Target watching with a beady eye

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When it comes to monitoring the location and migration of cells within the body, reporter groups with magnetic properties can be irresistible. In this issue, Lewin and colleagues[1] label stem and progenitor cells ex vivo with superparamagnetic iron oxide nanoparticles that have been coated with dextran covalently bound to peptide sequences from the HIV-derived Tat protein. These Tat-derived sequences enable the paramagnetic label to be efficiently internalized into target cells, which can subsequently be tracked in vivo using the magnetic resonance imaging (MRI) technique. By allowing the direct in vivo imaging of cell trafficking, this approach may not only provide information for the optimization of stem cell-based therapies, but also advance our basic understanding of developmental biology, pathology, and general pharmacology.

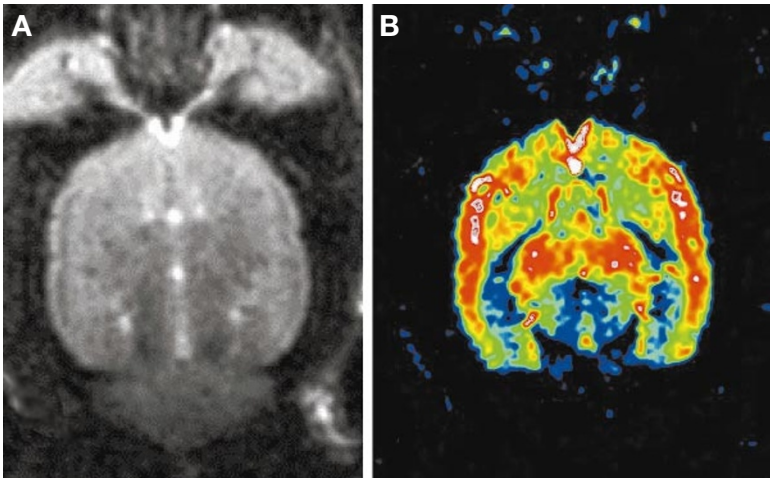

Figure 1. Imaging the consequences of drug–receptor interactions. (A) "Anatomical" MRI: Coronal T2-weighted cross section through rat brain 4 mm inferior to the bregma. (B) "Molecular" MRI: Drug-induced changes of cerebral blood volume in the same brain cross section following peripheral administration of the $GABA_A$ antagonist bicuculline. The signal intensities reflect receptor density (see ref. 8).

The study by Lewin and coworkers[1] reflects the current trend in imaging toward approaches that provide real-time information on biological processes. Over the past decade, MRI has evolved from a radiological imaging approach to a method for providing information on physiological tissue parameters, such as tissue blood flow or tissue oxygenation. Functional MRI of the brain, which allows the generation of brain activity maps similar to those obtained using well-established positron emission tomography (PET), is also becoming increasing popular (Fig. 1). More recently, refinements on the MRI approach are heading toward "molecular" or "target-specific" imaging (i.e., the mapping of ligand–target interactions).

Target-specific imaging that provides direct insight into biological processes at a molecular or cellular level will be an important aid in addressing fundamental questions in biomedical research. Already, techniques have been developed to monitor gene expression in living animals. They require an interplay between the gene product (e.g., an enzyme or receptor) of a marker gene and an appropriate marker substrate. In vivo imaging of gene expression has also been reported using radiolabeled substrates and PET[2], a bioluminescent reporter system (luciferase/-luciferin) and optical imaging[3], and superparamagnetic magnetite receptors probes and MRI as the readout technology[4–6].

For molecular imaging of a ligand/-drug–target interaction, PET is currently (and for the foreseeable future) the method of choice because of its high sensitivity. Even so, the PET approach does have the drawback of requiring the design and synthesis of a suitable PET ligand, which has to be prepared in situ because of the short half-life of the positron-emitting nuclei. Furthermore, in certain instances, MRI might be exploited to provide similar information to PET, either by following the PET concept of using magnetically labeled ligands[7] or by mapping the consequences of a ligand–receptor interaction on physiological tissue parameters (e.g., see Fig. 1)[8].

How does MRI compare with other imaging methods, such as PET or imaging of bioluminescence, that are being applied to the imaging of gene expression[2–6], receptor–ligand interaction[7,8], or cell migration/trafficking[1,9]? One strength of the MRI approach is that, being a radiological imaging method, it allows the direct comparison of anatomical and "molecular" images. With present technology, spatial resolutions of <100 µm can be achieved in vivo in small animals, both exceeding the resolving power of PET and significantly better than that of bioluminescence imaging, which is severely hampered by low tissue penetration and scattering of light.

On the other hand, MRI is limited by its intrinsically low sensitivity, requiring relatively high amounts of labeled substrate. It is inherently a difference technique; that is, the target information is derived from the signal changes induced by the para- or superparamagnetic MRI substrate with respect to a reference state. In contrast, PET and bioluminescence imaging measure the radiation emitted by the probe directly (corresponding to a reference state zero)—a distinct advantage for quantitative analysis.

From a broader perspective, it is clear that molecular imaging approaches will have a significant impact on biomedical research and drug discovery and development. Imaging the target, its location in the body/tissue/cell, its interaction with other molecules (e.g., substrate–target interaction/receptor occupancy), and the functional consequences thereof will be important not only in preclinical research, but also potentially in clinical work. The key success factor in such studies is the design of the appropriate imaging probe (labeled ligand) rather than the imaging technology itself, be it MRI, PET, or any other modality. Only the concerted interdisciplinary effort of chemists, molecular biologists, biomedical specialists, and the imaging experts will make full use of the advantages offered by molecular imaging techniques. The paper by Lewin and colleagues[1] is an example how such a strategy can be successfully implemented.

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