

I2 Imaging: Cancer Biology and the Tumor Microenvironment

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Abstract

The use of imaging techniques to understand the role of the tumor microenvironment in cancer progression was the topic of a National Cancer Institute (NCI)-sponsored think tank entitled "I2 Imaging: Cancer Biology and the Tumor Microenvironment," held in Alexandria, Virginia on June 8 to 10, 2006. Participants discussed both recent progress in the use of imaging to dissect cellular and molecular interactions within the tumor microenvironment and the challenges that remain. Recommendations made to the NCI included (a) holding an annual meeting at which biologists, clinicians, and imaging scientists could exchange data, facilitating new collaborations within this multidisciplinary field; (b) funding both research and training specifically designed to foster a cross-disciplinary focus; (c) creating and making available a variety of resources to interested investigators, such as a repository of stromal cells and extracellular matrix molecules; and (d) taking steps to encourage translation of the basic research findings into the clinic. (Cancer Res 2006; 66(23): 11097-9)

Introduction

The effect of imaging on cancer research, both basic and clinical, has increased sharply in recent years. The greatest effect has come from the development of techniques to image chemical and functional as well as anatomic properties, but development of new imaging modalities, improvements in resolution (spatial, temporal, and chemical), and the availability of a wider range of imaging agents have also been important. Over the same period, and in part because of improved imaging capabilities, it has become clear that characterizing the cells and molecules that make up the tumor microenvironment, and the functional interactions among them is critical both to understanding tumor initiation and progression, and to developing and evaluating targeted agents for cancer prevention and treatment. Making the best use of the capabilities that imaging provides requires seamless integration of imaging scientists, cancer biologists, and clinicians; yet, the integration of these diverse disciplines poses challenges. Even within the imaging community, integrating physicists, chemists, and instrument designers with experts in cancer has been difficult. To determine how best to promote the effective integration of imaging and cancer biology, the National Cancer Institute (NCI) held a think tank entitled "I2 Imaging: Cancer Biology and the Tumor Microenvironment." The meeting was held in Alexandria, Virginia on June 8 to 10, 2006.

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The think tank was organized as part of the NCI's Integration and Implementation (I2) program in Imaging. I2 Imaging is a trans-NCI effort to identify novel imaging-based projects with the potential for high payoff in cancer research. One of the areas of emphasis within I2 Imaging is facilitating cancer biology studies of the tumor microenvironment. As a part of this effort, this think tank brought together imaging scientists, cancer biologists, and oncologists to recommend a course of action to the NCI. Discussions were organized around imaging needs in two major cancers: breast and lung. Characterization of the tumor microenvironment is more advanced in the breast, and imaging has played a significant part in studies done to date. In contrast, there have been few studies of the stromal composition of normal lung or lung cancer tissue and, in addition, imaging of the lung at the high resolution needed for microenvironment studies is difficult. Thus, these two cancers served to highlight the different opportunities and challenges in imaging the tumor microenvironment. The think tank began with overview presentations on the lung by Burton Dickey, the breast by Kornelia Polyak, and imaging by Robert Gillies. Each of the participants then gave a brief description of their research interests. This was followed by a series of structured discussions, culminating in a series of recommendations.

Scientific Opportunities and Challenges in Imaging the Tumor Microenvironment

The tumor microenvironment depends on the composition, functional interactions, and three-dimensional arrangement of its components, and these all change over time. Only imaging techniques can simultaneously reveal spatial relationships and functional activity (e.g., gene and protein expression, post-translational protein modifications, and enzyme activity) and potentially do so *in vivo*, noninvasively, over time. The accomplishments and ongoing research interests of the think tank participants illustrate both what can be learned about the tumor microenvironment from state-of-the-art imaging studies and the challenges that remain.

The challenges that remain in imaging the tumor microenvironment can be divided into those for basic and those for clinical research, albeit with some overlap. For basic research, some issues of access are of concern. Technologically sophisticated facilities for small animal imaging have become more common, in part due to the Small Animal Imaging Resource Program funded by NCI. The regional facilities that exist offer at least potential access for all investigators. As more cancer biologists, however, become aware of what imaging can do for their research, equipment access may become a serious limitation. Each of the different imaging modalities has strengths and weaknesses, and close collaboration between cancer biologist and imagers is needed to select the best imaging device and molecular probe to answer the question.

There are general methodologic limitations of current techniques for *in vivo* imaging that are especially problematic for tumor microenvironment studies because of the number of components that must be distinguished in high resolution. Improved methods are needed for targeting imaging probes within the body, getting probes inside cells, and simultaneously probing a large number of targets. For optical imaging, better near-IR probes and advances in instrumentation are needed to permit imaging tumor development at other than s.c. sites. Optical imaging, both basic and clinical, also requires more sophisticated image analysis software. Basic and clinical research share a need for reliable and better validated probes for complex physiologic processes. For example, there are a number of probes for imaging different aspects of hypoxia with different levels of chemical, spatial, and temporal resolution; yet, proliferation cannot be measured in real time.

Many processes central to tumor microenvironment research cannot be imaged in any meaningful way at present. Few probes exist for intracellular signaling processes crucial to cell communication. Stromal activation, including myofibroblast development and changes in local matrix components, cannot be assessed. Inflammation is known to play a role in tumor initiation and progression, but it is a very complex process, and no single marker will sufficiently characterize its role. Although activation of nuclear factor- κ B is a general indicator of inflammation, inflammation probably has fundamentally different effects on tumor progression depending on the leukocyte cell types that predominate and the concentrations and gradients of chemokines and cytokines. Inflammation is only one factor in the tumor microenvironment that demands the development of a very large set of probes for cell-type and differentiation-specific imaging. Dr. Polyak's pioneering work isolating and characterizing different types of cells present in normal and tumor stroma in the breast shows that there is enormous heterogeneity among stromal cells, even within a single tissue. Imaging probes are needed to assess the existence of these many cell types *in situ* and to determine their contribution to the tumor microenvironment. Better methods to follow cellular trafficking, both locally within the tumor microenvironment and to and from distant sites, would be useful for addressing many questions, including metastasis and the influx of mesenchymal stem cells. Finally, to permit realistic mathematical modeling of tumor microenvironment processes, it is important that imaging studies yield reliable quantitative kinetic measurements of every cell, molecule, and process that is probed.

For clinical imaging, the use of molecular and cellular probes of the tumor microenvironment may lead to general improvements in the ability to detect and characterize tumors in patients and improve the ability to assess prognosis and response to therapy. For the two tumor types discussed at the think tank, current imaging techniques require substantial improvements in sensitivity and specificity. Tumor microenvironment studies offer the potential to distinguish tumors from granulomas, better define tumor margins, detect micrometastases, and identify those small tumors with the highest potential to become clinically significant. Clinical imaging needs magnetic resonance imaging probes of higher relaxivity to improve resolution and optical probes to enhance the limited range of endogenous fluorescence. This would be useful in bronchoscopic examination of the lung, among other applications. Other issues specific to lung imaging are the limited resolution available for some modalities because of breathing-

related movement and the difficulty of detecting tumors bronchoscopically in distal areas. Clinical imaging may improve if better methods are developed for integrating the information obtained from multiple imaging modalities.

Recommendations

The meeting participants were asked to recommend ways in which the NCI could facilitate progress in this important area. Some of the recommendations were general to the field, whereas others were specific either to basic biology or clinical issues. Many of the general recommendations, unsurprisingly for a fundamentally multidisciplinary field, involved ways to break down natural and artificial barriers between scientists in different disciplines, facilitating both communication and research. The natural barrier to collaboration between imaging scientists and biologists or clinicians is a lack of appreciation of the challenges and opportunities in the respective fields. The participants considered this meeting, which was organized to address this issue, to be a good first step. They recommended that the effort be extended to an annual meeting on imaging the tumor microenvironment. It was felt that this meeting could either stand on its own or be a satellite of any of several ongoing annual meetings. Although the NCI could support the meeting, at least in part, it could be cosponsored by one or more of the relevant professional societies. They further recommended that the Tumor Microenvironment Network (TMEN), which will be established this year as a result of an NCI RFA to be reviewed in July 2006, serve as a nucleus to facilitate interactions with interested scientists well beyond the groups funded through the RFA. A focus on imaging within TMEN was encouraged.

Beyond communication, the NCI was encouraged to devise more incentives for multidisciplinary research projects. The anticipated ability to submit R01 grant applications with multiple Principal Investigators, now in pilot phase but expected to be opened to unsolicited grant applications soon, was considered a great opportunity for equal partnership between imaging scientists and either biologists or oncologists. How well this opportunity will be realized will depend on how such applications fare in review in NIH Study Sections, where multidisciplinary expertise and orientation is not always present. Considering the challenges inherent in truly multidisciplinary research projects, it was recommended that reviewers be encouraged to give special consideration to such projects. The NCI was encouraged to consider offering funding opportunities for pilot collaborations in the area of imaging the microenvironment, which could result in particularly strong multi-PI applications in the future. A few such studies have been initiated within the basic science-oriented Division of Cancer Biology (DCB) through a supplement program entitled Activities to Promote Research Collaborations. This program funds collaborations between a DCB grantee and one or more collaborators, who need not be supported by DCB and must bring a fundamentally different expertise to the collaboration. Consideration of a similar program, but targeted to imaging of the microenvironment, was encouraged.

Beyond research grants, the participants recommended that the NCI encourage multidisciplinary research at the level of training. Training grants that explicitly involved multiple mentors from different departments and disciplines would be one way to develop a cadre of investigators with a multidisciplinary orientation. Special efforts were recommended to attract young chemists to imaging studies. Their expertise is essential to imaging probe development,

and in most chemistry departments, there is currently little incentive to address applied biological problems. Exchanges of individuals between laboratories in different disciplines relevant to imaging the microenvironment was encouraged, not only at the trainee level, but for established investigators through NCI support of sabbaticals, which are rarely funded any longer by research institutions.

Beyond increasing the potential for funding multidisciplinary research, participants interested in preclinical or clinical applications of imaging to studies of the tumor microenvironment made recommendations specific to their areas of research. For preclinical research, a repository of available stromal cells and extracellular matrix molecules derived from both tumors and normal tissues, along with antibodies and other reagents for identifying subsets or relevant molecules and cells, would greatly facilitate research generally. In addition, by lowering the expertise and resource barriers necessary to enter this field, it would encourage the involvement of needed experts from other disciplines, including imaging. Similarly, ongoing NCI efforts to facilitate access of researchers to human tissue have considerable potential to facilitate both preclinical and clinical studies directly relevant to human cancer. For preclinical studies, animal models, particularly genetically engineered mice, are a crucial resource. The NCI-funded Mouse Models of Human Cancer Consortium (MMHCC) has greatly expanded the number of mouse models available and supports a repository that distributes many of these mouse strains free. Although these developments provide useful new resources, the rapid expansion of models and approaches to using them led participants who are not experts in this field to express a level of frustration with information overload. Selecting the best model for

their research is difficult even with the extensive information available on the MMHCC web site, leading to the recommendation that some mechanism be established to guide non-experts through the selection of an optimal animal model for a particular project.

In clinical research, imaging has the potential to provide non-invasive biomarkers for prevention, early detection, and response to treatment. There are barriers to realizing this potential that NCI may help to overcome. Promising new imaging probes can be developed in the laboratory, but lack of support for studies such as pharmacodynamics and pharmacokinetics, which are necessary to bring them into the clinic, often limits progress. In addition, clinical imaging improvements frequently require participation of the pharmaceutical and device industries, but marketing considerations provide limited incentives to such participation. The meeting attendees suggested NCI to consider funding mechanisms to bring industry into collaborations at the appropriate stage. One possibility suggested was an R21/R33-like (Phased Innovation Award) grant, which would have a first phase involving laboratory research in an academic setting. Upon achievement of specified milestones, a second phase of support would begin in which an industry collaborator would participate. Meeting participants also generally encouraged NCI to strengthen the role of imaging in Specialized Programs of Research Excellence grants as a means of facilitating translation of potential advances in imaging into the clinic.

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