Scientific Research Publishing

Advances in Breast Cancer Research, 2022, 11, 141-151
https://www.scirp.org/journal/abcr
ISSN Online: 2168-1597
ISSN Print: 2168-1589

Epithelial-Mesenchymal Transition and Breast Cancer Stem Cells in Breast Cancer Progression

Wanyue Han*, Qingshan Li*, Qing Zhang, Fan Xu#

The Affiliated Hospital of Chengde Medical University, Chengde, China
Email: 904176573@qq.com, #xufan83122@163.com

How to cite this paper: Han, W.Y., Li, Q.S., Zhang, Q. and Xu, F. (2022) Epithelial-Mesenchymal Transition and Breast Cancer Stem Cells in Breast Cancer Progression. *Advances in Breast Cancer Research*, **11**, 141-151.
https://doi.org/10.4236/abcr.2022.112012

Received: March 25, 2022
Accepted: April 24, 2022
Published: April 27, 2022

Abstract

Breast cancer stem cells (BCSCs) are a small subpopulation of cancer cells having the ability of self-renewing and multi-lineage differentiation, which have also been termed as "tumor-initiating cells". And in recent years, the role of epithelial mesenchymal transition (EMT) in malignant tumors has been valued. This paper will briefly review and discuss the relationship between BCSCs and EMT.

Keywords

Epithelial-Mesenchymal Transition, Breast Cancer Stem Cells, E-Cadherin, Vimentin, Signaling Pathway

1. Introduction

Breast cancer stem cells (BCSCs) are one of the important factors for recurrence, metastasis and drug resistance of breast cancer. Epithelial-mesenchymal transition (EMT) not only enables cancer cells to gain stem cell properties, but also allows cells to acquire metastatic and migratory abilities, thus promoting tumor metastasis. In this review, we describe the biological characteristics, surface markers and signaling pathways of BCSCs and EMT, as well as the relationship between BCSCs and EMT in order to bring new ideas for the treatment of breast cancer.

2. Epithelial-Mesenchymal Transition

EMT usually occurs in epithelial cells which are characterized by loss of cell connectivity and polarity and the acquisition of mesenchymal phenotypic characteristics. Epithelial cells that undergo EMT promote tumor cell invasion and motility by altering cell-cell interaction and cell-stromal interaction. About 90% of tumor

*These authors contributed equally to this work and should be considered as co-first authors.
#Corresponding author.

patients died due to tumor invasion and metastasis, indicating that regulation of EMT process is of great significance for tumor prevention and treatment.

2.1. Biological Characteristics of EMT

EMT is involved in the development of tissues and organs together with disease progression. EMT is divided into three types (**Figure 1**): Type I: intervened in embryo implantation and organ formation; Type II: intervened in regeneration, repair and fibrosis after tissue injury; Type III: intervened in cancer progression and metastasis. Breast cancer cells with EMT have the ability of metastasis and migration to form metastatic tumor at a distant [1]. Reversing EMT likely suppress the invasion and migration of breast cancer cell [2].

2.2. EMT Markers

EMT can confer cells with migratory ability, enable cells to fuse, or generate secondary epithelia, which is essential for morphogenesis and organogenesis [3]. EMT is characterized by down-regulation of epithelial markers, including E-cadherin, β-catenin, Claudin-1, and up-regulation of the mesenchymal markers, including vimentin, N-cadherin and α-smooth muscle actin. Down-regulation of E-cadherin and up-regulation of vimentin are important indicators of EMT [4]. E-cadherin knockout contributes to the migratory capacity of cells, while exogenous E-cadherin inhibits the formation of metastatic tumors [5]. Vimentin can induce the change from an epithelial cell morphology to a spindle-shaped morphology [6], which decreases the adhesion between cancer cells, promoting the migration to the surrounding area.

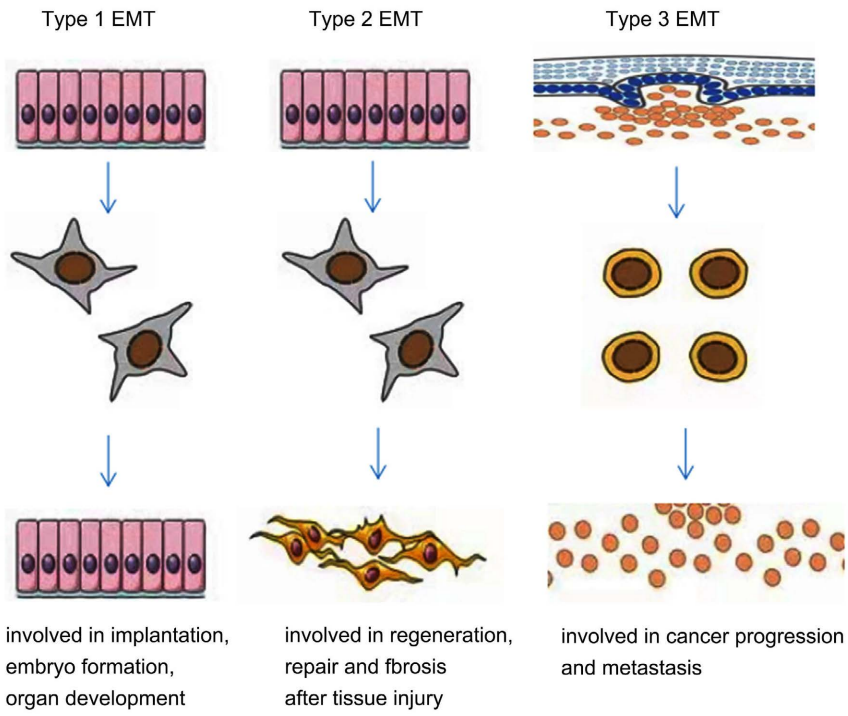

Figure 1. Three types of EMT.

2.3. EMT-Related Signaling Pathways and Transcription Factors

EMT is related to many signaling pathways, such as transformation growth factor-β (TGF-β), Wnt/β-catenin, Notch pathways [7] [8] [9], as well as NF-κB, PI3K/AKT and MAPK pathways (**Figure 2**). On the one hand, TGF-β pathway can suppress E-cadherin expression and enhance vimentin expression via classic Smad pathway and non-Smad pathway to promote EMT [10]. On the other hand, TGF-β can cause cytoskeletal changes through degradation of glycosyl triphosphatase to reduce the tight junctions between cells [11]. Wnt pathway can inhibit β-catenin degradation, activate downstream target genes (such as cyclinD1, c-myc, WISP), and initiate EMT to promote tumor growth and metastasis. Li *et al.* [12] confirmed that activation of Notch-1 signaling pathway could initiate NF-κB pathway, down-regulate E-cadherin to promote EMT. PI3K, MAPK and Wnt signaling pathways act synergistically to reduce E-cadherin, thereby promoting EM [13].

EMT-related transcription factors mainly include ZEB, Snail and TWIST [14] which are absent in differentiated adult cells, but are reactivated in cancers. These transcription factors bind directly to a core 5'-CACCTG-3' present in the promoter sequence of E-cadherin to induce epigenetic silencing, which marks the beginning of EMT [15]. ZEB family has two members, ZEB1 and ZEB2. ZEB can inhibit the transcription and expression of E-cadherin. ZEB2 can promote EMT by inhibiting the expression of claudin-4 and ZO-3, and inducing the expression of vimentin and N-cadherin [16]. The Snail family has three members, Snail1 and Snail2 can suppress E-cadherin expression, Snail2 has a low binding affinity for the E-cadherin promoter. High expression of Snail1 activates intranuclear ERK2, down-regulates E-cadherin and up-regulates vimentin, thereby inducing EMT. TWIST includes TWIST1 and TWIST2, TWIST can directly inhibit expression of E-cadherin via combining with E-box or up-regulating the transcription of Slug [17]. TWIST can also promote the methylation of H4K20, a histone that is related to E-cadherin inhibition and N-cadherin promoter activation. Functionally, these transcription factors can act synergistically to repress epithelial features, for example, ZEB1 expression activates Snail, E-cadherin down-regulation up-regulates TWIST, activates Snail1, and together trigger ZEB1 expression to maintain EMT [18]. EMT develops under the combined action of transcription factors and related signaling pathways. The Wnt and Notch pathways can activate the transcription factor Snail, and directly activate ZEB1expression, while Six1 can activate the Wnt signaling pathway.

3. Breast Cancer Stem Cells

Stem cells can proliferate and differentiate into cells with various functions. Cancer stem cells (CSCs) are derived from malignant transformation of stem cells in adult tissues, and the dedifferentiation of lineage-committed cells that acquire stem cell-like properties after mutation [19]. CSCs have following properties such as self-renewal, generation of more stem cells and more differentiated cells that form large primary tumors. BCSCs are the first solid tumor cancer

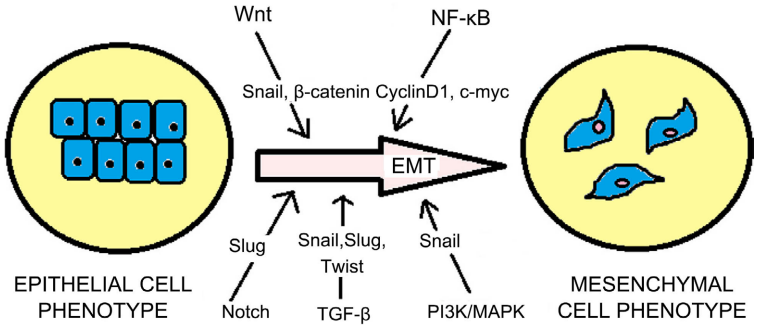

Figure 2. The signal regulation network diagram of EMT BCSCs.

stem cells to be isolated [20]. BCSCs are derived from the deregulation in self-renewal and differentiation of normal stem cell, many characteristics of BCSCs are similar to breast stem cells. In addition, BCSCs can also be derived from differentiated mature breast cells or newly differentiated breast progenitor cells through EMT [21].

3.1. Surface Markers of BCSCs

$CD44^{+}CD24^{-/low}$ is a common marker of BCSCs. 100 $CD44^{+}CD24^{-/low}$ cells can trigger xenograft tumors in mice [20]. Study has shown that CD44 was positively correlated with stem cell-like features, and CD24 was positively correlated with epithelioid features [22]. BCSCs with high CD44 expression are abundant in triple-negative breast cancer (TNBC) patients, especially in those with lymph node metastasis. Elevated CD44 expression can reduce overall survival and disease-free survival of TNBC patients, and low/negative CD24 TNBC patients have poor prognosis [23]. The ratio of CD44/CD24 is the highest in basal mesenchymal cell line MDA-MB-231, the reason is that basal cell lines are generally considered more malignant than luminal A cell lines, suggesting that the ratio of CD44/CD24 may be a semiquantitative indicator assessing stemness [24].

Another marker of BCSCs is ALDH1. Ginestier *et al.* [25] demonstrated that 500 $ALDH1^{+}$ cells could form stable tumors. 20 cells with $ALDH1^{+}$, $CD44^{+}CD24^{-/low}$ phenotypes are sufficient to generate tumors. High ratio of CD44/CD24 is prone to cell proliferation and tumorigenesis. $ALDH1^{+}$ is a stronger marker for cell migration and tumor metastasis [24], and $ALDH1^{+}$ cells are more prone to form tumor and develop drug resistance than $CD44^{+}CD24^{-/low}$ cells. There are many undifferentiated or poorly differentiated cancer cells in ALDH1-high expression tissues, and these cells have strong invasiveness [26].

3.2. BCSCs-Related Signaling Pathways

When pathways related to the generation of BCSCs are mutated and abnormally activated, BCSCs in a quiescent state will directly enter the proliferation cycles and self-renewal inducing breast cancer development [27]. Notch, Hedgehot and Wnt pathways are important pathways for differentiation and proliferation of BCSCs (**Figure 3**). JAK2-STAT3 and Hippo signaling pathways are also active in breast cancer cells (**Figure 3**).

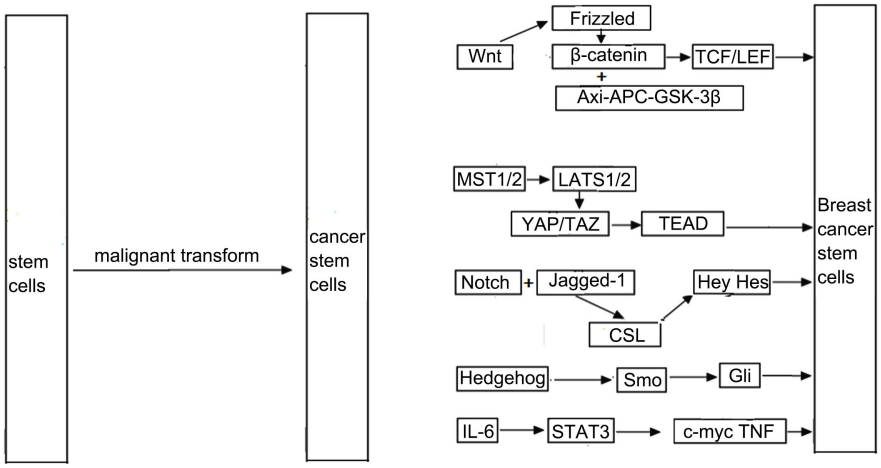

Figure 3. The signal regulation network diagram of BCSCs.

Notch pathway contains four trans-membrane receptors (Notch-1, -2, -3, -4), CSL DNA binding proteins and downstream target genes (Hes and Hey) to maintain the balance among cell proliferation, differentiation and apoptosis. Abnormal high expression of Notch-4 is observed in TNBC, using Notch-4 as a marker for mesenchymal-like BCSCs is more suitable than $CD44^{+}CD24^{-}$. Notch-4 upregulates Slug expression. Breast cancer cells with high Notch-4 expression exhibit enhanced sphere-forming abilities, elevated expression of BCSC markers, stronger tumorigenic capacity in tumor xenograft mice, and poor prognosis [28].

Hedgehog signaling pathway is another important pathway associated with BCSCs. A previous study showed that after treatment with paclitaxel, Hedgehot signaling pathway in breast cancer cells was activated accompanied by increase of BCSCs [29]. The expression of Smoothened is obviously increased in $CD44^{+}CD24^{-/low}$ cells. Cyclopamine can inhibit the expression of downstream targets Gli-1 by suppressing Smoothened protein activity in the Hedgehog signaling pathway [30], inhibit MDA-MB-231 cell proliferation and migration, and reduce sphere-forming ability of cells [31].

Wnt signaling pathway is composed of Wnt protein, Frizzled, β-catenin, GSK-3β, antigen presenting cells (APC), and Axin. Binding of Wnt ligands to Frizzled activates the APC-GSK-3β complex, inducing the translocation of β-catenin binding to the TCF/LEF, resulting in indefinite proliferation of normal breast tissues [32]. Compared with differentiated breast cancer cells, BCSCs exhibited relatively enhanced Wnt signaling and higher drug resistance. It has been shown that inhibition of WNT1 could suppress the transformation of tumor cells to cells with $CD44^{+}CD24^{-}ALDH^{-}$ phenotype, thereby inhibiting the occurrence and progression of breast cancer [33].

Signal transducer and activator of transcription 3 (STAT 3) is closely related to breast cancer. It has been found that STAT3 was usually not expressed in normal breast tissue, while the positive rate of STAT3 in tumor samples from breast cancer patients exceeded 50% [34]. Studies showed that IL-6 could acti-

vate STAT3, amplify $CD44^{high}CD24^{low}$ stem cell-like subset by inducing transcription of target genes (cyclind, c-myc, Bcl-2, IL-6, IL-10, TNF), suggesting that JAK-STAT pathway plays a key role in generation of BCSCs [35]. Additionally, IL-6 can also activate PIM1, a proto-oncogene, to initiate the generation of BCSCs through STAT3 activation [36].

Hippo signaling pathway activates its downstream effector, YAP/TAZ, which then binds to the transcription factor TEAD, thereby regulating the proliferation of BCSCs [37]. YAP/TAZ may maintain the stem cell properties of BCSCs through interacting with transcription factor KLF5 [38]. SMARCA4 knockout cells exhibit cisplatin-resistance and Hippo-YAP/TAZ target gene activation, YAP1 inhibitor can reduce viability and invasive ability of BCSCs [39].

4. Relationship between BCSCs and EMT

4.1. EMT Promotes the Generation of BCSCs

Primary cancer stem cells are generated by the fusion of cancer cells with bone marrow mesenchymal stem cells (BMSCs) generates [40]. Parent cancer cells can endow their progenies with tumorigenic properties, while BMSCs endow cancers cells with stemness characteristics, and mesenchymal phenotype (acquisition of high migratory and invasive properties after EMT). EMT promotes the generation of $CD44^{high}CD24^{low}$ mesenchymal cell population (considered as BCSCs), which have high mammosphere-forming ability under low attachment conditions [41]. There are two types of BCSCs with distinct properties: EMT-BCSCs are characterized by a more dormant/quiescent mesenchymal-like state, and $CD44^{+}CD24^{-/low}$ expression. These cells are located at the tumor edge and are prone to form micrometastases at distant sites. EMT-BCSCs could maintain the stem-like characters of BCSCs. MET-BCSCs are characterized by a proliferative/epithelial-like state, and ALDH expression, these cells are located at tumor center and are prone to restore epithelial-like state [42].

4.2. BCSCs Promote EMT Occurrence

BCSCs can induce EMT in human mammary epithelial cells [43]. Mesenchymal cell markers are highly expressed in BCSCs with $CD44^{+}CD24^{-/low}$ phenotype, multiple EMT-related signaling pathways are abnormally activated in BCSCs [34]. It was demonstrated that EMT was related to histological differentiation and histological types of tumor. Among different histological types of breast cancer, basal-like breast cancer is more prone to undergo EMT and has enhanced invasive and metastatic ability [4]. Studies showed that basal B/claudin-low breast cancer cells expressed both EMT and stem cell surface markers [44]. CD44 upregulates ZEB1 expression to maintain the mesenchymal properties of breast cancer cells, ZEB1 overexpression can also promote CD44 expression which enables cancer cells to gain stem cell properties [45]. Xue *et al.* found that PIM1 overexpression induced EMT and BCSC properties, while knockdown of Pim1 decreased the expression of EMT-related transcription factors (Snail, TWIST), mesenchymal marker (N-cadherin), and BCSC

marker (ALDH-1) [36]. EMT and BCSCs act synergistically to promote breast cancer progression.

4.3. Core Signaling Pathways in BCSCs and EMT

Inhibiting the Wnt/β-catenin signaling pathway can markedly affect EMT-mediated tumor cell metastasis [46]. Targeting the Wnt signaling pathway in breast cancer can regulate tumor stem cells, inhibit or even reverse EMT [47], suggesting that Wnt/β-catenin signaling pathway plays an essential role in regulating BCSCs and EMT.

The Notch signaling pathway is involved in EMT, breast cancer metastasis, maintaining BCSC phenotype, and increasing their tolerance to apoptosis. A previous study showed that after the Notch signaling pathway was activated by Jagged-1, E-cadherin expression was significantly decreased, while mesenchymal markers N-cadherin and vimentin expression were elevated, thus activating EMT [48]. Another study [49] showed that 3,6-DHF could inhibit the Notch signaling pathway by suppressing Notch1 expression, thereby regulating the proliferation of BCSCs, and inhibiting EMT.

5. Conclusion

We have summarized the markers and signaling pathways associated with BCSCs and EMT, and discussed their relationship. BCSCs and EMT not only interact with each other, but also are closely associated with breast cancer growth and progression. It is suggested that accurate identification of BCSCs by using markers and targeted inhibition of BCSCs- and EMT-related signaling pathways may be possible to develop personalized therapeutic strategies for patients with breast cancer in order to improve clinical outcomes of patients.

Funding

The study was supported by Natural Science Foundation of Hebei Province (H2021406036).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Blick, T., Widodo, E., Hugo, H., *et al.* (2008) Epithelial Mesenchymal Transition Traits in Human Breast Cancer Cell Lines. *Clinical & Experimental Metastasis*, **25**, 629-642. https://doi.org/10.1007/s10585-008-9170-6

[2] Wang, X., Chen, S., Shen, T., *et al.* (2020) Trichostat in A Reverses Epithelial-Mesenchymal Transition and Attenuates Invasion and Migration in MCF-7 Breast Cancer Cells. *Experimental and Therapeutic Medicine*, **19**, 1687-1694. https://doi.org/10.3892/etm.2020.8422

[3] Yang, J., Parker, A., Geert, B., *et al.* (2020) Guidelines and Definitions for Research

on Epithelial-Mesenchymal Transition. *Nature Reviews Molecular Cell Biology*, **21**, 341-352. https://doi.org/10.1038/s41580-020-0237-9

[4] Sarrió, D., Rodriguez-Pinilla, S.M., Hardisson, D., *et al.* (2008) Epithelial-Mesenchymal Transition in Breast Cancer Relates to the Basal-Like Phenotype. *Cancer Research*, **68**, 989-997. https://doi.org/10.1158/0008-5472.CAN-07-2017

[5] Liang, Y., Li, H.-Z., Lu, S.-M., *et al.* (2011) Down-Regulation of TWIST Decreases Migration and Invasion of Laryngeal Carcinoma Hep-2 Cells by Regulating the E-Cadherin, N-Cadherin Expression. *Journal of Cancer Research and Clinical Oncology*, **137**, Article No. 1487. https://doi.org/10.1007/s00432-011-1023-z

[6] Sun, Y., Yi, Y., Gan, S., *et al.* (2021) miR-574-5p Mediates Epithelial Mesenchymal Transition in Small Cell Lung Cancer by Targeting Vimentin via a Competitive Endogenous RNA Network. *Oncology Letters*, **21**, 459. https://doi.org/10.3892/ol.2021.12720

[7] Miyashita, N., Enokido, T., Horie, M., *et al.* (2021) TGF-β Mediated Epithelial-Mesenchymal Transition and Tumor-Promoting Effects in CMT64 Cells Are Reflected in the Transcriptomic Signature of Human Lung Adenocarcinoma. *Scientific Reports*, **11**, Article No. 22380. https://doi.org/10.1038/s41598-021-01799-x

[8] Xue, W., Dong, B., Zhao, Y., *et al.* (2021) Upregulation of TTYH3 Promotes Epithelial-to-Mesenchymal Transition through Wnt/β-Catenin Signaling and Inhibits Apoptosis in Cholangiocarcinoma. *Cellular Oncology*, **144**, 1351-1361. https://doi.org/10.1007/s13402-021-00642-9

[9] Razali, R.A., Lokanathan, Y., Dain Yazid, M., *et al.* (2019) Modulation of Epithelial to Mesenchymal Transition Signaling Pathways by *Olea europaea* and Its Active Compounds. *International Journal of Molecular Sciences*, **20**, Article No. 3492. https://doi.org/10.3390/ijms20143492

[10] Wan, R., Xu, X., Ma, L., *et al.* (2020) Novel Alternatively Spliced Variants of Smad4 Expressed in TGF-β-Induced EMT Regulating Proliferation and Migration of A549 Cells. *OncoTargets and Therapy*, **13**, 2203-2213. https://doi.org/10.2147/OTT.S247015

[11] Hubchak, S.C., Runyan, C.E., Kreisberg, J.I., *et al.* (2003) Cytoskeletal Rearrangement and Signal Transduction in TGF-beta1-Stimulated Mesangial Cell Collagen Accumulation. *Journal of the American Society of Nephrology*, **14**, 1969-1980. https://doi.org/10.1097/01.ASN.0000076079.02452.92

[12] Li, L., Zhao, F., Lu, J., *et al.* (2014) Notch-1 Signaling Promotes the Malignant Features of Human Breast Cancer through NF-κB Activation. *PLoS ONE*, **9**, Article ID: e95912. https://doi.org/10.1371/journal.pone.0095912

[13] Ngeow, K.C., Friedrichsen, H.J., Li, L., *et al.* (2018) BRAF/MAPK and GSK3 Signaling Converges to Control MITF Nuclear Export. *Proceedings of the National Academy of Sciences of the United States of America*, **115**, E8668-E8677. https://doi.org/10.1073/pnas.1810498115

[14] Baldini, E., Tuccilli, C., Pironi, D., *et al.* (2021) Expression and Clinical Utility of Transcription Factors Involved in Epithelial-Mesenchymal Transition during Thyroid Cancer Progression. *Journal of Clinical Medicine*, **10**, Article No. 4076. https://doi.org/10.3390/jcm10184076

[15] Reinhold, W.C., Reimers, M.A., Lorenzi, P., *et al.* (2010) Multifactorial Regulation of E-Cadherin Expression: An Integrative Study. *Molecular Cancer Therapeutics*, **9**, 1-16. https://doi.org/10.1158/1535-7163.MCT-09-0321

[16] Goossens, S., Vandamme, N., Van Vlierberghe, P., *et al.* (2017) EMT Transcription Factors in Cancer Development Re-Evaluated: Beyond EMT and MET. *Biochimica*

et Biophysica Acta (*BBA*): *Reviews on Cancer*, **1868**, 584-591. https://doi.org/10.1016/j.bbcan.2017.06.006

[17] Serrano-Gomez, S.J., Maziveyi, M. and Alahari, S.K. (2016) Regulation of Epithelial-Mesenchymal Transition through Epigenetic and Post-Translational Modifications. *Molecular Cancer*, **15**, Article No. 18. https://doi.org/10.1186/s12943-016-0502-x

[18] Dave, N., Guaita-Esteruelas, S., Gutarra, S., *et al.* (2011) Functional Cooperation between Snail1 and Twist in the Regulation of ZEB1 Expression during Epithelial to Mesenchymal Transition. *Journal of Biological Chemistry*, **28**, 12024-12032. https://doi.org/10.1074/jbc.M110.168625

[19] Lawson, J.C., Blatch, G.L. and Edkins, A.L. (2009) Cancer Stem Cells in Breast Cancer and Metastasis. *Breast Cancer Research and Treatment*, **118**, 241-254. https://doi.org/10.1007/s10549-009-0524-9

[20] Al-Hajj, M., Wicha, M.S., Benito-Hernandez, A., *et al.* (2003) Prospective Identification of Tumorigenic Breast Cancer Cells. *Proceedings of the National Academy of Sciences of the United States of America*, **100**, 3983-3988. https://doi.org/10.1073/pnas.0530291100

[21] Velasco-Velázquez, M.A., Homsi, N., De La Fuente, M., *et al.* (2012) Breast Cancer Stem Cells. *The International Journal of Biochemistry & Cell Biology*, **44**, 573-577. https://doi.org/10.1016/j.biocel.2011.12.020

[22] Park, S.Y., Lee, H.E., Li, H., *et al.* (2010) Heterogeneity for Stem Cell-Related Markers According to Tumor Subtype and Histologic Stage in Breast Cancer. *Clinical Cancer Research*, **16**, 876-887. https://doi.org/10.1158/1078-0432.CCR-09-1532

[23] Zou, W., Yang, Y., Zheng, R., *et al.* (2020) Association of CD44 and CD24 Phenotype with Lymphnode Metastasis and Survival in Triple-Negative Breast Cancer. *International Journal of Clinical and Experimental Pathology*, **13**, 1008-1016.

[24] Li, W., Ma, H., Zhang, J., *et al.* (2017) Unraveling the Roles of CD44/CD24 and ALDH1 as Cancer Stem Cell Markers in Tumorigenesis and Metastasis. *Scientific Reports*, **7**, Article No. 13856. https://doi.org/10.1038/s41598-017-14364-2

[25] Ginestier, C., Hur, M.H., Charage-Jauffret, E., *et al.* (2007) ALDH1 Is a Marker of Normal and Malignant Human Mammary Stem Cells and a Predictor of Poor Clinical Outcome. *Cell Stem Cell*, **1**, 555-567. https://doi.org/10.1016/j.stem.2007.08.014

[26] Deng, S., Yang, X., Lassues, H., *et al.* (2010) Distinct Expression Levels and Patterns of Stem Cell Marker, Aldehydedehydrogenase Isoform1 (ALDH1), in Human Epithelial Cancers. *PLoS ONE*, **5**, e10277. https://doi.org/10.1371/journal.pone.0010277

[27] Zang, C.X., Liu, R.J., Zhao, W.G., Sun, Y., Tang, S.F. and Sun, C.G. (2019) Research Progress of Breast Cancer Stem Cell Related Signal Pathway and Its Inhibitor. *Journal of Chinese Oncology*, **25**, 27-31.

[28] Zhou, L., Wang, D., Sheng, D., *et al.* (2020) NOTCH4 Maintains Quiescent Mesenchymal-Like Breast Cancer Stem Cells via Transcriptionally Activating SLUG and GAS1 in Triple-Negative Breast Cancer. *Theranostics*, **10**, 2405-2421. https://doi.org/10.7150/thno.38875

[29] Sims-Mourtada, J., Opdenaker, L.M., *et al.* (2015) Taxane-Induced Hedgehog Signaling Is Linked to Expansion of Breast Cancer Stem-Like Populations after Chemotherapy. *Molecular Carcinogenesis*, **54**, 1480-1493. https://doi.org/10.1002/mc.22225

[30] Feng, T., Zeng, L.R., Xu, P.P. and Hang, R.Z. (2019) Effect of Cyclopamine on Hedgehog and Notch Signaling Pathway in Human MDA-MB-231 Triple Negative Breast Cancer Cells. *Chinese Journal of Cancer Prevention and Treatment*, **26**,

831-835.

[31] Song, L., Liu, D., Zhao, Y., *et al.* (2018) Sinomenine Reduces Growth and Metastasis of Breast Cancer Cells and Improves the Survival of Tumor-Bearing Mice through Suppressing the SHh Pathway. *Biomed Pharmacother*, **98**, 687-693. https://doi.org/10.1016/j.biopha.2017.12.065

[32] Xu, X., Zhang, M., Xu, F., *et al.* (2020) Wnt Signaling in Breast Cancer: Biological Mechanisms, Challenges and Opportunities. *Molecular Cancer*, **19**, Article No. 165. https://doi.org/10.1186/s12943-020-01276-5

[33] Jang, G.-B., Kim, J.-Y., Cho, S.-D., *et al.* (2015) Blockade of Wnt/β-Catenin Signaling Suppresses Breast Cancer Metastasis by Inhibiting CSC-Like Phenotype. *Scientific Reports*, **5**, Article No. 12465. https://doi.org/10.1038/srep12465

[34] Wei, W., Tweardy, D.J., Zhang, M., *et al.* (2014) STAT3 Signaling Is Activated Preferentially in Tumor-Initiating Cells in Claudin-Low Models of Human Breast Cancer. *Stem Cells*, **32**, 2571-2582. https://doi.org/10.1002/stem.1752

[35] Iliopoulos, D., Hirsch, H.A., Wang, G., *et al.* (2011) Inducible Formation of Breast Cancer Stem Cells and the Irdynamic Equilibrium with Non-Stem Cancer Cells via IL6 Secretion. *Proceedings of the National Academy of Sciences of the United States of America*, **108**, 1397-1402. https://doi.org/10.1073/pnas.1018898108

[36] Gao, X., Liu, X., Lu, Y., *et al.* (2019) PIM1 Is Responsible for IL-6-Induced Breast Cancer Cell EMT and Stemness via C-Myc Activation. *Breast Cancer*, **26**, 663-671. https://doi.org/10.1007/s12282-019-00966-3

[37] Shen, J., Cao, B., Wang, Y., *et al.* (2018) Hippo Component YAP Promotes Focal Adhesion and Tumour Aggressiveness via Transcriptionally Activating THBS1/FAK Signalling in Breast Cancer. *Journal of Experimental & Clinical Cancer Research*, **37**, Article No. 175. https://doi.org/10.1186/s13046-018-0850-z

[38] Liu, R., Shi, P., Nie, Z., *et al.* (2016) Mifepristone Suppresses Basal Triple-Negative Breast Cancer Stem Cells by Down-regulating KLF5 Expression. *Theranostics*, **6**, 533-544. https://doi.org/10.7150/thno.14315

[39] Kim, J., Jang, G., Sim, S.H., *et al.* (2021) SMARCA4 Depletion Induces Cisplatin Resistance by Activating YAP1-Mediated Epithelial-to-Mesenchymal Transition in Triple-Negative Breast Cancer. *Cancers*, **13**, Article No. 5474. https://doi.org/10.3390/cancers13215474

[40] He, X., Li, B., Shao, Y., *et al.* (2015) Cell Fusion between Gastric Epithelial Cells and Mesenchymal Stem Cells Results in Epithelial-to-Mesenchymal Transition and Malignant Transformation. *BMC Cancer*, **15**, Article No. 24. https://doi.org/10.1186/s12885-015-1027-1

[41] Sarrio, D., Franklin, C.K., Mackay, A., *et al.* (2012) Epithelial and Mesenchymal Subpopulations within Normal Basal Breast Celline Sex Hibit Distinct Stem Cell/Progenitor Properties. *Stem Cells*, **30**, 292-303. https://doi.org/10.1002/stem.791

[42] Bushnell, G.G., Deshmukh, A.P., den Hollanger, P., *et al.* (2021) Breast Cancer Dormancy:Need for Clinically Relevant Models to Address Current Gaps in Knowledge. *NPJ Breast Cancer*, **7**, Article No. 66. https://doi.org/10.1038/s41523-021-00269-x

[43] Mani, S.A., Guo, W., Liao, M.J., *et al.* (2008) The Epithelial-to-Mesenchymal Transition Generates Cells with Properties of Stem Cell. *Cell*, **133**, 704-715. https://doi.org/10.1016/j.cell.2008.03.027

[44] Hennessy, B.T., Gonzalez-Angulo, A.-M., Stemke-Hale, K., *et al.* (2009) Characterization of a Naturally Occurring Breast Cancer Subset Enriched in Epitheli-

al-to-Mesenchymal Transition and Stem Cell Characteristics. *Cancer Research*, **69**, 4116-4124. https://doi.org/10.1158/0008-5472.CAN-08-3441

[45] Preca, B.-T., Bajdak, K., Mock, K., *et al.* (2015) A Self-Enforcing CD44s/ZEB1 Feedback Loop Maintains EMT and Stemness Properties in Cancer Cells. *International Journal of Cancer*, **137**, 2566-2577. https://doi.org/10.1002/ijc.29642

[46] Wang, M., Meng, J.-Y. and He, S.-F. (2014) Xihuang Pill Induces Mesenchymal-Epithelial Transition and Inhibits Loss of Apical-Basal Polarity in Colorectal Cancer Cell through Regulating ZEB1-SCRIB Loop. *Chinese Journal of Integrative Medicine*, **20**, 751-757. https://doi.org/10.1007/s11655-014-1812-8

[47] Zhao, Z.Z., Liu, S. and Lin, H.S. (2021) Research Progress of Cell Fusion Inducing EMT and Generating Breast Cancer Stem Cells. *China Journal of Chinese Medicine*, **36**, 1910-1914.

[48] Shao, S., An, G.L., Zhao, L., Luo, M.N., Ning, Q., Meng, D., Zhao, X.H. and Lei, J.J. (2020) Notch1 Mediates Breast Cancer Epithelial-Mesenchymal Transition through Slug. *Journal of Xi'an Jiaotong University* (*Medical Sciences*), **41**, 881-887.

[49] Chen, J.L., Chang, H., Peng, X.L., Gu, Y.Y., Yi, L., Zhang, G.Y., Zhu, J.D. and Mi, M.T. (2017) 3,6-DHF Regulates EMT in Breast Cancer Cells by Regulating Notch Signaling Pathway. *Scientific Reports*, **6**, Article No. 28858. https://doi.org/10.1038/srep28858