Meeting Report

Epithelial-Stromal Interactions and Tumor Progression: Meeting Summary and Future Directions

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Abstract

The Epithelial-Stromal Interactions Workshop was organized with the purpose of accelerating progress in understanding the interrelationship between tumor cells and their microenvironment and applying this knowledge to the control of tumor progression. The format of the meeting was the presentation of brief reports that focused on concepts rather than specifics, with extensive discussion periods to identify the issues and barriers hindering progress in this area. This report summarizes the findings of this meeting, highlighting the intimate relationship between tumor cells and their environment and addressing the opportunities that manipulation of host-tumor interactions has for therapeutic intervention. Several specific recommendations are made to advance knowledge and progress in this field.

Workshop Synopsis

The Epithelial-Stromal Interactions Workshop started with overviews of models currently used to study the tumor microenvironment. G. Cunha (University of California, San Francisco, CA) described experiments in which the recombination of prostatic epithelial and stromal components in the immunoprotected kidney capsule revealed that tumor stroma can induce permanent changes in epithelial cells that recapitulate the tumor phenotype (further information is found in Ref. 1). The dramatic changes in angiogenesis, extracellular matrix, and stromal proteases in response to keratinocytes at different stages of tumor progression were highlighted by N. Fusenig (German Cancer Research Center, Heidelberg, Germany) using a matrix-inserted surface transplantation model in nude mice (2). The profound effects of the microenvironment on tumor cells was brought home by experiments described by I. J. Fidler (M. D. Anderson Cancer Center, Houston, TX) in which properties such as tumor growth, metastasis, angiogenesis, and drug resistance were influenced by the “soil” in which the tumor “seed” was planted (3). M. J. Bissell (Lawrence Berkeley National Laboratory, Berkeley, CA) demonstrated using a three-dimensional culture system that the modulation of surface receptors, including those for the extracellular matrix, can provide signals that can revert malignant mammary epithelial cells to a normal morphology and behavior (4). This session reinforced the often overlooked notion that a tumor is an organ, composed of multiple cell types and a structural framework that are intimately connected and interdependent. The dramatic influence of the stroma on tumor cells, at least those at an early stage of tumor progression, provides an opportunity to target these normal stromal cells to control the malignant behavior of genetically unstable cells that become rapidly resistant to standard therapeutic strategies.

The second session was chaired by J. Brugge (Harvard University, Cambridge, MA) and focused on molecules used by epithelial cells to sense their environment. Cell adhesion molecules, including integrins (V. Quarra; Scripps Research Institute, La Jolla, CA), cadherins and the associated catenins (A. Reynolds; Vanderbilt University, Nashville, TN), and selectins (A. Varki; University of California, San Diego, CA), were highlighted. The influence of these molecules on properties relevant to tumor progression, including cellular growth, death, differentiation, and migration, was apparent from experimental results using in vitro and in vivo model systems (5–7). Tumor cells find themselves in different environments as they progress from an epithelial monolayer to a connective tissue context during invasion, to the dynamic environment of the blood stream after intravasation, and finally to the context of the organ representing the site of metastasis. Each of these changes influences cell-cell and cell-matrix interactions sensed by cell adhesion molecules and represents a potential opportunity for therapeutic intervention. In addition to the biochemical signals normally associated with communication between an epithelial cell and its environment, D. Ingber (Harvard University) stressed the importance of structural components in the environment that influence cell shape and tension. He demonstrated that mechanosensing of the environment plays a critical role in regulating properties such as cell migration and growth in tumors and during normal developmental processes (8). This session increased the appreciation for the complexity of the signal transduction pathways received by an epithelial cell from its environment, which influences its physiological state.

The third session was chaired by L. Chung (University of Virginia, Charlottesville, VA) and described soluble molecules that play a role in the response of a tumor cell to its microenvironment. Factors such as fibroblast growth factor (N. Greenberg; Baylor University, Houston, TX), transforming growth factors α and β (C. Arteaga; Vanderbilt University, Nashville, TN), and agonists and antagonists of the Wnt signaling pathway [S. Aaronson; (Mt. Sinai Medical Center, New York, NY and J. Rubin, (National Cancer Institute, Bethesda, MD)] were demonstrated to alter cellular properties relevant to tumor progression in both in vitro and in vivo model systems (9–11). In addition, the contribution of enzymes produced by inflammatory cells to the tumor progression process was demonstrated in a transgenic model of squamous cell carcinoma by L. Cossens (University of California, San Francisco, CA). In this example, the metalloproteinase MMP-93 was demonstrated to influence the number of tumors and grades (12), potentially through an effect on the release of

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1 This workshop was held from September 13–15, 2000 at the Bethesda Marriott Hotel in Bethesda, MD. It was organized by L. M. M., G. R. C., and S. M. and supported by the National Cancer Institute, Division of Cancer Biology, Tumor Biology and Metastasis Branch. In addition to the organizers, the meeting attendees included Drs. Stuart A. Aaronson, Carlos L. Arteaga, Mina J. Bissell, Joan S. Brugge, Leland W. K. Chung, Lisa Coussens, Isaiah J. Fidler, Norbert E. Fusenig, Norman M. Greenberg, Meenhard Herlyn, Donald E. Ingber, Rakesh K. Jain, Robert S. Kerbel, Lance A. Liotta, Vito Quaranta, A. Hari Reddi, Albert B. Reynolds, Ekklu Ruosluhti, Jeffrey S. Rubin, Neeraja Sathyamoorthy, Ajit Varki, Lalage Wakefield, and Bruce R. Zetter.

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3 The abbreviation used is: MMP, matrix metalloproteinase.
factors stored by the extracellular matrix (13). The complexity of the stromal milieu, which includes soluble factors and insoluble matrix-associated molecules, was appreciated in this session, as was the need to define and understand individual signaling pathways and the cross-talk between multiple pathways that impact tumor development and progression.

The third recommendation is to develop better models for the study of stromal contributions to tumor progression and to assist in the dissemination of these models to the cancer research community. The Mouse Models Consortium is viewed as an excellent model for a host-tumor interactions and tumor progression. Studies focused on the identification and characterization of stromal components and analysis of their normal interrelationships and interactions with tumor cells should be encouraged. Specific topics on which additional studies are required are detailed in Table 1. To achieve this goal, funding for investigator-initiated proposals (e.g., R01, R21, and so forth) could be enhanced through institute-supported initiatives (e.g., Program Announcements). The advantage of interdisciplinary approaches and collaborative research focused on host-tumor interactions was recognized. In particular, interaction between investigators with expertise in pertinent reductionist systems and those with relevant interaction between investigators with expertise in pertinent reductionist systems and those with relevant

Conclusions

This workshop generated enormous excitement over the potential for reward that could be gained by a greater understanding of the influence that the tumor microenvironment exerts on malignant epithelial cells. It is clear that the stroma is an integral part of the tumor and that it contributes to some of the most destructive characteristics of malignant cells. It is provocative that, at least under some conditions, the stroma can exert a dominant force over the malignant phenotype. Cancer research over the past decade has been focused largely on events occurring within the boundaries of the plasma membrane of the cancer cell. Understanding the genetic aberrations that occur during tumor progression and elucidating the details of the molecular pathways that are altered as a result of these aberrations have resulted in a revolutionary change in the approach to therapeutic intervention. A similar focus on understanding the events that occur outside the plasma membrane but influence the behavior of the cancer cell have an equal, if not greater, potential for therapeutic benefit as a result of the genetic stability of the cellular components and the accessibility of the molecular targets. Manipulating host-tumor interactions has the potential of reverting the malignant phenotype and establishing normal control mechanisms.

There are many barriers to understanding the contribution of the stroma to the tumor phenotype. Stroma is remarkably complex and consists of molecular, mechanical, and cellular components. The extracellular matrix is composed of proteins, glycoproteins, proteoglycans, and glycosaminoglycans in a complex arrangement that provides structure, generates biological signals, stores factors that generate biological signals, and exerts mechanical influences on an epithelial cell. Cellular components that influence a tumor cell include other epithelial cells, fibroblasts, inflammatory cells, and endothelial cells, each of which represents a heterogeneous population of cellular phenotypes. The stroma has spatial and temporal complexity: it is organ specific and heterogeneous within and between tumors and changes with time and with the progression of the malignant epithelial cell. The specific molecules that are responsible for tumor-induced changes in the microenvironment and the reciprocal modifications of the tumor by the microenvironment are largely unknown, as are the intracellular pathways that result from these influences. Dissecting the components of the stroma requires model systems in which a single variable can be manipulated and assessed. Cellular, molecular, and mechanical aspects of the stroma need to be able to be studied in systems that are simple enough to be understood yet complex enough to mimic human cancer. There have been significant advances in mouse genetic models, but few have attempted to alter stromal components with these models. Time and financial constraints negatively impact the routine use of mouse models. In vitro studies are complicated by changes in behavior and gene expression when cells are removed from their native environment. Highly sophisticated in vitro models have been developed but are not easily exported to other investigators. Finally, it is not clear that any of the existing models provide predictive information on the efficacy of small molecules for human clinical trials. Thus, realizing the potential of manipulating host-tumor interactions for the benefit of the cancer patient will require a considerable investment to overcome these obstacles.

Recommendations

Several recommendations resulted from this workshop. The first arose from the realization that the molecular revolution that has so markedly benefited cancer research prompted a reductionist approach to cancer and a lack of appreciation for much of the early literature that demonstrates the influence of host factors on tumor progression. The recommendation was made to compile a compendium of classic papers that provide evidence supporting this point. The compendium should be updated regularly to include important recent papers that illustrate important concepts and model systems in which to dissect the contribution of specific stromal elements to tumorigenicity and progression. This information should be easily and widely accessible, making a web-based format particularly appealing.

The second recommendation is to increase the pool of investigators contributing to an understanding of epithelial-stromal interactions in tumor progression. Studies focused on the identification and characterization of stromal components and analysis of their normal interrelationships and interactions with tumor cells should be encouraged. Specific topics on which additional studies are required are detailed in Table 1. To achieve this goal, funding for investigator-initiated proposals (e.g., R01, R21, and so forth) could be enhanced through institute-supported initiatives (e.g., Program Announcements). The advantage of interdisciplinary approaches and collaborative research focused on host-tumor interactions was recognized. In particular, interaction between investigators with expertise in pertinent reductionist systems and those with relevant in vivo models to study stromal-epithelial interactions and tumor progression should be encouraged. Mechanisms such as supplemental applications to encourage research collaborations are recommended to facilitate the necessary interactions. Finally, an increased appreciation for the contribution of stroma to tumor progression by investigators, and in particular by study section members, needs to be achieved. The inclusion of sessions devoted to the tumor microenvironment at major scientific meetings, special meetings on the topic, and workshops associated with study section meetings are highly encouraged.

The third recommendation is to develop better models for the study of stromal contributions to tumor progression and to assist in the dissemination of these models to the cancer research community. The Mouse Models Consortium is viewed as an excellent model for a mechanism by which this goal can be accomplished. A Host-Tumor
Table 1 Areas of investigation recommended for increased funding

<table>
<thead>
<tr>
<th>Characterization of stromal components</th>
<th>Normal cellular response to the microenvironment</th>
<th>Tumor response to the microenvironment</th>
<th>Genetic studies</th>
<th>Detection and treatment</th>
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<tr>
<td>Structure/function studies on the molecular components of normal and tumor stroma</td>
<td>Influence of mechanical forces on the biology of normal cells</td>
<td>Influence of stromal components on tumor cell growth, death, differentiation, and migration for different tumor types</td>
<td>Support for studies that identify genetic alterations in stromal cells and lineage development</td>
<td>Improved technology for the in vivo imaging of tumors to follow changes in the microenvironment</td>
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<tr>
<td>Molecular markers to define the cellular components of organ-specific stroma in both human and mouse</td>
<td>The wound healing response</td>
<td>The nature of the inductive signals that produce tumor stroma</td>
<td>Support for mapping mouse genes that modify tumor development through the stroma</td>
<td>Support for studies on the relevance of stromal factors in drug delivery</td>
</tr>
<tr>
<td>Improved technology to reliably isolate and characterize organ-specific stromal cell populations</td>
<td>Genomic and proteomic technologies to profile changes in the stroma at various stages of tumor progression</td>
<td>Influence of mechanical forces on the biology of tumor cells</td>
<td>Support for the development of assays that can be used to screen small molecule drugs for modulation of epithelial-stromal interactions</td>
<td>Support for the development of in vitro and in vivo model systems</td>
</tr>
<tr>
<td>Genomic and proteomic technologies to profile changes in the stroma at various stages of tumor progression</td>
<td>Molecular mechanisms underlying the induction of epithelial cell and mesenchymal cell lineages</td>
<td>The relationship between wound healing and the tumor stromal response</td>
<td>Development of assays that can be used to screen small molecule drugs for modulation of epithelial-stromal interactions</td>
<td>Detection and treatment of stromal components</td>
</tr>
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Interaction Consortium devoted to the development of both in vitro and in vivo model systems is recommended. To initiate planning of a consortium, a series of think tank meetings are recommended to identify specific subtopics and working groups that would be essential for the effective development of appropriate in vivo and in vitro models. Input from investigators involved in diverse fields, including developmental biology, biophysics, engineering, systems analysis, and so forth should be included in the development of the consortium. Attention should be paid to the need to develop in vivo models that mimic spontaneous development of tumors such as that seen in the human population (autochthonous models), models in which the natural history and metastatic spread of the tumor mimics that seen in humans, and, importantly, models of in situ (preinvasive) disease, which has become a prevalent form of several human tumors and one in which treatment interventions are likely to have their highest impact. Mechanisms to assess the relevance of model systems to human cancer need to be established. Mechanisms should be developed to facilitate accessibility to genetically manipulated mice useful for this purpose and to increase the feasibility of their generation and use by a solution to the burden of the extensive use of mouse models. In addition to animal models, more in vitro, organotypic cultures systems need to be developed, facilitated by interaction with investigators in the tissue engineering field. For dissemination of models to the cancer research community, a series of workshops should be sponsored that provide hands-on training in robust models that are currently available for the study of stromal influences on neoplasia. Web sites should be developed to facilitate the rapid dissemination of new models and refinements of existing systems.

Summation

In summary, this workshop represented a heightening of awareness of the opportunities available to make significant advances in controlling cancer through the manipulation of tumor context. The message of the intimate relationship between the tumor cell and the stroma and its crucial contribution to tumor development and progression needs to be brought to the forefront of cancer research, and significant effort needs to be placed on expanding our knowledge of the molecular mechanisms that underlie these interactions. Current indications with antiangiogenesis therapies suggest that the approach of targeting genetically stable components of a tumor has exciting potential for significant advances in therapeutic intervention. With appropriate investments, it is likely that a fertile new territory can be rapidly charted and harnessed for the treatment and management of cancer.

References

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