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Imaging Theme Issue

MINI-REVIEW

Preclinical Magnetic Resonance Imaging and Systems Biology in Cancer Research

Current Applications and Challenges

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Biologically accurate mouse models of human cancer have become important tools for the study of human disease. The anatomical location of various target organs, such as brain, pancreas, and prostate, makes determination of disease status difficult. Imaging modalities, such as magnetic resonance imaging, can greatly enhance diagnosis, and longitudinal imaging of tumor progression is an important source of experimental data. Even in models where the tumors arise in areas that permit visual determination of tumorigenesis, longitudinal anatomical and functional imaging can enhance the scope of studies by facilitating the assessment of biological alterations, (such as changes in angiogenesis, metabolism, cellular invasion) as well as tissue perfusion and diffusion. One of the challenges in preclinical imaging is the development of infrastructural platforms required for integrating *in vivo* imaging and therapeutic response data with *ex vivo* pathological and molecular data using a more systems-based multiscale modeling approach. Further challenges exist in integrating these data for computational modeling to better understand the pathobiology of cancer and to better affect its cure. We review the current applications of preclinical imaging and discuss the implications of applying functional imaging to visualize cancer progression and treatment. Finally, we provide new data from an ongoing preclinical drug study demonstrating how multiscale modeling can lead to a more comprehensive understanding of cancer biology and therapy. *(Am J Pathol 2013, 182: 312—318; http://dx.doi.org/10.1016/j.ajpath.2012.09.024)*

The extensive pharmacological studies that have been aimed at developing and testing new anti-neoplastic compounds have clearly established the need for both highly accurate preclinical models, as well as the methods to longitudinally assess therapeutic response. These translational studies have

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driven significant technological advances in both anatomical and functional imaging and have resulted in the engineering of small animal imaging platforms, including luminescence, fluorescence, positron emission tomography, and magnetic resonance imaging (MRI). Currently, significant needs exist related to enhancing our ability to use quantitative anatomical, metabolic, and functional imaging, integrated into a systems approach to clinical medicine, to expand our understanding of cancer biology and to identify early markers of effective therapeutic intervention.

Mouse Models

Genetically engineered (GE) mice, since their introduction more than 30 years ago, have become increasingly important to our understanding of the interrelationship between genes, the organism, its environment, and the efficacy of new and existing treatment régimes. The early GE models were relatively simple, primarily relying on the integration of a promoter and transgene into the mouse genome, although technological advances such as inducible gene expression (eg, tetracycline, tamoxifen, or steroid hormones) and the Cre:LoxP gene ablation/modification systems have lead to more biologically relevant models with increased fidelity to the cellular and molecular basis for many human cancers.[1] In fact, the use of GE mice and xeno- and allo-grafting models have become the hallmark of translational platforms for the study of human cancers and their treatment.

Imaging

There are inherent difficulties associated with many GE models (eg, brain,[2] prostate,[3] and gastric[4]), as in humans, in identifying disease initiation, its progression, and its treatment without invasive surgery or sacrificing the animal. Preclinical imaging modalities have been developed to overcome these limitations and to enable longitudinal studies analogous to clinical imaging and trials. Two of these preclinical imaging modalities (ie, MRI and positron emission tomography) allow for functional and metabolic imaging. Importantly, MRI is unique in its ability to combine high resolution anatomical imaging with functional and metabolic analyses, making it one of the most flexible preclinical/clinical imaging platforms.

Need for Informatics and Systems Biology to Complete the Multiscale Investigational Platform in Cancer

Imaging data can both define the location of deep tissue tumors and provide data related to cancer progression and regression (response to therapy), because many longitudinal preclinical studies seek to combine *in vivo* imaging data with *ex vivo* pathology, as well as with genetic and molecular changes within the target tissue to quantify complex phenotypic traits. The complexity of the data generated, however, which by necessity must include those of the underlying model, requires cross-platform multiscale approaches. These platforms, by definition, must integrate the imaging data for a region of interest (eg, a tumor), which occurs at the organismal and macroscopic scales, with the data from the cellular or microscopic scale (eg, pathology, vascularity) and with data derived at the subcellular or molecular scale (eg, mRNA, proteomics, metabolomics). Currently, there are National Institutes of Health initiatives such as the cancer Biomedical Informatics Grid, and National Cancer Institute initiatives such as The Cancer Genome Atlas that seek to support the groundwork collaborations between cancer imaging laboratories and molecular and bioinformatics/bioengineering groups that are needed to develop these capabilities. Additional innovations, such as the Georgetown Database of Cancer (G-DOC), a systems medicine data integration, analysis, and visualization platform,[5] will eventually allow for real-time data analysis. These bioinformatics platforms will allow for correlative data comparisons, such as those available from The Cancer Genome Atlas, and for target validation, as well as for predictive modeling of tumors and their responses to intervention.

In this review, recent advances in the use of MRI in preclinical cancer research are highlighted, and we discuss and give an example of the central role that MRI combined with systems biology can fulfill in imaging-based preclinical studies.

Tumor Imaging

Ultrasound and Computed Tomography

Many outstanding imaging modalities exist for anatomical imaging (eg, ultrasound was one of the earliest translations of human imaging into preclinical modeling). Ultrasound provides a rapid and sensitive method for the identification of changes in skin architecture, volumetric analyses of surface tumors, such as xenografted human cancer cells, oncogene-induced changes in the mammary gland before palpable tumors arise,[6] and vascular blood flow by Doppler. Ultrasound is limited to some extent by its depth of imaging, its dynamic range, and its lack of contrast in some tissues, and also by its inability to perform functional and metabolic imaging. Similarly, computed tomography is widely used in both clinical and preclinical settings and provides extremely high resolution anatomical imaging, however, the use of computed tomography is limited in its metabolic and functional imaging as a stand-alone modality. Furthermore, computed tomography involves ionizing radiation exposure necessitating judicious use in both research and diagnostic settings.

MRI

MRI has long been used for anatomical imaging to allow the visualization of changes that occur during disease progression. In addition, magnetic resonance-based chemical imaging using hyperpolarized carbon-14 has shown great promise in visualizing alterations in tissue pH[7] and cellular redox activity,[8] and proton magnetic resonance spectroscopy (^{1}H-MRS) is a rapidly developing field of discovery,