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Review Article

Hylonome

Multi-modality imaging of musculoskeletal disease in small animals

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Micro X-ray computed tomography (MicroCT) is an established *in vitro* imaging modality in the field of musculoskeletal research. The high degree of contrast between mineralized tissue and soft tissue, combined with the ability to produce high resolution, volumetric data sets, make CT particularly well suited to bone imaging applications. MicroCT has been used extensively to examine the architecture of excised bone specimens derived from small rodent models to study: bone development, disease, and the efficacy of therapeutics. More recently, there has been a growing interest to study physiology and function in small rodent models of disease through the use of multiple non-invasive imaging modalities. Techniques such as magnetic resonance (MR), single photon emission computed tomography (SPECT), and positron emission tomography (PET) have the potential for translation to human studies of bone disease. Over the past several years, there has been significant development of dedicated instruments for small animal imaging applications in the modalities of: MR, SPECT, PET, dynamic-CT, and deep tissue, *in vivo* optical imaging.

MR is a single imaging modality capable of: high resolution, cellular imaging, spectroscopy, and quantifying metabolic function. While MR is a versatile imaging modality, SPECT and PET are functional imaging modalities that allow for molecular specific imaging in deep tissues of nano- and pico- molar quantities, respectively. SPECT is a readily available technique for which there are a wide number of nuclear tracers available that enable bench-top chemistry and molecular imaging. PET is a quantitative modality with high sensitivity, imaging trace amounts (pico-molar concentrations) of radio-labeled molecules. PET is most widely used to study metabolism through the labeling of glucose with fluorine-18, which has a half-life of 20 minutes. The differential uptake of glucose by tissues is used to study relative metabolic activity. Dynamic CT (DCT) is a novel technique used to study physiological parameters in tissue: perfusion, permeability, and blood flow. Unlike MicroCT where a single, high resolution data set is acquired, DCT acquires a series of lower resolution CT data sets. An injectable contrast agent (iodine) is administered as a bolus arterial injection. A series of CT images are acquired imaging the wash-in, and wash-out of contrast. Through the use of a two compartment kinetic model of the exchange of material from the vascular space to the interstitial space, quantitative maps of blood flow, tissue permeability, and perfusion may be derived. Though the perfusion of bone is largely unexplored through the use of DCT, it is particularly well suited to DCT due to the relatively long transit time of blood flow in bone. Finally, advancements in deep tissue techniques for optical imaging have enabled the labeling and tracking of: receptors, biochemical pathways, and cells in small animals. Osteoblasts have been labeled and imaged in an *in vivo* model of mouse bone disease. This technique is particularly useful in gaining further insight into the mechanisms of bone remodeling beyond simple measures of bone density.

Non-invasive imaging is an emerging tool in the study of bone disease. Through the use of multiple imaging modalities it is possible to study anatomy, physiology, and function in an *in vivo* model. Established clinical and novel pre-clinical imaging techniques have been used to study: cell function, cell trafficking, tissue metabolism, and blood flow. These non-invasive imaging studies further add to the understanding of the mechanisms and kinetics involved in bone remodeling in small animal models of disease, and have significant potential for translation to human studies.

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