

ATRA and EMT-Related Proteins in Breast Cancer

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The knowledge of the structure, function, and abundance of specific proteins related to the EMT process is essential for developing effective diagnostic approaches to cancer with the perspective of diagnosis and therapy of malignancies. The success of all-trans retinoic acid (ATRA) differentiation therapy in acute promyelocytic leukemia has stimulated studies in the treatment of other tumors with ATRA.

breast cancer

EMT

protein

ATRA

1. Introduction

In the last two decades, the total number of people diagnosed with cancer has almost doubled, from an estimated 10 million in 2000 to 19.3 million in 2020. Today, every 5 people around the world suffer from cancer during their lifetime. Cancer deaths have also increased, from 6.2 million in 2000 to 10 million in 2020. More than one in six deaths is caused by cancer. Breast cancer has now overtaken lung cancer as the world's most commonly diagnosed cancer, according to statistics released by the International Agency for Research on Cancer (IARC) in December 2020 ^[1]. Approximately 1 in 8 women (13%) will be diagnosed with invasive breast cancer during their lifetime, and 1 in 39 women (3%) will die of breast cancer ^[2]. That's why there is a growing need to learn about this disease as much as possible and the need to seek new and more effective drugs. In addition, breast cancer usually does not cause any symptoms if the tumor is small and is easiest to treat. Therefore, early cancer detection is essential for an accurate diagnosis to reduce the possibility of metastasis and relapse. The use of up-to-date analytical proteomic techniques, especially current chromatographic or electrophoretic separation methods together with mass spectrometry (MS), and the development of new analytical strategies is critical for the characterization of cancer cells and especially for identifying new diagnostic and prognostic biomarkers, which have mainly protein characters. The prominent role of proteomics is to identify biomarkers for early cancer screening and predict therapeutic response ^{[3][4][5]}.

Retinoids, the group of vitamin A derivatives, are currently receiving considerable attention because their properties predispose it to become an anticancer agent, as confirmed by the growing body of evidence highlighting the compound's anticancer activity. All-trans retinoic acid (ATRA) is administered orally in the first-line treatment of acute promyelocytic leukemia (APL) ^[6] in adults and neuroblastoma (NB) in children ^[7]. As the promising results obtained in these diseases have not yet translated to the solid tumor clinic, there remains a large room for further in-depth studies.

2. Molecular Subtypes of Breast Cancer

Breast cancer treatment has advanced significantly in the past five years. The principles of breast cancer therapy follow a curative purpose and must be determined in a multidisciplinary sense, taking into account molecular subtype and loco-regional tumor load. Advancements in therapeutic strategies make the prospect of long-term disease control in metastatic breast cancer an increasing reality.

It is well known that different combinations of the presence of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2) status, Ki67 protein and tumor grade define five basic molecular subtypes of breast cancer, luminal A, luminal B Her2+/luminal B Her2-, basal/triple-negative, normal-like, and Her2-enriched [8][9]. The status within each subtype is summarized in **Figure 1**.

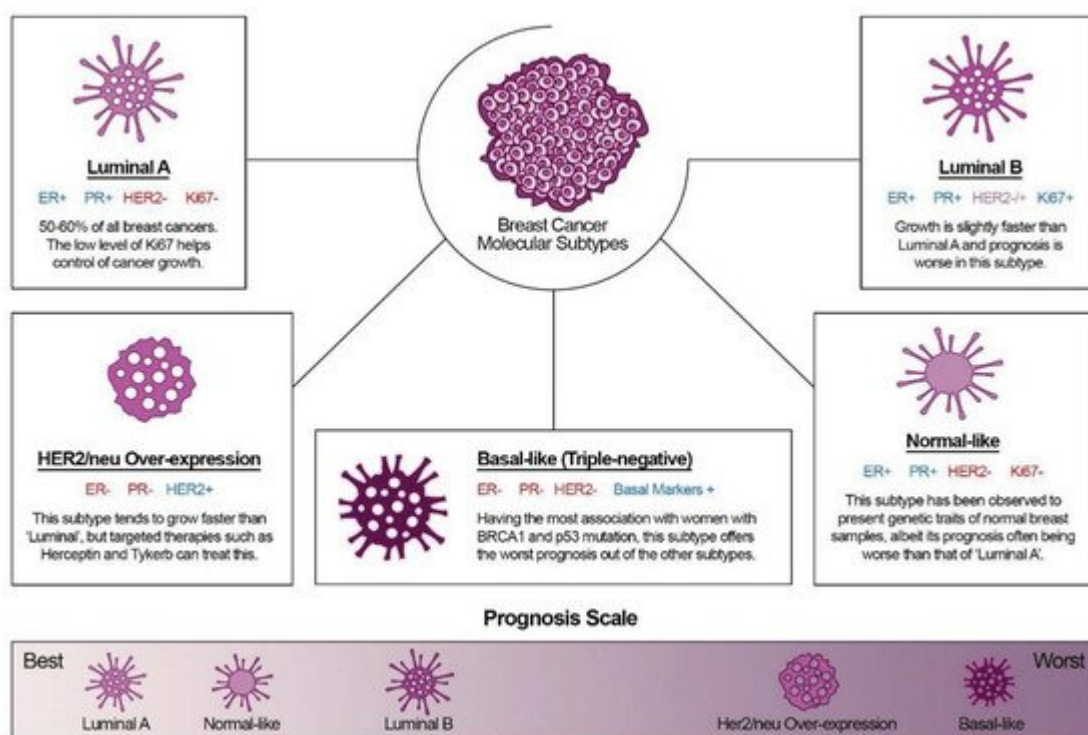


Figure 1. Breast cancer and its five molecular subtypes: prognosis of the disease. Reprinted with permission from [8]. Copyright 2018 ClinMed International Library.

- Luminal A (ER+/PR+/HER2-/Ki67-): This is the most common type of breast cancer and tends to be slower-growing and less aggressive than other subtypes. Luminal A tumors are associated with the most favorable prognosis in part because they are usually responsive to hormonal therapy [10]. Tumors also show good differentiation, low grade (1 or 2), and the percentage of their recurrence is low [11]. In addition, the low level of Ki67 protein helps control of cancer growth [8].
- Luminal B (ER+/PR+/HER2- or HER2+/Ki67+): This is a relatively small subgroup of tumors that proliferate significantly more, are less differentiated and express hormone receptors. In addition, this subtype was initially characterized clinically as always being positive for HER2, but more recently has been defined as being highly

positive for the protein Ki67 and/or HER2 ^[12]. Luminal B breast cancers have higher histological than luminal A and recur more often.

- Basal-like (ER–/PR–/HER2–): These cancers are also called triple-negative because they lack these receptors. This subtype, which has the most significant association with women with the BRCA1 and p53 gen mutations, offers the worst prognosis of the other subtypes, in part because treatment advances have lagged behind other molecular subtypes ^[13]. The majority (about 75%) of triple-negative breast cancers fall into the basal-like subtype defined by gene expression profiling. Proliferative activity is significant. Patients of luminal A and basal subtype form the regional lymph node metastases less frequently ^[14].
- HER2-enriched (ER–/PR–/HER2+): In the past, this subtype had the worst prognosis; however, the widespread use of targeted therapies for HER2+ cancers have substantially improved outcomes for these patients ^[15].
- Normal-like (ER+/PR+/HER2–/Ki67–): This subtype has been found to exhibit the genetic characteristics of normal breast samples, although its prognosis is often worse than the luminal A prognosis ^[8].

However, some data suggest that the current classification scheme for breast tumors may not fully capture cancer's genetic and molecular status. The revised classification will allow the more accurate treatment of cancer. Today, the search for better classifiers of tumors is significantly focused on applying omic approaches, which can analyze thousands of gene sequences, gene transcripts, or proteins in a single experiment. Bouchal and colleagues ^[9] recently demonstrated and confirmed the suitability of sequential windowed acquisition of all theoretical fragment ion mass spectra approach (SWATH-MS) for proteotyping of human tumor samples and also identified key proteins for the classification of breast tumors. Proteins that contribute most strongly to proteotype-based classification include inositol polyphosphate-4-phosphatase, type II (INPP4B), cyclin-dependent kinase 1 (CDK1), and receptor tyrosine kinase 2 (ERBB2) are associated with estrogen receptor (ER) status, HER2 status tumor, and grade status. Although more data are needed to validate classifiers, the results suggest that proteotype-based classification may improve the current conventional classification of breast tumors and thus provide adequate treatment.

3. Epithelial-Mesenchymal Transition

The epithelial-mesenchymal transition (EMT) is a dynamic process during which epithelial cells lose their cellular polarity and phenotypic properties and acquire mesenchymal cell properties. EMT process also allows cells to disrupt the basement membrane and invade neighboring tissues or distant organs ^[16]. EMT occurs naturally in the body, for example, during tissue regeneration or embryogenesis. Nevertheless, EMT process has been suggested that may be closely linked to the acquisition of aggressive properties by tumor cells, facilitating the initial stages of metastasis. EMTs occur in three different biological subtypes, which have very different functional consequences ^[17]. **Figure 2** shows different types of EMT, and at the same time, **Table 1** provides an overview of some of the most common markers that demonstrate these subtypes.

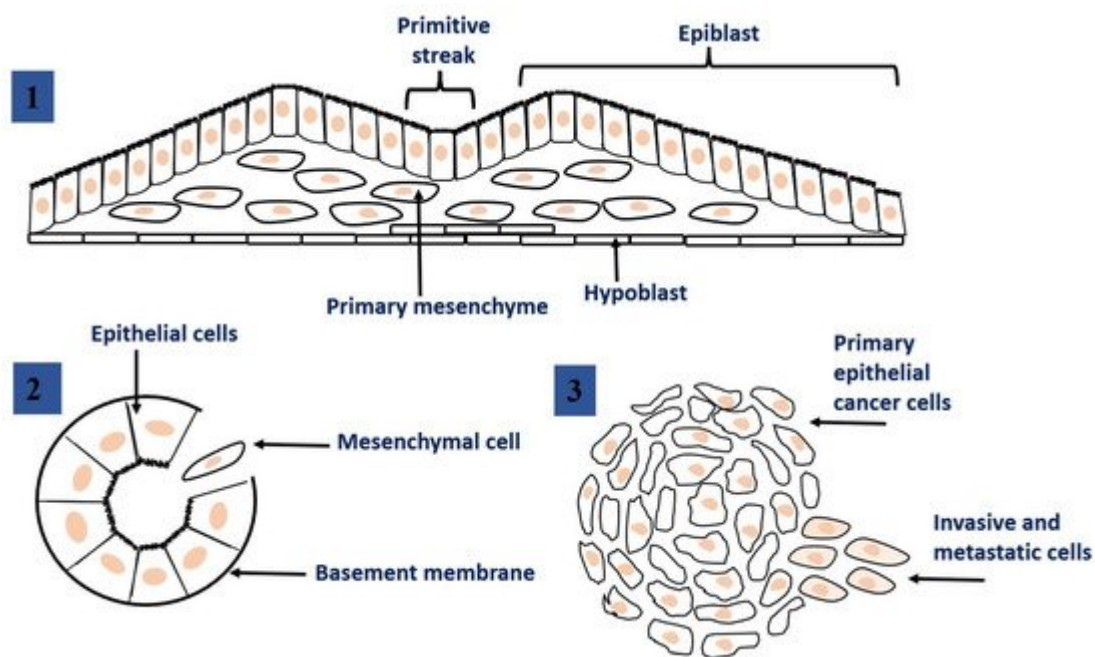


Figure 2. Epithelial to mesenchymal transition: the process of transformation of epithelial cells into mesenchymal cells. 1. EMT related to implantation, embryo formation, and organ development. 2. EMT related to cancer progression and metastasis. 3. EMT associated with tissue regeneration and organ fibrosis. This figure was adapted from ref. [17].

Table 1. An overview of some of the most common markers that demonstrate these subtypes.

Protein Name	MW (kDa)	Up/down Regulated during Cancer	Protein Function (www.uniprot.org)	References
Annexin 1 (ANX1)	38.7	UP	- potential marker of the development of breast cancer - possible role in the early events of malignant transformation	[18]
Bromodomain-containing protein 7 (BRD7)	74.1	Up/tumor suppression	- acts both as a coactivator and as a corepressor - possible role in chromatin remodeling - potential tumor suppressor in hepatocellular carcinoma	[19][20]

Protein Name	MW (kDa)	Up/down Regulated during Cancer	Protein Function (www.uniprot.org)	References
E-cadherin	97.5	Down	- calcium-dependent cell adhesion proteins - involved in mechanisms regulating cell-cell adhesions, mobility, and proliferation of epithelial cells	[21][22]
N-cadherin	99.8	Up	- acts as a regulator of neural stem cells quiescence by mediating anchorage of neural stem cells to ependymocytes in the adult subependymal zone - role in cell-to-cell junction formation between pancreatic beta cells and neural crest stem cells	[21][22]
β-Catenin	9.2	Up	- belongs to the cytoskeletal proteins - involved in regulation and coordination of cell-cell adhesion and gene transcription - accumulation of cytoplasmic β-catenin: useful predictor of hematogenous metastases	[23]
CD44	81.5	Up	- cell-surface receptor - role in cell-cell interactions, cell adhesion, and migration - expression is associated with resistance to therapy and poorer prognosis of many cancers -	[24][25]

Protein Name	MW (kDa)	Up/down Regulated during Cancer	Protein Function (www.uniprot.org)	References
			overexpression is a characteristic marker for tumorigenic cancer cells population of breast cancer, colon, pancreas, and prostate	
Type 1 collagen	138.9	Promotes survival of human breast cancer cells by overexpressing Kv10.1 potassium and Orai1 calcium channels.	- tumor microenvironment factors - regulates proliferation, survival, migration, and invasion	[17] [26]
Type IV collagen	164.0	Down	- the major structural component of glomerular basement membranes - cell adhesion function - involved in the process of tumor invasion and metastasis, including colorectal cancer and breast cancer	[27] [28]
Cytokeratin 18	48.1	Down	- role in filament reorganization - may affect various cellular processes (e.g., apoptosis, cell cycle progression, and tumor cell behavior) - decreases with the progression of EMT, and is frequently used as a marker for this process	[27] [29]
Class S100 of cytoskeletal proteins	9.0–13.0	Up/Down	- mainly involved in aspects of the regulation of proliferation, differentiation, apoptosis, Ca²⁺ homeostasis, energy metabolism - S100A2 downregulated in many cancers (associated with poor prognosis)	[17] [30]

Protein Name	MW (kDa)	Up/down Regulated during Cancer	Protein Function (www.uniprot.org)	References
			- S100A2 upregulated in some cancers, and other functions are unclear	
Desmin	53.5	Up	- muscle-specific type III intermediate filament essential for proper muscular structure and function - crucial role in maintaining the structure of sarcomeres, inter-connecting the Z-disks, and forming the myofibrils	[17]
Desmoplakin	331.8	Down	- downregulation in various cancers promotes tumor progression - role in carcinogenesis is still being elucidated	[27] [31]
Fibroblast-specific protein 1 (S100A4)	11.7	Up/ overexpressed in a range of different tumor types	- belongs to the S100 superfamily of cytoplasmic calcium-binding proteins and can be expressed by different cell types of mesenchymal origin - role in various cellular processes, including motility, angiogenesis, cell differentiation, apoptosis, and autophagy	[17] [32]
Fibronectin	2.5	Up	- fibronectins bind cell surfaces and various compounds, including collagen, fibrin, heparin, DNA, and actin - belongs to the extracellular matrix proteins	[33]

Protein Name	MW (kDa)	Up/down Regulated during Cancer	Protein Function (www.uniprot.org)	References
			- can be upregulated by SNAIL and TWIST in type 3 EMT	
$\alpha 5$ integrin	114.5	Up	- belongs to the cell-surface proteins - receptor for fibronectin and fibrinogen - may promote tumor invasion, and higher expression of this gene may be correlated with shorter survival time in lung cancer patients	[33]
$\beta 6$ integrin	85.9	Up	- belongs to the cell-surface proteins - increased $\beta 6$ expression occurs in up to one-third of solid tumors, including breast cancer, lung cancer, and pancreatic cancer - not found on most normal cells - potential therapeutic target in cancer research - over-expression often correlates with poorer overall survival	[33]
Laminin 1	177.6	Down	- belongs to extracellular matrix proteins - important for adhesion, differentiation, migration, and resistance to apoptosis of various cells, including cancer cells -	[27]

Protein Name	MW (kDa)	Up/down Regulated during Cancer	Protein Function (www.uniprot.org)	References
			thought to mediate the attachment, migration, and organization of cells into tissues during embryonic development	
Laminin 5	399.7	Up	- belongs to extracellular matrix proteins - highly expressed in several types of epithelial tumors - overexpression has been described in 70% of triple-negative breast carcinomas and has a role in the aggressive phenotype of some breast cancers and may provide a prognostic marker for triple-negative breast carcinoma	[33] [34]
Mucin 1	122.1	Down	- can act both as an adhesion and an anti-adhesion protein - in activated T-cells, influences directly or indirectly the Ras/MAPK pathway - promotes tumor progression	[21] [22]
Occludin	59.1	Down	- able to induce adhesion when expressed in cells lacking tight junctions - downregulation = common feature of EMT in tumors derived from simple epithelial cells - the decreased expression suggests that tumorigenesis is accompanied	[27] [35]

Protein Name	MW (kDa)	Up/down Regulated during Cancer	Protein Function (www.uniprot.org)	References
			by loss of cell-cell adhesion followed by loss of differentiation and uncontrolled proliferation	
Smooth muscle alpha-actin (α -SMA)	42.0	Up	- expressed by tumor cells carcinoma - tumor cells expressing α-SMA are predicted to be the cells having the invasive nature, tend to metastasize, and have a poorer prognosis	[17] [33]
Snail	29.1	Up	- family of transcription factors - involved in the induction of the EMT, formation, and maintenance of embryonic mesoderm, growth arrest, and survival - upregulated in several cancers and associated with increased tumor migration	[33] [36]
Syndecan-1	32.5	Up	- a novel molecular marker for triple-negative inflammatory breast cancer - modulates the cancer stem cell phenotype	[33] [37]
Twist	21	Up	- plays an essential role in cancer metastasis - over-expression of Twist or methylation of its promoter is common in metastatic carcinomas - acts as a transcriptional regulator	[33] [36]

Protein Name	MW (kDa)	Up/down Regulated during Cancer	Protein Function (www.uniprot.org)	References
			- inhibits myogenesis	
Vimentin (VIME)	53.7	Up	- belongs to the cytoskeletal proteins - class-III intermediate filaments found in various non-epithelial cells, especially mesenchymal cells - highly expressed in fibroblasts, some expression in T- and B-lymphocytes, and little or no expression in Burkitt's lymphoma cell lines - expressed in many hormone-independent mammary carcinoma cell lines	[17] [36]
Y-box-binding protein 1	35.9	Reduces ovarian cancer cell proliferation	- associated with tumor and the emergence of treatment resistance - DNA- and RNA-binding protein involved in various processes	[19] [38]
ZEB proteins ZEB1 ZEB2	124.1 133.8	Up Up	- transcriptional repressors - key role in solid cancer metastases by allowing cancer cells to invade and spread through transcriptional regulation of EMT - ZEB expression also associated with cancer acquisition stem cell properties and resistance to therapy - considered reliable prognostic markers of solid tumor aggressiveness	[33] [36] [39]

Protein Name	MW (kDa)	Up/down Regulated during Cancer	Protein Function (www.uniprot.org)	References
ZO-1	187.0	Down/up	- an important role in podosome formation and associated function, thus regulating cell adhesion and matrix remodeling - down-or upregulation observed in various tumors	[27] [35] [40]

- EMTs associated with implantation, embryo formation, and organ development are organized to generate different cell types that share common mesenchymal phenotypes. These type 1 EMTs can generate mesenchymal cells that have the potential to subsequently undergo a reverse process—a mesenchymal-epithelial transition (MET) to generate secondary epithelium.
- Type 2 EMTs are associated with tissue regeneration and organ fibrosis. Organic fibrosis, which occurs in many epithelial tissues, is mediated by inflammatory cells and fibroblasts that release various inflammatory signals. Reliable markers for the characterization of mesenchymal products generated by EMT, which occur during the development of fibrosis in various organs, are the following proteins: fibroblast-specific protein 1, a class S100 of the cytoskeletal protein, α -SMA, and collagen I [\[41\]](#)[\[42\]](#).
- Type 3 EMTs are associated with cancer progression and metastasis. In the case of this EMT, the cancer cells on the invasive anterior side of the tumors transform into a mesenchymal phenotype. Many in vivo as well as in vitro experiments have shown that cancer cells can acquire a mesenchymal phenotype and express mesenchymal protein markers such as smooth muscle alpha-actin (α -SMA), fibroblast specific protein 1 (FSP1), vimentin, and desmin [\[43\]](#).

The incomplete EMT status in cancer cells allows them to possess more transient states and to express mixed epithelial and mesenchymal genes, so these cells can be more aggressive compared to cells with the complete EMT phenotype [\[44\]](#). Cancer cells affecting metastases are similar to the epithelium and can be identified as morphologically and molecularly derived from the primary tumor. For this reason, cancer cells must reverse the mesenchymal phenotype of reverse EMT, a process known as the mesenchymal-epithelial junction (MET) [\[45\]](#).

At present, it is relevant to identify some essential proteins that address important, still unanswered questions. The downregulation of epithelial markers and the upregulation of mesenchymal protein markers are both characteristics of EMT (**Figure 3**). A critical molecular feature of this process is the downregulation of the E-cadherin expression. E-cadherin is a key protein in cell polarity and epithelial organization. The reduction or loss of E-cadherin has become one of the hallmarks of EMT and was frequently associated with metastasis and invasion in a variety of

human malignancies [46]. N-cadherin, vimentin, snail, twist, and fibronectin are known as mesenchymal markers, which are closely linked to several human malignancies [47]. In addition, Snail can also inhibit the expression of other epithelial genes such as Muc1 and promote the expression of fibronectin and vimentin, which activate EMT and are associated with tumor metastasis, recurrence, and poor prognosis of breast cancer.

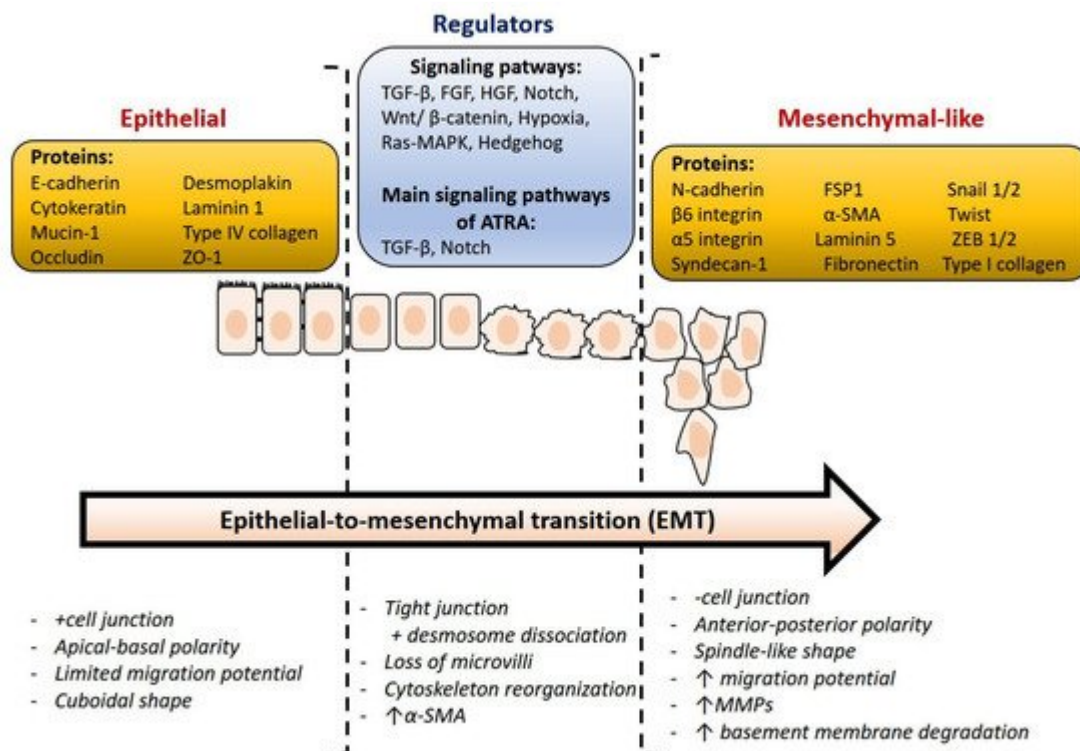


Figure 3. Overview of relevant markers and main molecular changes during epithelial-to-mesenchymal transition. This figure was adapted from ref. [27].

Niu et al. investigated the morphological and molecular changes that occur during the EMT process after bromodomain-containing protein 7 (BRD7) overexpression. BRD7 is a tumor suppressor known to inhibit cell proliferation and cell cycle progression and to induce apoptosis in breast cancer. In addition, in vitro tests indicated that BRD7 has the ability to inhibit mobility, migration and invasion of breast cancer cells [19]. At the same time, YB1 (Y-box-binding protein 1) was identified by nano-LC-MS/MS using LTQ Velos Orbitrap MS coupled to UltiMate RSLCnano LC as a new interacting BRD7 protein. It was further confirmed that EMT is a common change that occurs with altered expression of either BRD7 or YB1, and that BRD7 suppresses mesenchymal genes and activates epithelial genes [19]. Additionally, the possible contribution of annexin 1 (ANXA1) to breast tumorigenesis was investigated using stable quantitative MS proteomics based on isotope labeling. ANXA1 has been reported to promote migration and invasion of metastatic breast cancer cells as a modulator of EMT, such as phenotypic transition, through the transforming growth factor signaling pathway [18]. It has been revealed that ATRA modulates EMT of mammary tumor cells via the TGF- β and NOTCH pathways [48], and that modulation of the NOTCH1 signal transduction pathway plays a major role in ATRA activated anti-motility responses. The TGF pathway was also found to be a second signal transduction system that is essential for ATRA anti-migration. Doe et al. confirmed that the retinoic acid receptor alpha gene (RARA) regulates EMT-inducing transcription factors such as SLUG, FOXC2,

ZEB1 and ZEB2, and factors activating TGF- β -SMAD signaling, including TGFBR1, TGFBR2, TGFB2 and SMAD3 [49].

Although it is widely believed that EMT contributes to metastasis, there is a lack of definitive in vivo evidence to support this theory. Some published papers report that although therapeutic inhibition of EMT might not prevent metastasis, combining chemotherapy with EMT inhibition might help to prevent the emergence of resistance [50][51]. Targeting EMT can serve as an effective strategy for cancer treatment, and EMT research will be promising in the coming years.

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