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PREFACE

The Tumor Stromal Microenvironment as Modulator of Malignant Behavior

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It has been argued that tumors are not masses of proliferating cells in an isolated environment, but rather "wounds that do not heal" due to the molecular and cellular similarities between chronic wound repair and the reaction of carcinomas [1]. This proposal suggests that understanding both the local and systemic molecular and cellular mechanisms that mediate a sustained chronic wound healing microenvironment may be important in understanding how the tumor microenvironment promotes tumor progression and metastasis, and even how to improve anti-cancer treatments.

The complex stromal reaction that occurs during cancer growth and in response to therapy involves many different cell types and tissue systems, including inflammatory and immune cells, fibroblasts, myofibroblasts, endothelial cells, lymphatic endothelial cells, and various bone marrow-derived progenitor cells [2]. While some accounts depict this stromal reaction as a response to a persistent secretion of growth factors and cytokines produced by carcinoma cells, it may be that a pre-malignant cellular or tissue injury elicits a local inflammatory and acute wound healing reaction, or results in an altered stromal composition, thereby initiating transformed epithelial cell proliferation and expansion. Furthermore, since tumor cells have a genetically-unstable background, the various types of factors and cytokines released by such cells might lead to or maintain an altered chronic wound healing environment that further perpetuates a reactive stroma, leading to enhanced tumor progression and even metastasis.

While the signaling pathways responsible for the behavior of malignant carcinoma cells have been the primary focus of cancer research and therapeutic resistance over the last three decades, the reactions of the microenvironment to invading cancer cells are less defined and deserve much more attention. In addition to fibroblasts, other cell types such as immune cells and endothelial cells react with tumor cells to either enhance or repress their growth capabilities. It is unclear if the transformed epithelium directs the reactive stroma to promote tumor growth, or if the stromal reaction due to events such as injury, chronic inflammation or radiation exposure is the trigger that promotes cancer growth.

Within the last 2 decades, much has been elucidated regarding the role and some of the mechanisms by which stromal cells regulate carcinoma cell growth in established tumors. However, there remains a great deal to be learned regarding the role of distinct cellular compartments during early stages of breast cancer formation and the progression to metastasis. For example, it is well-established that ionizing radiation is a carcinogen in animal models and humans. In this issue, Barcellos-Hoff [3] discusses recent data from women treated with radiation therapy and its effect on stromal-epithelial interactions as a determinant for subsequent cancer development. Experimental evidence demonstrating that radiation alters the composition of the stroma in animal models prior to the development of cancer is linked to changes in the fate of the epithelium and ultimately the biology and behavior of the tumor phenotype.

Cichon et al. [4] also focus on the role of the microenvironment during early pre-malignant changes and

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the role of various cell types and enzyme activities in early in situ breast cancer. Not only has it been challenging to identify the mechanisms by which changes in the stroma might influence the progression of the disease, but significant evidence reveals that changes in the stromal cells might even precede frank disease progression. These authors highlight the roles and changes observed within myoepithelial cells, fibroblasts and matrix proteases during the transition between DCIS and invasive breast cancer, underscoring the need for further studies into the mechanisms and complex heterotypic interactions between epithelium and stromal cell crosstalk in the early stages of breast cancer.

Disruption of tissue integrity and inflammation have long been known to instigate the proliferative outgrowth of local tumor cells or circulating dormant cells through stimulation by local cytokines/chemokines produced by recruited neutrophils and other inflammatory cells [5]. A less well-studied, but equally important, role of acute and chronic inflammation is one in which the vasculature reacts and remodels to accommodate cell recruitment and the formation of granulation tissue. This process can, in principle, be co-opted as an "angiogenic switch", a rate limiting step for tumor formation [6], and the promotion of tumor growth and expansion.

During chronic wound healing, inflammation, and even cancer growth, bone marrow-derived myofibroblasts, fibroblasts, endothelial cells and other non-hematopoietic cells are recruited to these sites, and contribute to the wounded vasculature and tumor stroma [7–9]. The bone marrow provides a continual source of precursor cells, where these hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) possess multilineage differentiation potential to generate various monocytic and mesenchymal lineages that differentiate into endothelial, fibroblastic, and dendritic cell types. El-Haibi and Karnoub [10] review the role that differentiated bone marrow-derived cells play in the biology of cancer and in the promotion of metastatic dissemination and even in the formation of a stromal niche necessary for the seeding and formation of secondary tumors. These cell types not only govern complex interactions within the local tissue but also with the systemic circulatory system. Factors released at the local site of the tumor stroma act systemically to alter bone marrow biology and the cellular constituents of the peripheral circulation. This ultimately leads to further recruitment of specialized cell types to the microenvironmental stroma. In principle, however, the biological responses in bone marrow and the changes in circulating cell types might also affect other tissues in the host that are not directly involved in tumor growth; this, in turn, might prime otherwise non-hospitable microenvironments for the seeding and/or outgrowth of carcinoma cells.

The important role of the tumor stromal microenvironment as a key instigator as well as a key regulator of malignant growth is clearly established. Since the stroma represents a population of heterogeneous but genomically-stable cells, this offers the possibility of understanding and predicting the response of stromal cells to anti-cancer therapies. This in turn might promise to enhance the effects of chemo- or radiation therapy. Indeed Shiao and Coussens [11] describe the effects of chemotherapy and radiation therapy on altering the tumor microenvironment and highlight recent discoveries on how immune responses may be exploited to improve the effects of therapy.

The different cell types and tissue systems that interact in normal tissues reinforce the notion that complex heterotypic interactions must also be essential for cancer progression. While normal tissues inhibit the development of cancer, tumor tissue stroma promotes and also accelerates the development of cancer [12]. Demonstrations that normal stroma can repress tumor growth imply that a reactive stroma would have to be damaged or altered in some fashion to permit outgrowth of a malignant cell. This does not, however, exclude the possibility that the malignant epithelium alters its environment to create favorable growth conditions. In the future, combination therapies treating not only the epithelium, but also the tumor stroma and associated local and systemic wound healing processes will be necessary to successfully treat cancer. Rather than thinking about cancer as a result of individually transformed cells, considering cancer from a tissue perspective, and taking advantage of all the local and distally-recruited participants will ultimately be the future in understanding and treating the disease.

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