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REVIEW

Imaging of Small-Animal Models of Infectious Diseases

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Infectious diseases are the second leading cause of death worldwide. Noninvasive small-animal imaging has become an important research tool for preclinical studies of infectious diseases. Imaging studies permit enhanced information through longitudinal studies of the same animal during the infection. Herein, we briefly review recent studies of animal models of infectious disease that have used imaging modalities. *(Am J Pathol 2013, 182: 1–9; http://dx.doi.org/10.1016/j.ajpath.2012.09.026)*

Small-animal imaging has become an important research tool in studies of infectious diseases and has significantly contributed to both our understanding of pathogenesis and preclinical investigations on drug development. Noninvasive imaging research permits enhanced information through longitudinal studies of animal models of human diseases. Infectious diseases are important causes of morbidity and mortality in humans worldwide. During the past decade, several different small-animal imaging modalities have been applied to studies of infectious disease, including magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), bioluminescence imaging (BLI), and intravital imaging. Multiple-modality imaging has become even more attractive because it permits evaluation of the same animals by different imaging technologies, thus reporting on alterations in anatomical characteristics, metabolism, function, and the location of infectious agents. The development of imaging applications in animal models of infectious diseases using these modalities can quickly move from basic research to the clinic. Herein, we review some recent applications of small-animal imaging technologies to the study of infectious diseases.

Overview of Imaging Technologies

MRI is a noninvasive imaging modality with high resolution (approximately 50 to 100 μm for small-animal studies) and excellent intrinsic soft tissue contrast. MRI can be used to image anatomical structures, blood flow, and diffusion in the clinic and in experimental animals. Contrast agents (gadolinium or iron-based agents) can be used to specifically label cells or tissues for diagnostic applications. Although micro-CT is the gold standard for imaging bone in mice, contrast agents are required to enhance soft tissues. CT permits longitudinal studies of anatomical characteristics like MRI. It is a high-resolution (>50 μmol/L), fast (minutes) X-ray–based technique. A concern with CT, particularly with longitudinal studies, is the radiation dose, which may be high enough to induce changes in the biological pathways being studied, and the need for contrast agents for soft tissue imaging.

PET is a highly sensitive (pmol/L) molecular imaging technique that can be used to visualize a variety of *in vivo*

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biological processes. Although the resolution of micro-PET (1 to 2 mm) is not as high as that of CT or MRI, it is adequate for small-animal imaging. The molecule 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG) is routinely used in the clinical setting for the detection of cancer, based on increased uptake of glucose by malignant cells. In addition to ^{18}F-FDG, many other radiotracers can be used in micro-PET studies.

Single-photon emission CT (SPECT) uses radiotracers that permit visualization of specific physiological information, such as blood flow and perfusion, or to measure biodistribution of a radiolabeled molecule or cell. The radioisotopes used are typically longer lived than those used for PET [eg, technetium-99m (half-life of 6 hours) or indium-111 (half-life of 67 hours)]. SPECT is performed in combination with CT to provide anatomical detail; however, the additional exposure to radiation has to be considered in planning longitudinal studies.

Ultrasonographic (US) imaging has high spatial resolution (approximately 50 μm) and contrast in soft tissue. In addition to being portable, US is a fast and economical technique. US has been extensively used for echocardiographic studies of small animals. Recent advances in technology and in contrast agent development have improved resolution such that US studies of many organ systems of small animals are possible.

In vivo BLI has been applied in many studies of small animals and cells. It can be used to monitor gene expression and to track cells. Bioluminescent and fluorescent probes have been engineered to monitor enzymes and the activity of other biologically important molecules. These probes can be used to follow disease progression or response to treatment. Tumor cell lines and microbial pathogens that express luciferase or fluorescent proteins are commonly used for preclinical studies, as are transgenic animals that stably express bioluminescent or fluorescent proteins.

Noninvasive imaging of animals using these technologies reduces animal numbers by permitting the use of animals as their own controls. In addition, therapeutic agents can be developed and tested using imaging technologies that are directly translatable to the clinic. Longitudinal imaging of chronic diseases permits continuous monitoring of disease progression and response to treatment. Table 1 summarizes the advantages and limitations of imaging technologies commonly used in studies of small-animal models of infectious diseases.

Parasitic Infections

Chagas Disease

Trypanosoma cruzi is the causative agent of Chagas disease, a neglected tropical disease, endemic to Latin America, and is being diagnosed in nonendemic areas as a result of immigration.[1] Cardiac manifestations of Chagas disease include acute myocarditis and chronic dilated cardiomyopathy, accompanied by congestive heart failure, arrhythmias, cardioembolism, and stroke.[2] Approximately 30% of infected individuals develop chronic manifestations, including cardiomyopathy, megasyndromes of the gastrointestinal tract, or both. MRI and echocardiography have been useful in the diagnosis of patients infected with *T. cruzi*.[3–5] An extensive review of advances in imaging animals infected with *T. cruzi* has recently been published.[6] Herein, we will focus on the mouse model that has been extensively studied using a variety of imaging modalities, including MRI, echocardiography, and PET imaging using [18F]-FDG.[7–14]

MRI has been most useful for evaluating the right ventricle of mice (Figure 1), which is difficult to visualize with standard echocardiography,[8,12,14] whereas echocardiography has been effective for evaluating left ventricular function.[7,13,15] SPECT imaging has been applied in human studies[16]; however, it has not been reported in animal studies. On the other hand, PET studies have only been reported in the animal model of *T. cruzi* infection (Figure 1). [^{18}F]-FDG-PET has detected changes in glucose metabolism, presumably due to inflammation, early during the course of *T. cruzi* infection and before significant changes in heart structure or function are detected.[13] Infection can also result in loss of smooth muscle tone and destruction of ganglia throughout the bowel and bladder, resulting in megasyndromes of the esophagus, colon, intestines, and bladder, accompanied by severe constipation, difficulty swallowing, and malnutrition (Figure 1).[17] MRI[18–20] and X-ray methods[21,22] have been useful for studying these organs in mice and for evaluating therapeutic strategies. For example, by using MRI, we demonstrated that the administration of the calcium channel blocker, verapamil, early (but not late) in the murine infection reduces the infection-associated increase in right ventricular internal diameter.[15,23] Treatment of infected mice with an endothelin-converting enzyme inhibitor also reduced right ventricular internal diameter, thus illustrating the role of endothelin in the pathogenesis of *T. cruzi*–induced cardiomyopathy.[24] MRI of the mouse model has also demonstrated a loss of adipose tissue, which is consistent with increased expression of enzymes associated with lipolysis.[25]

African Trypanosomiasis

Another neglected tropical disease (World Health Organization classification) is human African trypanosomiasis (HAT) or sleeping sickness. HAT is a parasitic disease transmitted by the tsetse fly that continues to be an important cause of human morbidity and mortality in sub-Saharan Africa due, in part, to armed conflicts resulting in population shifts. HAT is caused by infection with *Trypanosoma brucei rhodesiense* (East Africa) or *T. brucei gambiense* (West Africa). East African disease is actually a zoonosis among game animals, and humans become the accidental host. Disease progression is rapid, with early invasion of the central nervous system (CNS), and, if untreated, death occurs within 9 months. The Gambian type is a chronic disease, with invasion of the CNS occurring late, with a variety

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