Review article

Molecular Imaging

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Molecular imaging is a new medical discipline that integrates cell biology, molecular biology and diagnostic imaging. It is generally defined as the *in vivo* characterization and measurement of biological processes at the cellular or molecular level. Compared to conventional diagnostic imaging, it examines the specific molecular abnormalities that are the origin of disease, rather than providing images of the resulting condition. Molecular imaging has two basic applications. The first is diagnostic imaging, which is used to determine the location and extent of targeted molecules specific to the disease being assessed. The second is therapy, which is used to treat specific disease–targeted molecules. The basic data about molecular imaging are reviewed in this paper.

Key Words: Diagnostic Imaging; Positron-Emission Tomography, Magnetic Resonance Imaging; Molecular Biology; Review.

Introduction

Molecular imaging is a new medical discipline that integrates cell biology, molecular biology and diagnostic imaging. It is generally defined as the *in vivo* characterization and measurement of biological processes at the cellular or molecular level. The earlier diagnosis of disease will be possible, since changes at the molecular level always precede anatomical structural changes. Compared to conventional diagnostic imaging, it examines the specific molecular abnormalities that are the origin of disease, rather than providing images of the resulting condition (1). Clinical applications of molecular imaging include the use of nuclear medicine, computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US). The nuclear medicine applications utilize devices such as single photon emission computerized tomography (SPECT) and

positron emission tomography (PET). Molecular imaging has two basic applications. The first is diagnostic imaging, which is used to determine the location and extent to targeted molecules specific to the disease being assessed. The second is therapy, which is used to treat specific disease–targeted molecules. The basic principle of the diagnostic imaging application is derived from the ability of cell and molecular biologist to identify specific receptor sites associated with target molecules that characterize the disease process to be studied (2, 3).

Application

Significant scientific effort has gone into the understanding of complex biological systems. These efforts have yielded much information about the molecular changes that are causative or arise as a result of disease. Molecular imaging is a relatively newer field that is attempting to use these molecular data to generate images that report on changes in gene expression. It has been demonstrated that generating images based on molecular differences rather than anatomical differences between tissues has resulted in more sensitive detection of diseased tissues and has allowed imaging of drug efficacy against particular drug targets (2). Positron emission tomography images the biology of diseases at the molecular level, often before anatomic changes are visible or, in some cases, before symptoms appear. Diseases are biological processes and it is these processes that PET examines.

PET/CT is an imaging technology that combines the biological examination of patients by PET with the CT images of the body's structural detail. This technology improves the diagnostic accuracy and treatment management of patients. It provides surgeons, radiation oncologists and other physicians with precise anatomical landmarks associated with the disease condition as determined by PET. PET whole-body imaging capability helps physicians improve their ability to detect and determine the location, extent and stage of cancer, neurological disorders and cardiac disease. By improving diagnosis, PET scans aid physicians in selecting better courses of treatment, as well as assessing whether treatment is effective or should be changed. Recent published clinical trials have shown that in a wide array of cancers, the use of PET has caused the treatment to be changed for 15 to 50% of patients, depending on the specific clinical question. In addition, PET and PET/CT provide both the patient and their physician with a degree of certainty that is often unavailable through other imaging methods (4). PET holds an edge over SPECT for imaging colon and head and neck cancers. SPECT offers opportunities to pair long-lived radioisotopes with low-molecular-weight agents that target cell receptors. Because of the relatively long half-life of gamma-emitting radioisotopes, SPECT tends to be easier to work with than PET agents, but PET produces much higher resolution. Radiation scattering reduces spatial resolution, as it is not possible to precisely locate the origin of the scattered photons from the body. SPECT is generally not in the same league as PET for cancer imaging. The sensitivity of PET for staging lung cancer in the mediastinum is 76% to 100%, according to various studies. In comparison, the sensitivity of SPECT for this role is 43% to 75% (4). But the value of SPECT should not be underestimated. It is diagnostically powerful and versatile, despite its alleged second-class status. Its molecular imaging capabilities include: uncovering, staging, and monitoring numerous cancers; examining deep venous thrombosis; measuring multi drug resistance to chemotherapy; imaging angiogenesis and apoptosis for early diagnoses and measures of therapeutic response; and diagnosing and evaluating Parkinson's disease and other neurodegenerative conditions (1,

4). SPECT lends insight to the Darwinian world of cellular multi drug resistance to therapy. Chemotherapy triggers natural selection, killing off susceptible cells while allowing resistant cells to replicate. Although cancer cells can employ various pathways to combat therapy, research was concentrated on efforts on the so-called multi drug resistance gene and its product, P-glycoprotein. It is expressed in many tissue types, including the liver, where it pumps substrates into the bile, and the kidneys, where it pumps xenobiotics into the urine. In the absence of P-glycoprotein, the lipophilicity of Tc-99m MIBI enables it to translocate across the cell membrane, and its cationic charge allows it to concentrate inside the cell and be sequestered in the mitochondria. Agent uptake is consequently high. With the presence of P-glycoprotein, Tc-99m MIBI acts like a therapeutic agent and is pumped out of the cell, so uptake is low. Because uptake is quantifiable, the radiopharmaceutical can measure the effectiveness of drugs designed to treat multi drug resistance (4, 5).

Gene expression imaging is one form of molecular imaging used to visualize, characterize, and quantify, spatially and temporally, normal as well as pathologic processes at cellular and sub cellular levels within intact living organisms. This rapidly developing field can be expected to provide useful new tools with which to study gene expression in transgenic animals and in humans during gene therapy.

The application of magnetic resonance imaging (MRI) to molecular imaging begins with a review of the basis for magnetic resonance image generation and how manipulation of different parameters of the system can be applied to molecular imaging. Several examples demonstrate the utility of MRI to generate high-resolution, noninvasive images of molecular events occurring *in vivo* (6). A century after the discovery of X-rays, the low-energy range of the electromagnetic spectrum also attained broad application in radiology. Radiofrequency waves allow excitation in a magnetic field of the magnetic resonance of spin-bearing nuclei in tissue. Using the intense signal of the water protons, morphological images of the human body can be obtained, while at a higher frequency resolution also endogenous metabolites as well as pharmaceuticals, which contain MR-visible nuclei, can be detected noninvasively and *in vivo*. Accordingly, *in vivo* MR spectroscopy is a technique which is sensitive to molecules and molecular properties and which can be applied to repeated examinations. Its major limitation is the low signal intensity vs. noise, which implies long measurement times and poor spatial resolution. Using spectroscopic imaging, the distribution of metabolites within an organ can be monitored selectively and displayed as a molecular image.

Sarcomas are often characterized by significant histopathology heterogeneity, both between and within tumors. This heterogeneity reflects physiologic, biochemical and genetic processes that are amenable to characterization by functional imaging. Although anatomically based imaging modalities such as plain radiography, X-ray computed tomography (CT) and magnetic resonance imaging (MRI) remain the primary diagnostic modalities for staging sarcomas, nuclear medicine approaches including gamma camera scintigraphy and positron emission tomography (PET) are being used increasingly to provide complementary information in specific clinical situations. These include biopsy guidance within anatomically complex masses, staging, therapeutic response assessment and evaluation of residual mass lesions after treatment (7). Nuclear cardiology has historically played an important role in detection of cardiovascular disease as well as risk stratification. With the growth of molecular biology, new therapeutic interventions and the requirement

for new diagnostic imaging approaches have come. This progress has been made possible with the availability of transgenic animal models along with many technological advances. Future adaptations of the developing experimental procedures and instrumentation will allow for the smooth translation and application to clinical practice (6). In the management of prostate cancer, combined anatomic and metabolic imaging is already in clinical use. In daily clinical practice, fusion of magnetic resonance imaging and magnetic resonance spectroscopic imaging is improving the evaluation of cancer location, size, and extent and is simultaneously providing assessment of tumor aggressiveness (8).

Discussion

Long-term program goals include enabling preclinical disease detection for a wide range of medical disorders and creating personalized, targeted therapies for them. This will be based on molecular profiling of cell and tissue function and delineating data on cell physiology and function to guide development of personalized treatment and computational modeling. The biology teams develop molecular imaging agents, which will bind specifically to the targeting therapy which is based on an extension of the diagnostic imaging principle. Basically, it is assumed that if the molecular probe does target the specific disease molecules of interest, the same molecular agent can be loaded with an agent that will deliver therapy to the targeted cells (1, 2).

The eventual clinical owners of molecular imaging may be a specialty group that is a hybrid by conventional measures. For example, the clinical owner should have fundamental knowledge in basic cellular and molecular biology but must also be certified as well as competent in the specific diagnostic imaging specialty applied (i.e. nuclear, MRI or US). Another issue relates specifically to the therapy applications in oncology. Clearly, radiology and its associated diagnostic imaging subspecialties is the most logical owner of molecular imaging (1).

It is very important to develop a database of all ongoing molecular imaging efforts, including imaging programs and development of molecular imaging probes. Also it is necessary to provide funding which will provide much-needed support for promising molecular imaging programs and also encourage more investigation in the field. By linking programs in molecular imaging, molecular probes, and molecular libraries, it will bring together the critical elements for development of new, more specific therapies for a wide range of medical maladies. Decoding of the human genome has yielded a catalog of three billion genetic sequences, which constitute the building blocks for discoveries related to the genetic pathways and networks responsible for health and disease. Effort contributed to the identification of tens of thousands of potential genetic pathways and molecular targets that provide opportunities for development of new therapies. As a result, development of a molecular library to catalog the existing and emerging information is a priority (4).

Conclusion

Molecular imaging and the benefits it offers for cancer research and clinical care, which include noninvasive, *in vivo* imaging of specific cellular and molecular processes, nearly simultaneous monitoring of multiple molecular events, real-time imaging of the trafficking and targeting of cells, optimal patient-specific adjustment of drug and gene therapy, and assessment of disease progression at a molecular pathologic level, bring the revolution in medical care and patients treatment.

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