

Molecular Imaging Overview

Background

Molecular imaging is the noninvasive visualization in space and time of normal as well as abnormal cellular processes at a molecular or genetic level of function. It is used to provide characterization and measurement of biological processes in living animals and humans (in vivo). For example, after the patient receives a special molecular probe, a PET scan can reveal the presence of lymphoma cancer cells in specific areas of the body, earlier and more accurately than previous diagnostic methods. The discipline of molecular imaging evolved rapidly over the past decade through the integration of cell biology, molecular biology and diagnostic imaging.

Imaging Probes

A key component is the imaging probe which homes in on the specific target of interest in the body and is visualized by a special scanning method. In creating a probe the basic principle is to identify a specific receptor site associated with the target molecule that characterizes the disease process being studied. A molecular imaging agent that binds specifically to this target molecule is then developed. The agent is labeled with a radioactive substance or other methodology that allows detection by the imaging device. When administered the molecular imaging probe locates and binds to target molecules in high enough concentration to be detected by the scanner. Although the concept is simple, the process is complex requiring extensive expertise and equipment. The probe must be safe, not alter the disease process being studied, be able to reach the target in sufficient concentration while not accumulating in other tissues, and be retained long enough to be detected – all significant challenges to overcome. Currently there are over 500 probes with many more in development.

There are three basic probe imaging strategies:

1. **Direct imaging** uses a probe specific for cell surface receptors, intracellular molecules or gene expression, which interacts directly with the target providing an image intensity correlating to the amount of target actively present.
2. **Indirect imaging** is more complicated as it often uses both a reporter gene and a reporter probe which interact within specifically targeted cells to produce a metabolite trapped in the cells that visualizes when scanned.
3. **Surrogate imaging** detects downstream effects of endogenous molecular-genetic processes using established radiopharmaceuticals and clinical imaging protocols.

Current Imaging Developments

Three different noninvasive, in vivo imaging technologies are evolving at the heart of molecular imaging to provide spatial and temporal dimensions of understanding:

1. **Radionuclide Imaging** devices visualize very low concentrations of radionuclide probes in real time and provide quantitative information, but with low image resolution. They can be used for whole body imaging.
 - a. The **PET (Positron Emission Tomography) scan** visualizes probes labeled with positron emitting radioisotopes; it is increasingly popular for both research and clinical medicine.
 - b. The **SPECT (Single Photon Emission Computed Tomography) Scan** uses probes labeled with radioactive isotopes, which emit gamma rays detected by a gamma camera to create the scan.

- c. **Quantitative Autoradiography** is a technique used in the laboratory to visualize radioactively labeled molecules in substances.
 - d. **Radionucleotide imaging combined with a computed tomography (CT) or a nuclear resonance imaging (MRI) scan** provides high anatomic definition along with functional imaging for precise location of the selected molecular activity.
2. **Magnetic Resonance Imaging (MRI)** uses paramagnetic-labeled probes and produces high imaging resolution, but a large concentration of the probe must be given which can overwhelm the system being investigated.
 3. **Optical Imaging** uses fluorescent and bioluminescent probes that emit radiation in the visible or near-infrared wavelengths, which can be scanned by optical cameras. Unfortunately, light can travel only a few millimeters through tissue so it is limited to skin, breast, small animals and endoscopic procedures – not deep tissues.

Uses of Molecular Imaging in Biomedical R&D and clinical medicine

Molecular imaging has two basic applications: (1) **diagnostic imaging** to determine the location and extent of targeted molecules for the disease being studied, and (2) **therapy** to treat specific disease-target molecules by adding a therapeutic agent onto the probe.

Examples of applications:

- Research and development:
 - To understand normal functioning of molecules, cells, organ systems and whole organisms
 - To assess progressive developmental, degenerative and disease changes within living (in vivo) special rodent models over time, as well as later evaluation of therapeutic interventions
 - To identify, study and diagnose the biological nature of disease early and throughout its evolution
 - To provide biological information for the development and assessment of therapies
 - To evaluate candidate drugs: (1) provide in vivo biological characterization of the disease and response to the drug, (2) assess if effectiveness in humans is similar to initial mouse studies, (3) to titrate drug to disease response in tissue for accurate dosing, (4) to provide pharmacodynamic and pharmacokinetic characterization, and (5) to determine whether the drug modified the biological disease process or restored a normal process affected by disease
 - To measure gene expression for effectiveness of gene therapy
- Clinical management of disease:
 - To detect disease early, even years before symptoms appear or it can be detected by conventional diagnostic tests
 - To differentiate reversible from irreversible damage to cardiac tissue in coronary artery disease or benign from malignant cancer lesions
 - To evaluate all organs for metastatic cancer
 - To rapidly determine effectiveness of a therapy for quick change to a different therapy if it is not effective
 - As a targeted therapeutic delivery mechanism combining a molecular imaging probe with a drug or other therapy – target the disease with low incidence of toxicity to normal tissues
 - To estimate disease prognosis

Areas of Current Development

- Development of new probes and contrast agents
- Development of new imaging modalities
- Development of multiple modality imaging (i.e. PET plus CT) to simultaneously visualize function and structure
- Development of powerful bioinformatic applications to handle the huge amount of data
- Transition into clinical application of research technologies
- Teaching a new generation of radiologists and other specialists to utilize these complex interdisciplinary imaging technologies
- Evolving decisions as to which clinical specialists will control the domain of molecular imaging

Expectations for Molecular Imaging

Molecular imaging will become more important as genomics and proteomics expand the number of relevant molecules to visualize. Systems biology and knowledge management tools will also help scientists and clinicians interpret the growing number of molecular images. Futurists anticipate that scanners could become so small and inexpensive that they will move from research settings to doctors' offices and then homes—think of the handheld tricorder like device on Star Trek. Molecular scans which could only be done in a few research centers a decade ago (e.g., PET) have since become widely disseminated. The same can be expected of future molecular imaging technologies, especially as nanotechnology investments bring about smaller devices that can diffuse rapidly into research and clinical settings.

Our interviews show that many scientists anticipate that molecular imaging will illuminate a large number of biomarkers that mark disease processes. Beyond disease, some see that molecular imaging could prove even more important for revealing healthy and “super healthy” biological processes as well. Already, brain scans show that advanced meditators can create remarkable neurological changes that energize areas of the brain associated with happiness. Molecular markers for other parameters such as resiliency, stress levels, immune function, balance and energy flow could help us shift from a disease treatment paradigm to a prevention and even a health enhancement focus.

Questions About Molecular Imaging

Over the next 5 years what contributions do you anticipate from molecular imaging at the frontier of biological knowledge?

What totally new kinds of measurement might arise from molecular imaging that would profoundly change biomedical R&D by 2029?

Will molecular imaging shift the focus from understanding disease to learning about health, enabling a “predict and prevent” form of medicine?

Sources

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