GUEST EDITORIAL

Involvement of the Tumor Microenvironment in the Pathogenesis of Breast Cancer

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Breast cancer is the leading cancer diagnosis and cause of cancer death among women worldwide, resulting in enormous health and economic burdens.^{1,2} Breast cancer is also a highly biologically heterogeneous group of diseases, originating from uncontrolled cellular growth of the glandular tissue of the breast. Because of this heterogeneity, patient outcomes vary and are largely driven by subtype-specific biology and treatment approaches.

The mammary ductal epithelium is composed of luminal epithelial cells surrounded by a layer of myoepithelial cells, which provide structural support and contractile properties and separate the ductal structure from the stromal tissue. The stromal tissue consists of extracellular matrix and various cells such as fibroblasts, adipocytes, and immune cells. Ductal breast cancer arises because of uncontrolled proliferation of the luminal epithelial cells, leading to carcinoma *in situ*, which can progress to invasive and metastatic breast cancer. The progression of *in situ* cancer to invasive cancer involves the breakdown of the myoepithelial cell layer and migration of malignant luminal epithelial cells into the stroma, resulting in invasive carcinoma.

Much research effort has been put into understanding the molecular drivers of the invasive process, and the data point to a key role for the tumor microenvironment.³ One of the earliest studies to examine gene expression changes in breast cancer tissues identified expression changes distinct to each stage of breast cancer progression and among the stromal and epithelial cell types. This study found that the transition from *in situ* to invasive cancer involves changes to transcripts encoding proteins involved in remodeling the extracellular matrix, invasion, and cell migration.⁴ Other studies have identified significant epigenetic alterations in cells of the tumor microenvironment, resulting in aberrant gene expression changes.⁵ Furthermore, distinct gene expression signatures derived from the tumor microenvironment are predictive of clinical

outcomes in breast cancer patients.⁶ Recent integrated transcriptomic and genomic studies of early breast cancer progression have established signatures that are unique to the intrinsic breast cancer subtypes; however, common among these signatures is the critical contribution of the microenvironment.⁷ Using mass spectrometry-based proteomic profiling of human cancers, the Clinical Proteomic Tumor Analysis Consortium reported the classification of five tissue-based cancer subtypes (breast, colon, ovarian, renal, and uterine) into 10 proteome subtypes of various tumor lineages. Two distinct subtypes involving the tumor stroma were identified, with approximately one-third of the breast cancers examined falling into these two subtypes.⁸ Taken together, these studies highlight the importance of stromal biology in our understanding of breast cancer biology, progression, and disease outcomes.

The breast tumor microenvironment can be divided into two main regions: the local environment, encompassing the tumor cells and surrounding stromal cells, such as myoepithelial cells, fibroblasts, immune cells, adipocytes, and endothelial cells; and the metastatic environment, which involves other cell types and tissues, such as vascular endothelial cells, lymph nodes, and other common sites of breast cancer metastases, including bone, brain, and lung.

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This Editorial introduces this month's special Tumor Microenvironment in Breast Cancer Theme Issue, a series of reviews on advances in our understanding of tumor microenvironment in breast cancer pathogenesis.

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This special theme issue of *The American Journal of Pathology* includes reviews covering major topics related to both the local and metastatic breast cancer microenvironment.

Dogra and Hannafon⁹ provide a comprehensive overview of the emerging role of extracellular vesicle-mediated communication by transfer of RNAs in the breast tumor microenvironment. This review discusses extracellular vesicle RNA transfer through homotypic interactions between tumor epithelial cells and heterotypic interactions involving tumor epithelial cells and other stromal cell types and how this signaling can promote oncogenic transformation, cancer progression, metastasis, and therapeutic resistance. Potential strategies for pharmacologic interventions aimed at these signaling mechanisms are also briefly discussed. Bernard and Wellberg¹⁰ provide a thoughtful review of the tumor promotional role of the adipocyte in breast cancer development and progression. As substantial evidence exists linking obesity with breast cancer incidence and poor prognosis and rates of obesity are steadily increasing, a better understanding of the biological contribution of obesity to breast cancer is critical to improving outcomes. This review describes what is currently known about how adipocytes and increased adiposity contribute to breast cancer progression within the local tumor environment and systemically. The authors also discuss the potential for the reversibility of the obesity-associated breast cancer effect and the limitations to such approaches. As the leading cause of breast cancer mortality is metastases, Jana et al¹¹ provide an important overview of the many ways that breast cancer cells modulate lymph node stromal and hemopoietic cells to evade the immune system and enhance both local and systemic metastasis. This review highlights an important, but perhaps underappreciated, role of lymph nodes in anti-tumor immunity and their involvement in the response to immunotherapy. Lastly, as new computational approaches emerge to evaluate the pathobiology of tumor microenvironments, Malherbe¹² provides an overview of the use of artificial intelligence and machine learning approaches combined with imaging to develop a better understanding of the tumor microenvironment for breast cancer detection and prognosis. How the integration of biomarkers, risk factors, and

imaging data may allow for better prediction models and improving patient-based outcomes is also discussed.

In summary, this collection of reviews provides a well-synthesized and broad overview of the current status of basic research, preclinical modeling, clinical observations, and novel computational approaches regarding the role of the tumor microenvironment in the pathogenesis of breast cancer.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A: Cancer statistics, 2021. *CA Cancer J Clin* 2021, 71:7–33
2. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A: Global cancer in women: burden and trends. *Cancer Epidemiol Biomarkers Prev* 2017, 26:444–457
3. Soysal SD, Tzankov A, Muenst SE: Role of the tumor microenvironment in breast cancer. *Pathobiology* 2015, 82:142–152
4. Abba MC, Drake JA, Hawkins KA, Hu YH, Sun HX, Notcovich C, Gaddis S, Sahin A, Baggerly K, Aldaz CM: Transcriptomic changes in human breast cancer progression as determined by serial analysis of gene expression. *Breast Cancer Res* 2004, 6:R499–R513
5. Hu M, Yao J, Cai L, Bachman KE, van den Brule F, Velculescu V, Polyak K: Distinct epigenetic changes in the stromal cells of breast cancers. *Nat Genet* 2005, 37:899–905
6. Finak G, Bertos N, Pepin F, Sadokova S, Souleimanova M, Zhao H, Chen H, Omeroglu G, Meterissian S, Omeroglu A, Hallett M, Park M: Stromal gene expression predicts clinical outcome in breast cancer. *Nat Med* 2008, 14:518–527
7. Lesurf R, Aure MR, Mork HH, Vitelli V; Oslo Breast Cancer Research Consortium (OSBREAC), Lundgren S, Borresen-Dale AL, Kristensen V, Warnberg F, Hallett M, Sorlie T: Molecular features of subtype-specific progression from ductal carcinoma in situ to invasive breast cancer. *Cell Rep* 2016, 16:1166–1179
8. Chen F, Chandrashekar DS, Varambally S, Creighton CJ: Pan-cancer molecular subtypes revealed by mass-spectrometry-based proteomic characterization of more than 500 human cancers. *Nat Commun* 2019, 10:5679
9. Dogra S, Hannafon BN: Breast cancer microenvironment cross talk through extracellular vesicle RNAs. *Am J Pathol* 2021, 191:1330–1341
10. Bernard JJ, Wellberg EA: The tumor promotional role of adipocytes in the breast cancer micro- and macro-environment. *Am J Pathol* 2021, 191:1342–1352
11. Jana S, Muscarella RA Jr, Jones D: The multifaceted effects of breast cancer on tumor draining lymph nodes. *Am J Pathol* 2021, 191:1353–1363
12. Malherbe K: Tumor microenvironment and the role of artificial intelligence in breast cancer detection and prognosis. *Am J Pathol* 2021, 191:1364–1373