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REVIEW

Progress of Multimodal Molecular Imaging Technology in Diagnosis of Tumor

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Abstract: The multimodal molecular imaging technology, integrating the advantages of variant imaging methods, can provide more comprehensive and accurate information in cancer diagnosis, and realize timely personalized diagnosis of tumor at molecular and cellular level, quantitatively dynamic monitoring of tumor, etc. This review introduces the basic concepts of multimodal molecular imaging, implementation methods and recent research progress of the applications in tumor diagnosis. The development trend of multimodal molecular imaging in tumor diagnosis is also prospected.

Key Words: Multimodal imaging; Molecular imaging; Molecular probe; Nanomaterial; Gene reporter; Tumor; Review

1 Introduction

Malignant tumor is a major disease threatening human health seriously. The incidence of malignant tumor in China is the highest in the world, and making cancer the leading cause of death in recent years[1,2]. Improving the diagnosis and monitoring levels of tumor constantly is of great significance to improve the curative effect, prognosis and life quality of tumor patients. Traditional techniques of tumor imaging including ultrasound, X-ray imaging, computed tomography (CT), magnetic resonance imaging (MRI), and radionuclide examination, etc., have been widely used in clinic. However, each technology has its own limitations.

With the development of medical imaging techniques, the integration of molecular imaging technology with other disciplines including molecular biology, material science, chemistry and biology engineering has become a new research field. By means of imaging technology, researchers can study the inner working mechanisms of human body, and visualize qualitatively and/or quantitatively the complex biochemical process at molecular and cellular level as well as living tissue. Therefore, molecular imaging technology is quite feasible for disease diagnosis, drug design, therapeutic evaluation, monitoring of the action of functional molecules *in vivo*, etc. In particular, multimodal molecular imaging technique can be employed to obtain a variety of information of lesion site by importing molecular imaging probes with multiple functions in the body at the same time, and then performing a variety of imaging examination. By combination with the advantages of different imaging techniques, the complex biochemical process could be showed *in vivo* by a fine and specific non-invasive mode, together with more comprehensive and accurate information[3–7]. It was demonstrated that multimodal molecular imaging technology showed an attractive application prospect in early diagnosis of tumors, personalized detection, monitoring of specific cells and functional molecules, gene tracking, prognosis judgment, curative effect evaluation of targeted drugs, etc[3–7]. Based on the analysis of a series of research on molecular imaging techniques published recently, the advantages and limitations of various imaging technology are summarized in this review, and the implementation methods of multimodal molecular imaging

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technology and correspondent application progress in diagnosis and treatment of tumor are discussed. The development trend of multimodal molecular imaging in tumor diagnosis is also prospected.

2 Molecular imaging modes of tumor diagnosis

2.1 X-ray and CT imaging

X-ray and CT imaging are the earliest used imaging modes for tumor diagnosis in clinic, and are widely employed to visualize lesion sites at present. CT can provide excellent anatomical images with high spatial and temporal resolution, but the soft tissue resolution and imaging sensitivity are relatively poor. In addition, the high X-ray exposure may cause adverse effects on human body. Conventional iodine contrast agent for CT has obvious shortcomings such as rapid clearance from body, short imaging time, high renal toxicity and allergic reactions, etc. Recently, nanotechnology was gradually applied to construct contrast agents with high efficiency and low toxicity for CT imaging[8–14]. For example, packaged or fused organic compounds with nanotechnology could increase the cycle time of iodine in the body and reduce renal toxicity[8–11]. With good biocompatibility, controllabe particle size and ease for surface modification, gold nanoparticles, as contrast agent for CT, also illustrated a good application prospect in molecular imaging of tumor[12]. The limitation of single CT imaging was efficiently overcome using functional imaging with specific molecular affinity, and/or by combination with other imaging modality such as optical and magnetic imaging techniques[13,14].

2.2 MRI technique

MRI is a kind of imaging technology with no radiation. It can provide a variety of information of the body noninvasively including anatomy, physiology and molecular information[15]. MRI can realize multiple sequence and multi-parameter imaging since MRI has good temporal and spatial resolution, excellent soft tissue contrast and deep tissue penetration[16]. Because MRI has relatively low sensitivity, the contrast agents like gadolinium complexes are normally used in MRI to enhance the imaging effect. MRI methods are focused on the imaging of molecular signatures, and the development of novel molecular contrast agents for expanding the strength of MRI in characterizing tissue physiological and molecular changes. Molecular MRI technique is also suited to measure molecular and cellular processes including metabolism, apoptosis, cell proliferation and biosynthetic pathways of different metabolites of cancer *in vivo*. Thus, MRI plays an important role in many aspects of oncology practice, including early disease detection, diagnosis, staging, personalized treatment, and treatment monitoring[17].

2.3 Radionuclide imaging

Radionuclide imaging mainly includes the positron emission computed tomography imaging (PET) and single photon emission computed tomography imaging (SPECT), which have several outstanding advantages including high sensitivity, unlimited depth, whole body imaging, quantitative analysis, fusion of diagnosis and treatment, and biochemical changes evaluation at molecular level *in vivo*. With the development of molecular biology and radiation chemistry, many tracers with high specificity and affinity for cancer emerged in recent years. In conjugation of these tracers with specific molecular probe, the metabolic changes in tumor cell or tissue can be detected prior to morphological changes by radionuclide imaging. Although a large number of clinical and preclinical studies have confirmed its unique advantages and feasibility in tumor detection and treatment response prediction, radionuclide imaging is still needed to combine with other imaging methods including CT and MRI in clinical applications due to its low spatial resolution and lack of anatomical information[18–21]. Radiation safety and the requirement of accelerator to produce radionuclide also limit the use of radionuclide imaging.

2.4 Optical imaging

Because of its unique properties such as low cost, high sensitivity and biosafety, simple operation and high throughput, optical molecular imaging gradually become an ideal method for studying the changing rule of tumor cells at molecular level. Optical imaging mainly includes two imaging techniques: bioluminescent (BLI) and fluorescence imaging (FI). Bioluminescent imaging uses the luciferase gene (FLUC, RLUC, GLUC) to label cells or DNA, and its expression product reacts with the substrates such as firefly luciferin to produce fluorescence. Many contrast agents are applied in fluorescence imaging, including a variety of fluorescent protein gene (e.g. GFP, RFP, YFP, etc.), organic fluorescent dyes, fluorescent nanoparticles, quantum dots, etc. Using optical molecular imaging techniques, researchers could directly detect dynamic process of metabolism *in vivo*, explore the activities of proteins, proteases and genes, which have important value in researching the occurrence, development, metastasis of tumor *in vivo*, and monitor the specific molecular and gene expression[22–26]. However, the instability of fluorescent molecules, the potential toxicity, light scattering, and lack of the depth tissue information limit the application of optical imaging *in vivo*. The development of new techniques, such as multi-functional optical molecular probes, near infrared optical imaging (NIRF), various kinds of 3D optical tomography imaging techniques including the fluorescence molecular tomography imaging (FMT), bioluminescent tomography imaging (BLT), Cherenkov