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PROSPECTS

Tumor Microenvironment

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It is my privilege to be the Guest Editor of this special edition of the Journal of Cellular Biochemistry Prospects Series focused on the "Tumor Microenvironment."

It is now well recognized that complex intrinsic and extrinsic influences transform a normal epithelial cell into a malignant one. Enormous advances have been made over the last several decades in identifying the molecular and genetic changes associated with this malignant transformation. This has led to the identification of oncogenes and tumor suppressor genes and associated signaling mechanisms that modulate growth, survival, and proliferation. These studies have generated novel therapeutic reagents such as tamoxifen, herceptin, and gleevec, all of which target the cancer cell.

Recent research on tumor–host interactions collectively reveals that: (a) tumors are not masses of autonomous cells but function like organs composed of many interdependent cell types that contribute to tumor development and metastasis, (b) the interactions between the tumors and their microenvironments are bidirectional and dynamic, and (c) the tumor and its stroma co-evolve during tumor initiation and progression. The microenvironment is composed of stromal cells that include fibroblasts, immune and inflammatory cells, adipocytes, glial cells, smooth muscle cells, and resident and recruited vascular cells. It also includes the extracellular matrix, growth factors/cytokines, and other proteins produced locally and/or systemically. Microbial flora may also be present in the microenvironment.

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The National Cancer Institute (NCI) has been an active proponent in stimulating research in the area of tumor–host interactions for over a decade and issued its first RFA in 1994 entitled "The Role of Tumor Microenvironment in Breast and Prostate Cancer." Tumor microenvironment is an area of high research priority at the NCI for the last few years. The NCI has supported a number of workshops, think tanks, and initiatives related to this area of science. The scientific workshops, starting in 2001, were organized around specific areas and the summaries of the workshops and their recommendations were shared with the cancer community at large, through publications. The range of topics included (a) specific cancer sites such as the Prostate [Cress and Mohla, 2004], Head and Neck [Grandis et al., 2004], Skin Melanoma [Herlyn et al., 2001], and Bone Metastasis [Reddi et al., 2003]; (b) tumor microenvironment-aspects of cancer biology such as Lymphangiogenesis [Alitalo et al., 2004], Fibrin Turnover in Lung Inflammation and Neoplasia [Idell et al., 2001], Epithelial–Stromal Interactions and Tumor Progression [Matrisian et al., 2001], Extracellular Proteolysis and Cancer [Matrisian et al., 2003], Shifting Paradigms in Tumor Metastasis [Parsons et al., 2002], Inflammation [Peek et al., 2005], and Imaging [Sloane et al., 2006].

In 2003, the Division of Cancer Biology sponsored a series of Think Tanks, with topics that spanned the entire spectrum of cancer biology (the cancer initiation-progression-metastasis continuum); the goal being to identify emerging themes, anticipate research needs and facilitate progress in those areas. Nine Think Tanks including tumor microenvironment, inflammation, tumor stem cells, cancer etiology, tumor immunology, and systems biology were organized. One of the major overarching themes that emerged was the critical need to fully characterize the microenvironment of normal and

tumor tissues. It was also recommended that the NCI establish a network, which would facilitate development of resources (3D models, imaging agents, validated reagents, and stromal cell markers) and make them available to the research community at large. A report summarizing the recommendations of the think tank was published [Sogn et al., 2005].

In response to think tank recommendations, the NCI made a concerted effort in supporting a number of research and training initiatives, focusing on tumor–host interactions. An RFA on "Molecular Interactions between Tumor Cells and Bone" was issued in 2003. Two initiatives, (a) Applications for Competing Supplements to Develop and Use Organotypic Models of Cancer, and (b) Competing supplements for equipment request to support studies on tumor microenvironment, were issued in 2002 and 2003. In 2005, the NCI established a new training program, "New NCI-Sponsored Tumor Microenvironment Training Program: Techniques in the Establishment and Manipulation of Organotypic Model Systems." So far, approximately 75 NCI-funded investigators have spent up to 3 weeks in one of six "expert" laboratories that were identified and have learned to establish organotypic models in their own laboratories. In 2006, the NCI issued an RFA for establishing the Tumor Microenvironment Network (TMEN). Ten institutions, each with their own Research Program, are currently part of the TMEN. The names of the Principal Investigators and overviews of their Research Programs can be viewed at the newly created TMEN Website: http://dcb.nci.nih.gov//branchdetail.cfm?branch=36.

In response to the recommendations made by experts at a recently held workshop, "I2 Imaging: cancer biology and the tumor microenvironment," [Sloane et al., 2006], *the NCI, in partnership with the American Association for Cancer Research*, has started a new program which allows a week-long intensive course on in vivo and live cell imaging techniques specifically for cancer biologists. Postdoctoral fellows and early career-level faculty in fields related to basic cancer biology are the target audience. A total of 16 participants will be selected to participate the first year, to be held at Duke Center for In Vivo Microscopy, Durham, NC, June 24–29, 2007. (http://cip.nci.nih.gov/cip/pdfs/CancerResearchImagingCampBrochure.pdf)

Novel paradigms governing tumor–host interactions are presented in this volume. These include: (a) the consideration that tumor is not a mass of autonomous malignant cells but is more like an "organ" with its repertoire of cells, matrix, vasculature and immune cells, growth factors, and other secreted molecules, (b) the emerging roles of carcinoma-associated fibroblasts, and bone marrow-derived cells, (c) tumor stem cells and the role of the stem cell niche, (d) inflammation as a key mediator of tumorigenesis, (e) the role lymphangiogenesis in tumor dissemination, (f) the "normalization" of tumor vasculature as a potential therapeutic strategy, and (g) novel strategies to target tumor stroma. Overall, I hope this volume will provide the readers a helpful overview of current status of research in tumor microenvironment, emerging research and translational opportunities, and the current therapeutic strategies to target the tumor stroma. New information resulting from research in this area may generate strategies to alter the tumor microenvironment, which either kills the tumor cells or renders them benign. A more complete understanding of tumor–host interactions may also provide unique opportunities for chemoprevention.

This Special Edition of the Journal provides 13 comprehensive prospects written by leading experts encompassing several aspects of the tumor microenvironment.

Li, Fan, and Houghton provide an overview of stromal cells in cancer. They discuss the role and origin of carcinoma-associated fibroblasts, the significance of bone marrow-derived cells, stromal immune cells, and vascular cells in cancer initiation and progression, as well as the therapeutic potential of targeting tumor stroma.

Tse and Kalluri's review provides an elegant discussion on the many different signaling mechanisms that encourage epithelial to mesenchymal transition (EMT), the importance of EMT in tumor dissemination, progression, and metastasis. They analyze the relevance of mesenchymal to epithelial transition (MET) in the formation of metastatic tumors, and provide a rational argument for targeting these pathways to control metastasis.

Radisky, Kenny, and Bissell's review offers a critical insight on the origin of tumor-associated myofibroblasts. Using multiple experimental models of fibrosis and cancer, they discuss the possible origin of these cells through transdif-

ferentiation of non-malignant or malignant epithelial cells by EMT. Their review highlights the critical role played by matrix metalloproteinases (MMPS) and reactive oxygen species (ROS) in this process, resulting in a dynamic change in the tumor microenvironment, and raising the possibility that targeting epithelial-myofibroblast transdifferentiation pathway has therapeutic potential.

In their discussion on tumor–lymphatic interactions, Wong and Hynes provide an analysis of the complex dynamics involving tumor cells, lymphatic endothelial cells, and non-endothelial stromal cells and how critical interactions between these components in the tumor microenvironment influence tumor lymphatics as well as metastasis of tumor cells to the lymph nodes.

Stover, Bierie, and Moses analyze the role of TGF-β signaling in the tumor microenvironment and its impact on tumor carcinoma initiation, progression, and metastasis. They discuss the role of epithelial cell autonomous TGF-β signaling and its regulation of cancer initiation and progression in several experimental models and in human carcinoma.

Lee and Herlyn elucidate on the molecular mechanisms that contribute to melanoma progression, the role of a variety of stromal cells present in the skin microenvironment, the importance of hypoxia and intra-tumoral hypoxic regions in melanoma progression. They describe novel experimental models to study melanoma within a microenvironmental platform and their translational potential.

Morrissey and Vessella present a comprehensive overview of interactions between prostate tumor cells and the cells of the bone stroma, resulting in reactive stroma in the bone and bone metastasis. They dissect key events that permit interactions between the prostate tumor cells and bone, focusing on various growth factors and cytokines signaling pathways that eventually result in the colonization of bone as osteoblastic and osteolytic lesions. The authors introduce the concept of dormancy and survival of prostate cancer cells in the bone marrow.

Chu et al. present an in-depth review of the stromal biology of pancreatic cancer and describe the role of pancreatic stroma in the progression of pancreatic cancer, with special emphasis on the role of inflammation and its functional consequences. They delineate challenges and research opportunities in understanding pancreatic stromal biology and discuss potential therapeutic targets in pancreatic cancer.

Postovit et al. compare and contrast normal pluripotent stem cells with the stem cell-like functions of aggressive human melanoma cells, and discuss how embryonic microenvironment, through epigenetic reprogramming can reprogram cancer cells, may be a potential differentiation therapeutic strategy.

Johansson and co-workers focus on the molecular mechanisms underlying interactions between immune cells and evolving neoplastic cells that regulate cancer outcome in a model of skin cancer. Their review highlights the critical need to study the adaptive and innate immunity that regulate cancer development.

In their review on the role of the organ microenvironment in the biology and therapy of cancer metastasis, Fidler, Kim, and Langley discuss the "seed and soil" hypothesis and the models being used to study cancer metastasis. They discuss the invasive phenotype and tumor angiogenesis that is supported by the organ microenvironment. They provide a critique on a number of clinically relevant issues such as regulation of responses to chemotherapy and targeting bone metastasis of prostate cancer using antivascular therapy.

Fukumura and Jain delineate various phenotypic changes that dramatically alter this system as compared to the normal tissue vasculature. Proliferating tumor cells produce solid stress, which compresses blood as well as lymphatic vessels, causing vessel leakiness, lack of functional lymphatics, and an overall increase in interstitial fluid pressure in solid tumors. These events are a significant barrier to the delivery of therapeutics, and hypoxia and acidosis in solid tumors make radiation and chemotherapy less effective. The authors suggest a novel strategy that "normalizes" abnormal tumor vasculature, thus making these vessels more responsive to therapeutics. They also discuss successful clinical trials using the vessel "normalization" strategy.

Mitsiades and co-workers provide an elegant overview of the interaction of multiple myeloma (MM) cells with the normal cells of the bone milieu, which decreases the effectiveness of conventional therapies. They discuss these interactions both at the cellular and molecular levels, and detail their efforts in designing novel clinical therapeutics, including the proteasome

inhibitors, and thalidomide, which specifically targets the interactions between the MM and the bone marrow.

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