic models were established separately for some tissues [84, 85] and then formed a whole body model [86, 87]. The distribution metabolism and elimination are all involved, which are parts of toxicity study.

Thus the development of nanomedicine could be prompted by medical imaging, especially in the aspect of toxicology. According to the application of medical imaging in metabolism research, there is a feasible research scheme for toxicological study, as shown in Figure 1. Loaded with imaging-functionalized particles, the nanomedicines could be detected by medical imaging. Radioactivity label is preferred for PET or SPECT, magnetic nanoparticles could be attached for MRI, and quantum dots will be suitable for fluorescence image. Nanotechniques may show their advantage in designing probe for multimodality imaging. Then the dynamic distribution curve of nanomedicine in different tissues can be received from images, which can be used to establish the pharmacokinetic model. In the pharmacokinetic model, the processes of absorb, distribution, metabolism, and elimination are described quantificationally. These processes are also called biodistribution, an important aspect of toxicology. This scheme, using mathematic model to describe the biodistribution of nanomedicine, is a potential application of medical imaging in nanotoxicity research.

4. Conclusions

The rapid development of medical imaging and nanomedicine gives us a promising prospect of diagnosis and therapy. Sensitive, specific, and in vivo diagnosis and personal therapy benefit from the combination of medical imaging and nanomedicine. Nanomedicines, used as imaging contrasts, tracers, or probes can improve the sensitivity of imaging detection; thus, the sparsely expressed targets would be discovered. With the well-designed nanomedicine, medical imaging could also be used for tumor imaging [88], physiological mechanism study [89], and even DNA detection [90]. It is beneficial not only to imaging but also to the development of nanomedicine. The potential toxicity is the biggest barrier to the clinical application of nanomedicine. Quantificationational dynamic systemic researches on the distribution of nanomedicines in vivo are necessary to toxicology. Medical imaging is the most convenient method to analyze the biodistribution of nanomedicine and to assess the nanomedical treatment [91]. Nanomedicines can be detected in vivo by medical imaging, after they are loaded with imaging-functionalized particles or radioactive labeled. Therefore, imaging will allow the risk stratification and monitoring of therapy effects. With reference to metabolic studies of radioactivity tracer, the pharmacokinetic model of nanomedicine could also be established by means of dynamic medical imaging, which will contribute to the advancement of nanomedical toxicology. In summary, medical imaging and nanomedicine advance each other and will play an important role towards more advanced medicine. Attention should be focused not only on the success of nanomedicine application in medical imaging but also on the potential advantages of imaging for nanomedical toxicology research.

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References


