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The tumor microenvironment: The connective tissue/tumor cell/host organ system that modulates tumor progression

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It is now widely accepted that both reciprocal, direct physical interactions as well as receptor mediated signaling interplay between tumor cells, host cells, and their surrounding extracellular matrices constitute a unique organ system that defines the “tumor microenvironment.” This concept had its origins in the “seed and soil” hypothesis of Stephen Paget to describe the distribution of tumor metastasis, but has been more recently emphasized by the work of I. J. Fidler and colleagues who demonstrated the importance of orthotopic influence on the behavior of primary tumors in animal models. This new knowledge reveals increasing levels of complexity as our understanding of the influence of extracellular matrix structure and composition, as well as tumor/host cell-matrix interactions on tumor progression and patient outcome continues.

This Special Issue of the journal presents a series of original research articles, and comprehensive reviews, that emphasize an exciting sampling of emerging areas of research on the tumor microenvironment. The articles have been organized into general themes. These themes divide the special issue into three sections: 1) the mechanobiology of the extracellular matrix in tumor progression; 2) the influence of connective tissue composition on tumor growth and progression; and, 3) the role of host-tumor cell interactions in modulating the tumor microenvironment and metastatic niche.

Theme one focuses on tumor growth causing host tissue deformation that results in accumulation of solid stresses with profound effects on the mechanobiology of the tumor microenvironment that may promote malignant progression. In an original article for Section 1, Pirentis and colleagues develop a mathematical model of tumor growth to distinguish stress generation by tumor structural components and collagen fiber remodeling and then use an *in vivo* orthotopic breast cancer system to generate experimental data to test the fitness of their model. Their data emphasize the importance of matrix stresses in defining the peritumoral organization of the extracellular matrix.

As stated above, the second theme focuses on the composition of the tumor connective tissue and the influence of select extracellular matrix components on tumor behavior, and, Section 2 consists of two original articles and one review on this subject. One of the critical issues often encountered in researching the contributions of extracellular components of the tumor microenvironment to neoplastic behavior is the source of the molecule(s) of interest, i.e. tumor vs. host. In an original contribution utilizing cutting edge experiments with patient-derived xenografts (PDX), Pinessi et al. examine the relative contributions of stroma and tumor cell-derived thrombospondin-1, a major extracellular matrix regulator of cell-matrix interactions that is often deregulated in cancer. This work clearly demonstrates the

utility of the PDX model to investigate the relative contributions of tumor versus stroma for production of important elements of the tumor microenvironment.

The second article in Section 2 is an original contribution by Klauzinska et al. on the multifunctional, embryonic protein Cripto-1. The authors describe unique ELISA-based assays for screening small molecule modifiers of Cripto-1 function, Cripto-1 binding partners, as well as competitive quantification of Cripto-1 levels and identification of anti-Cripto-1 autoantibodies in cancer patient plasma. This important contribution demonstrates the utilization of novel experimental tools that can facilitate identification of factors in the tumor microenvironment with potential for therapeutic drug development.

The third article in Section 2 shifts the focus to an important element of the host response that has received much attention as a potential therapeutic target, namely, angiogenesis. In a brilliant and comprehensive review, Douglass and colleagues describe one of the key constituents of the tumor microenvironment, the sizeable heparan sulfate proteoglycan perlecan and the C-terminal fragment known as endorepellin which demonstrates potent anti-angiogenic activity. The authors rigorously describe the genetics of perlecan as well as the detailed downstream signaling events related to the anti-angiogenic activity of endorepellin. The authors also cautiously explore the potential prognostic and diagnostic uses for specific domains of endorepellin.

Theme three of this issue emphasizes the role of cell-matrix and cell-cell-matrix interactions on the development of the tumor microenvironment, and, is the focus of one original contribution and two review articles. The first contribution in this section expands on the theme of angiogenesis to address the central mechanisms involved in the formation of capillary networks in a three-dimensional extracellular matrix. The authors describe the essential role of well known extracellular matrix factors, such as interleukin-3, stromal-derived factor-1 α , platelet-derived growth factor (PDGF), etc., in pericyte tube co-assembly and basement membrane organization.

Tumor metastasis is the definition of malignant cancer for epithelial neoplasia. Recent findings demonstrate that a process critical for the spread of tumor cells from the primary site is the epithelial-mesenchymal transition (EMT). The second contribution in the section on Theme 3 of this edition is a review by Banyard and Bielenberg that provides an extensive overview of this process in cancer metastasis, as well as the associated reverse process, mesenchymal-epithelial transition that is associated with the expansion of metastatic foci. The authors compare and contrast the contribution of these processes to hematologic dissemination versus lymphatic spread of cancer. In addition, the review presents emerging data on the “hot” topic of exosomes during the development of the pre-metastatic niche.

Finally, this Special Issue of *Connective Tissue Research* concludes with a comprehensive summary and synthesis of the current concepts of cancer stem cells or cancer initiating cells. In particular, one of the most difficult concepts concerning the treatment of human cancer, tumor heterogeneity is discussed. In this article, Albini and colleagues review the possible networking activities between the different components of the extracellular matrix, and, the variation in matrix composition between tissues in the tumor microenvironments as well as

their influence on tumor behavior and progression. Despite the complexities that these interactions present for cancer therapy, the authors conclude with a summary of novel therapeutic strategies for the prevention of metastasis and disease recurrence.

Very sincere thanks to the authors for their thoughtful, high quality and scholarly contributions to this Special Issue of *Connective Tissue Research*. My gratitude also goes to the reviewers who contributed their time and expertise thereby helping to make this exciting and stimulating assemblage of articles possible.

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Guest Editor of this Special Issue

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