Viewpoint

Location, location, location: regulation of breast cancer progression by the microenvironment

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Introduction

The majority of human breast cancers arise from the transformation of epithelial cells. Numerous oncogenic events, including gene amplification, loss, and mutation, have been described that confer a growth-promoting advantage to breast tumors. A classic example of this is the identification of HER-2 amplification in a subset of breast tumors, and the successful use of anti-HER-2 directed therapy in prolonging the survival of patients with breast tumors that have HER-2 amplification. This example clearly highlights the importance of understanding the genetic changes in breast epithelial cells that are associated with breast cancer progression. However, the focus on breast epithelial cell transformation has resulted in the development of several cancer models that ignore another major regulator of breast cancer progression, namely the stroma and microenvironment. Several recent reports from both global gene expression studies and mouse models indicate that the microenvironment may be a critical modulator of breast cancer progression. Given that the microenvironment tends to be more genetically stable than breast tumor cells, it is possible that breast cancer therapies aimed at the microenvironment are less likely to develop acquired resistance. Herein I will briefly highlight several recent papers that show the importance of the microenvironment in regulation of breast cancer progression.

Global gene expression studies

Global gene expression patterns have revealed distinct subtypes of breast cancer, and can predict metastasis and survival. The development of gene array technology has quickly evolved to allow analysis of very small specimens derived by laser capture microdissection or cell fractionation. This has given an invaluable view of the gene expression changes within specific cell types during breast cancer progression. In this regard, Allinen and colleagues [1] performed an exhaustive analysis of gene expression changes using serial analysis of gene expression (SAGE) on specific cell types (luminal epithelial, myoepithelial, endothelial, leukocytes, and myofibroblasts) during breast cancer progression. While luminal epithelial cells showed gene abnormalities (loss of heterozygosity) and expression changes during progression, the most dramatic changes in gene expression occurred in the myoepithelial cells. This was despite the fact that the myoepithelial cells showed no genomic alterations. Interestingly, the gene expression changes in the myoepithelial cells often included secreted proteins and receptors, suggesting a paracrine regulation of breast epithelial cells. To support this, Allinen and colleagues showed that chemokines that are highly upregulated in myoepithelial cells (CXCL12 and CXCL14) can bind breast tumor epithelial cells and regulate their proliferation, migration and invasion. Inhibition of CXCR4, the receptor for CXCL12, has been shown to prevent breast cancer metastasis [2], providing the opportunity for therapeutic targeting of the microenvironment with potentially less chance of acquired resistance.

Mouse models

Mammary gland biologists have long believed in the usefulness of their models for understanding breast cancer progression, but new, sophisticated genetic and molecular approaches are really bringing these models to the forefront.

Integrin receptors transmit signals from the microenvironment and extracellular matrix to breast epithelial cells. They have long been implicated in both normal mammary gland development and tumorigenesis, and blocking of β1-integrin can reverse the transformed phenotype of epithelial cells *in vitro* [3]. White and colleagues [4] have now used cre/lox recombination

NMU = N-nitroso-N-methylurea.

technology to disrupt β1-integrin expression in the mammary gland and examined mammary tumorigenesis. They showed that β1-integrin is required for transformation of the mammary gland by polyomavirus middle T oncogene. Importantly, not only was β1-integrin required for initial transformation of epithelial cells, but deletion of β1-integrin in tumor cells impaired their proliferation. This study clearly indicates a role for extracellular matrix and the microenvironment in regulation of breast tumor progression, and again highlights a possible therapeutic target in breast cancer.

Changes in the stroma may modulate breast cancer progression, and a recent report showed that N-Nitroso-N-methylurea (NMU)-induced carcinogenesis in the rat actually acts upon the stroma, rather than the epithelium, to promote mammary tumorigenesis. Here, Maffini and colleagues [5] used sophisticated mammary gland recombination studies to treat either the stroma or the epithelium with NMU, and found that NMU-treated epithelial cells formed perfectly normal mammary glands when implanted into normal untreated stroma. However, normal mammary epithelial cells implanted into NMU-treated stroma resulted in mammary tumor formation. This study clearly challenges the dogma that tumorigenesis results from accumulating genetic alterations in epithelial cells. In essence, however, these models all point to the fact that both genetic changes in epithelial cells and gene expression changes in the stroma play critical roles in breast tumor progression.

Conclusions

Global gene expression analysis has challenged several well accepted models of breast cancer progression. Major alterations in gene expression occur within the stroma that surrounds breast tumors and premalignant lesions, and these changes may better define breast tumor progression than changes found within the breast tumor epithelial cells themselves. Supporting this, several models now exist showing that the microenvironment can have a profound effect on breast cancer progression. In addition, recent evidence suggests that gene expression patterns within primary breast tumors can predict metastasis and survival, indicating that the potential for a tumor to metastasize may be encoded in the initial oncogenic mutations within the tumor. It is possible that the initial gene expression changes in breast epithelium may be insufficient on their own to promote breast cancer metastasis, and that additional changes in the microenvironment, such as in myoepithelial cells, may determine the ability of the tumor to invade and metastasize. This theory is supported by evidence that myoepithelial cells show tumor suppressor properties [6].

In the end, the competing theories about breast tumor progression (increasing mutation in epithelial cells or changes in the microenvironment) and metastasis (gained during cancer evolution or encoded in the initial oncogenic mutations) will probably all be combined into an integrated model of breast cancer progression. New *in vitro* and *in vivo* models that incorporate the role of the microenvironment in breast cancer progression will serve to test the hypotheses provided by the gene expression analysis of breast cancer, and may provide novel targets for therapeutic intervention.

Competing interests

The author(s) declare that they have no competing interests

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