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Epithelial-mesenchymal transition and its role in breast cancer metastasis

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Abstract:

Breast cancer is the most common cancer in women and distant site metastasis is the main cause of death in breast cancer patients. Epithelial-mesenchymal transition (EMT) is defined by the loss of epithelial characteristics and the acquisition of a mesenchymal phenotype. EMT is a vital process for large-scale cell movement during morphogenesis at the time of embryonic development. Tumor cells usurp this developmental program to execute the multi-step process of tumorigenesis and metastasis. Understanding the biological intricacies of the EMT may provide important insights that lead to the development of therapeutic targets in pre-invasive and invasive breast cancer, and could be used as biomarkers for identifying tumor subsets with greater chances of recurrence, metastasis, and therapeutic resistance leading to death. The purpose of this article is to investigate the association between EMT and breast cancer.

INTRODUCTION

Breast cancer is the most common cancer in women and ranks second among cancer deaths in women (1). Developing metastasis is the main cause of death in breast cancer patients (2). The intrinsic classification of Perou and Sorlie1, reported in 2000, distinguished four subtypes of breast cancer: luminal A and luminal B (expressing the estrogen receptor (ER)), basal-like and human epidermal growth factor receptor 2 (HER2)- enriched (without ER expression). Basal-like breast cancer cells are constitutively more invasive. In addition, HER2-enriched tumors are also more likely to develop metastatic disease (3). In 2018, an estimated 2.1 million women were newly diagnosed with breast cancer, approximately one new case diagnosed every 18 seconds; additionally, 626,679 women with breast cancer died (4).

The epithelial to mesenchymal transition (EMT) is a complex program in which epithelial cells acquire a mesenchymal phenotype and motility through a cascade of biological events (5). The EMT process involves the formation of motile cells from epithelial cells that are not themselves motile such as the mesenchymal cells (6). For almost two decades the prospect that recapitulation of the developmental process called epithelial to mesenchymal transition (EMT) may play an important role in carcinoma progression has been vigorously debated. The concept of EMT was developed in the field of embryology but has recently been extended to tumor progression and metastasis (7). There are three types of EMT programs; type 1 relates to embryogenesis, gastrulation, and neural crest formation; type 2 is related to tissue regeneration and wound healing; and type 3 is associated with malignancy, invasion, and metastasis (8). The first EMT event after implantation occurs at gastrulation when the embryonic layers are defined. The EMTs that are associated with implantation, embryo formation, and organ development are organized to generate diverse cell types that share common mesenchymal phenotypes. This class of EMTs neither causes fibrosis nor induces an invasive phenotype resulting in systemic spread via the circulation (8, 9). Type 2 EMT is represented by EMT re-engaged in the context of inflammation. It is associated with wound healing, tissue regeneration, and organ fibrosis. In this process, tissue fibroblasts are generated from epithelial or endothelial cells during injury and chronic inflammation (10). Type 3 EMTs occur in neoplastic cells that have previously undergone genetic and epigenetic changes, specifically in genes that favor clonal outgrowth and

the development of localized tumors. These changes, notably affecting oncogenes and tumor suppressor genes, conspire with the EMT regulatory circuitry to produce outcomes far different from those observed in the other two types of EMT (11). Type 3 EMT plays, in fact, a crucial role in the development process of localized tumors: the cancer cells convert to a mesenchymal phenotype to move to the invasive front of the tumors (12). Although these three types of EMT represent considerably different biological processes, some genetic elements and mechanisms of regulation may be similar and well conserved. Studies suggest that in some situations, following the migration of a cancer cell that has undergone EMT to a distant site, a reverse process of mesenchymal to epithelial transition (MET) occurs. The MET is a state when a mesenchymal tumor cell reverts to the epithelial phenotype, especially in distant metastatic sites (13).

Regulation of epithelial cell plasticity during EMT is increasingly implicated in the progression of carcinoma (14). Epithelial cells that undergo EMT lose their epithelial cell characteristics to acquire a mesenchymal phenotype and become migratory and invasive (15). The existence of EMT changes in clinical breast cancer places EMT at the center of malignancy. Because breast cancer is a heterogeneous disease in terms of tumor histology, clinical presentation, and response to therapy and because breast cancer-related deaths are primarily due to metastatic progression, a deeper understanding of the mechanisms that underlie the EMT program in breast tumors will lead to the development of better therapeutic strategies (16, 17).

Molecular mechanisms of epithelial to mesenchymal transition

The process of EMT requires the coordination of a complex network of extracellular and intracellular signals involving factors for initiation and feedback mechanisms for a continuum of changes that occur within cells during the transition from a less epithelial to a more mesenchymal phenotype (18). EMT can be induced during in vitro cell culture under the influence of extracellular matrix components and growth factors, such as scatter factor/hepatocyte growth factor, transforming growth factor-beta (TGFbeta), epithelial growth factor family members, insulin-like growth factors 1 and 2, and fibroblast growth factors (19). Hypoxia also induces EMT. The EMT is generally induced in epithelial cells by heterotypical signals, specifically those released by the mesenchymal cells that constitute the stroma of normal and neoplastic tissues. Signal transduction pathways such as Hedgehog, Wnt, Notch, and integrin signaling can also coordinate EMT programs. Several transcription factors induce EMT through transcriptional control of E-cadherin, including SNAI1 (zinc finger protein snail 1), SNAI2, ZEB1 (zinc finger E-box-binding homeobox 1), ZEB2, TWIST, FOXC1 (forkhead box protein 1), FOXC2, TCF3 (transcription factor 3 - also known as E47), and GSC (homeobox protein goosecoid) (20, 21).

Wnt pathway

The Wnt pathway plays a critical role in cell proliferation and oncogenesis. Beta-catenin is a downstream signaling molecule that is activated by WNT signaling (22). Beta-catenin has a dual role in EMT:

1.A bridge to enhance cell-cell adhesion when bound to cadherin complexes in adherens junctions

2.A transcription cofactor with DNA-binding proteins of the Tcell factor (TCF)/lymphoid enhancer factor (LEF) family (22, 23).

Therefore, beta-catenin is considered an appropriate and ideal target for studying the molecular basis of EMT and malignant cancer formation (24). The Wnt pathway and loss of E-cadherin from adherens junctions activate b-catenin, which in turn induces several EMT-inducing transcription factors as well, such as Slug, Twist1, and Goosecoid. The Wnt and tyrosine kinase receptor pathways also modulate Snail nuclear transport and degradation through GSK3b (25). Several up-regulated target genes of the Wnt/b-catenin signaling pathway, such as fibronectin4 and matrix metalloproteinase-7 (MMP-7), 5 are correlated with mesenchymal phenotype and invasiveness (26).

Notch signaling pathway

It is believed that the processes that govern the acquisition of EMT are stimulated and regulated by many stimuli, signal transduction pathways, and transcription factors. Recently, the Notch signal pathway has been found to be a key regulator in the induction of EMT (27). The notch signaling path has two important roles: 1. maintaining a balance between cell proliferation, differentiation, and apoptosis 2. Preservation of progenitor cell population and determination of cell fate (28). The Notch pathway is induced by and required for TGF-b-induced EMT and modulates the EMT process by activating the nuclear factor-kB (NF-kB) pathway or by modulating the activity of TGF-b signaling itself. Notch activation in endothelial cells results in phenotypic, morphological, and functional changes consistent with mesenchymal transformation. Notch signaling is initiated when a Notch ligand binds to an adjacent Notch receptor between two neighboring cells. In mammals, the Notch family consists of 4 transmembrane receptors (Notch-1-4) and 5 ligands [Delta-like protein (Delta-like) 1, Delta-like 3, Delta-like 4, protein jagged (Jagged) 1, and Jagged-2] (29, 30).

Hypoxia has received considerable attention as an inducer of tumor metastasis. Notch serves as a critical intermediate in conveying the hypoxic response

into EMT. Recent research shows that hypoxia-induced Jagged 2 promotes breast cancer metastasis and self-renewal of cancer stem-like cells (31).

Hedgehog signaling pathway

Hh signaling controls tissue construction and remodeling by regulating the viability and migratory activity of various types of Hh responsive progenitor cells. The Hh signaling pathway is considered to have a vital role in vertebrate development, the homeostatic process, and tumorigenesis. Recent studies have found that the Hh signaling pathway is abnormally activated in small cell lung, breast, prostate, colorectal and pancreatic cancer. Significantly, the Sonic Hh (Shh) signaling pathway has been shown to contribute to tumor metastasis by inducing EMT in breast cancer (32, 33).

The Hh protein family consists of Hh ligands (Sonic-SHH, Indian IHH, and Desert-DHH) which bind cell surface transmembrane receptor Patched (PTCH) (34). Upon activation, these molecules bind with the transmembrane receptor known as Patched1 (PTCH1). Binding-induced alteration in structural conformation of PTCH1 leads to release of Smoothened (SMO) which mediates downstream activation of GLI family. SHH-mediated activation of GLI1 induces Snail, a major driver of EMT in basal cell carcinoma21. Furthermore, GLI1 stimulates Snail, represses E-cadherin, and enhances nuclear translocation of β-catenin to induce EMT in skin cancers22. SHH-GLI1-Snail axis stimulates EMT in ovarian, pancreatic, and neuroendocrine cancers as well. However, the association of Hedgehog signaling with EMT markers needs further exploration in breast cancer. Hedgehog signaling mediates EMT during embryonic development as well as cancer metastasis. During mammary morphogenesis, the Hedgehog pathway acts as a key regulator in epithelial-mesenchymal interactions and tubule maturation (35, 36).

TGF-β Signaling

The most classical experimental model is the induction of EMT by TGF-β in epithelial cell culture. Upon TGF-β induction, the type II receptor (TGFR2) is activated and phosphorylates the type I receptor (TGFR1), thereby activating the Smad pathway and inducing EMT (37, 38).

EMT and Its Plasticity Features

Breast cancer originates from epithelial tissue, which includes the following features: intact tight and adherent junction and “sheet-like” morphology with apical-basal polarity. Mesenchymal cells are characterized by loosely associated cells and disorganized cellular layers that lack polarity and tight cell-to-cell adhesion proteins (39). The morphology of mesenchymal cells is better adapted to cell migration. EMT is typically characterized by the loss of epithelial cell adhesion protein E-cadherin and cytokeratins and the gain of mesenchymal-associated molecules N-cadherin, Vimentin, and fibronectin. The process is described as “cadherin switching”, i.e., down-regulation of E-cadherin and up-regulation of N-cadherin (40) (Figure 1).

EMT and Breast Cancer

Both classical histological and molecular subtyping of breast cancers have identified the impact of the EMT on breast cancer prognosis (41). Clinical-histologic studies of basal-like breast cancers show that they are among the most aggressive and deadly breast cancer subtypes, displaying a high metastatic ability associated with mesenchymal features (42). The metastatic process includes different steps through which tumor cells have to exit from the primary tumor evading the basement membrane and the surrounding tissue, enter the bloodstream or lymphatics, migrate to a distant site

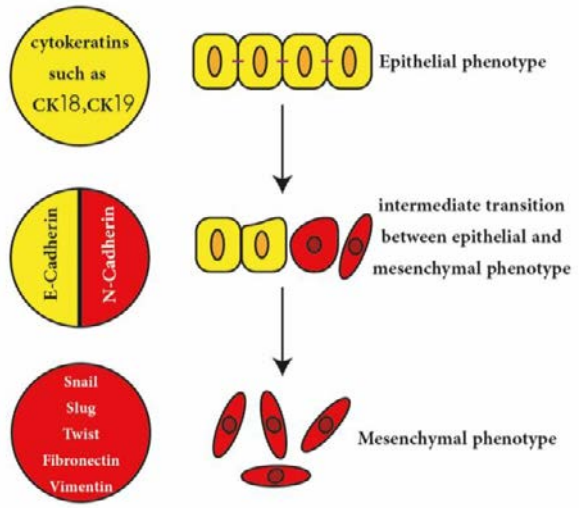

Figure 1. Schematic of the epithelial to mesenchymal transition (EMT).

and colonize to form metastasis. The other crucial step for metastasis is cancer dissemination, which involves circulating tumor cells (CTCs). Even the presence CTCs in the blood of metastatic breast cancer patients has been shown to be an independent predictor of progression-free survival and overall survival, the nature and the biological feature of these cells are still poorly understood (43).

Numerous mediators of EMT have been discovered, including transcription factors, signaling molecules, and microRNAs (miRNAs). A common theme among oncogenic EMT inducers is their crucial role in type I EMT. It has become increasingly evident that improper activation of developmental EMT inducers in adults gives rise to an out-of-context EMT-like program that contributes to the progression of breast cancer, as well as other cancers (44). A few examples of transcription factors and signaling pathways known to play a role in both type I and type III EMT include SIX1, Twist1 (TWIST1), Snail1 (SNAI1), and Ladybird homeobox (LBX1), and the Wnt and transforming growth factor-β (TGF-β) signaling pathways. Much of the evidence for a possible role of EMT in the progression of breast cancer has arisen from studies of in vitro culture of epithelial cell lines. However, EMT has largely been described as a cell culture phenomenon without direct clinical evidence or clear molecular markers in breast carcinoma (45, 46).

studies from Papadaki et al. and Kallergi et al. also detected EMT markers such as pan-cytokeratin, Twist, and Vimentin in CTCs from early and metastatic breast cancer patients. Although specific markers for CTCs still require validation within a larger clinical setting, current evidence supports the hypothesis that EMT is involved in the metastatic process in human breast cancer. However, due to the biological heterogeneity of CTCs, the technical difficulty still remains in the detection and isolation of CTCs (47, 48).

Biomarkers for EMT in breast cancer

A variety of biomarkers have been used to demonstrate EMT in breast cancer such as:

•E-cadherin: A change in the expression of E-cadherin is the typical epithelial cell marker of EMT. Suppression of E-cadherin function or expression leads to mesenchymal morphology and increased cell migration and invasion (49).

•Cluster of differentiation (CD) 44: a cell-surface protein that modulates cellular signaling by forming co-receptor complexes with various receptor tyrosine kinases. It plays an important role in the metastasis of breast cancer (50).

•Discoidin domain receptor 2 (DDR2): an atypical receptor tyrosine kinase. It is the collagen-specific receptor that reflects adaptation to the altered ECM microenvironment associated with the EMT. In breast cancer, DDR2 expression correlates with increased invasiveness, thus demonstrating its utility in identifying EMT (51).

•β-catenin: a cytoplasmic plaque protein that plays an important role in EMT (52).

•Vimentin: an intermediate filament that is used as a marker of mesenchymal cells to distinguish them from epithelial cells (53).

•α-smooth muscle actin (α-SMA): one of the six actin family members. Cells expressing α-SMA contribute to EMT in embryogenesis and to wound healing in normal epithelial cells. In cancer, evidence that the EMT is associated with α-SMA is mostly confined to breast cancer, where α-SMA is largely detected in breast tumors of the ‘basal phenotype’ (54).

MicroRNAs

miRNAs are an evolutionarily conserved class of small non-coding RNAs that control gene expression by targeting mRNAs by binding to the 31-untranslated region (3′UTR), leading to reduced translation of proteins, or degradation of the target mRNAs (55). MicroRNAs (miRNAs) have recently been described as crucial regulators of EMT and metastasis. The most frequently cited EMT-related miRNAs are those belonging to the miR-200 family, which consists of miR-200a/b/c, miR-141, and miR-429 (56). The miR-200 family, which suppresses EMT drivers ZEB1 and ZEB2, is selectively expressed in the sarcomatous component of metaplastic breast cancers. Furthermore, overexpression of miR-29a suppressed the expression of tristetraprolin, a regulator of epithelial polarity and metastasis, and led to EMT and metastasis in cooperation with oncogenic Ras signaling. Another miRNA involved in breast cancer metastasis and invasion in the context of the EMT is miR-10b. miR-10b is associated with mesenchymal features and invasive properties in breast cancer when overexpressed, through translational inhibition of HOXD10 (transcription factor associated with Wilms tumor) and upregulation of RHOC protein levels, enabling matrix extracellular degradation. miR-506, which is a novel miRNA, was found to be significantly related to breast cancer patient survival. It suppressed the expression of mesenchymal markers in the MDA-MB-231 human breast cancer cell line (57, 58).

These powerful programmatic regulators are poised to become important predictive/prognostic markers (59).

CONCLUSION

This review summarizes the evidence for the growing implication of EMT in the progression of breast carcinoma. EMT is a complex, stepwise phenomenon that occurs during embryonic development and tumor progression and involves major reprogramming

of gene expression that leads to alterations in cell fate and behavior. During the EMT, tumor cells acquire invasive traits through overexpression, mutation, or amplification of oncogenes and also repression of tumor suppressors, leading to the aberrant expression of signaling pathways. Validating biomarkers related to EMT in patient models will be highly crucial for identifying patients at risk of developing drug resistance and metastasis. In closing, it is indisputable that studies related to oncogenic EMT have critically contributed to, and will continue to contribute to, our understanding of the most devastating aspect of breast cancer and metastatic dissemination (60).

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