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Role of transcription factors in metastasis of breast cancer

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Abstract

Metastasis causes a majority of deaths in breast cancer patients. Metastasis is the spread of cancer to distant sites in the body away from the primary tumor, creating secondary tumors, or metastases. A tumor metastasizes when cancer cells strategically regulate genes that play a role in angiogenesis, epithelial-mesenchymal transition (EMT), migration, invasion, and regulation of the cell cycle to bypass apoptosis and increase proliferation and stemness. Several transcription factors have also been identified to play a role in metastatic breast cancer, as they enable invasion, intravasation, transport, extravasation, and colonization of metastasis through other processes such as angiogenesis and EMT, making them a prime target for cancer treatment. Understanding how transcription factors play a role in breast cancer metastasis will enable the development of targeted therapeutics for breast cancer. This paper reviews the roles of E2Fs, hypoxia-inducible factors (HIFs), EMT master regulators, sex determining region Y (SRY)-related high-mobility group (HMG) box (*SOX*), E26 transformation-specific (*ETS*), Yin Yang 1 (*YY1*), forkhead box M1 (FoxM1), BTB domain and CNC homology 1 (Bach1), sineoculis homeobox homolog (*SIX*), runt-related transcription factor 2 (*RUNX2*), myelocytomatosis (*MYC*), Kruppel-like factors (KLFs), and c-Jun in breast cancer metastasis.

Keywords

Breast cancer, metastasis, transcription factors, EMT

Introduction

Transcription factors, DNA-binding proteins, are vital to gene expression, as they allow RNA polymerase to bind to the DNA and begin transcribing the target gene. Transcription factors can significantly impact cancer development because of this crucial role in cell growth and functionality.

Breast cancer first develops in the breast lobules, tubes, or connective tissue [1]. It can be classified into four molecular subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (Her2)-

positive, or triple-negative (TN) breast cancer [1]. Each type of breast cancer has different qualities in prognosis and treatment, and multiple subtypes can be present in the same patient or even the same tumor, which is considered tumor heterogeneity.

This review will focus on the role of transcription factors emphasized in current research to understand the specific aspects of breast cancer metastasis that are impacted by transcription factors.

E2F transcription factors

The E2F family of transcription factors is an evolutionarily conserved family of eight genes that encode ten proteins [2]. The E2F family consists of both oncogenes and tumor suppressor genes that code for transcription activators, transcription repressors, and cell cycle regulators that also seem to regulate metastasis in the early and late stages of progression [2, 3]. E2F1, 2, and 3A are activators, E2F3B, 4, and 5 are passive repressors, and E2F6, 7A, 7B, and 8 are active repressors [2]. Several studies provide evidence that the RB-E2F pathway has a role in therapy resistance [2]. ER-positive breast cancer tumors were treated with tamoxifen, an estrogen receptor antagonist that is the primary therapy for ER-positive breast cancer [2]. E2F1, E2F4, and genes involved in RB-E2F pathway-regulated processes were enhanced in tamoxifen-resistant tumors [2].

In one study by Hollern et al. [3], genomic signaling pathway signatures were applied to mouse tumor model microarray data to hypothesize that E2Fs regulate tumor development and metastasis in mice. To test the hypothesis, the effects of the loss of transcription factors E2F1, E2F2, and E2F3 were observed in different crosses of mice [3]. Loss of E2F1 and E2F2 reduced the metastatic ability of the tumors, although tumor onset was accelerated [3]. The loss of E2F1 was also found to cause upregulation of E2F3A, which is necessary for cell proliferation [3]. E2Fs also have a role in tumor heterogeneity, as each member of the E2F family can respond to different stimuli in various ways to regulate several genes and processes [3]. The Akt pathway was activated by E2Fs in the polyomavirus middle T oncoprotein (PyMT) tumor model [3]. E2F loss also causes the expression of genes responsible for tumor angiogenesis, tumor cell remodeling of the extracellular matrix, tumor cell survival, and tumor cell interactions with vascular endothelial cells to facilitate metastasis to the lungs, all of which are crucial to metastasis and cancer progression [3].

In another study by Liu et al. [4], transcription and survival data in breast cancer patients from online databases were observed. E2Fs specifically play a role in TN breast cancer, the breast cancer subtype with the lowest survival rates [4]. mRNA expression levels for the eight known E2Fs were higher in breast cancer tissues compared to normal tissue [4]. High levels of E2F1, E2F3, and E2F8, specifically, significantly correlated with lower overall and relapse-free survival [4]. Overall, the study indicated that E2F1, E2F3, E2F7, and E2F8 are potential targets for individualized treatment, and E2F4 could be a prognostic marker for survival [4]. E2Fs were also found to mediate invasion in H-Ras-dependent invasion of breast cancer through the RB-E2F pathway [2].

The cyclin-dependent kinase (CDK)-RB-E2F pathway has also garnered interest among breast cancer researchers. CDKs regulate the cell cycle by binding to cyclins, which build up throughout each stage of the cycle. E2Fs bind to RB1 proteins in this pathway, creating E2F-RB1 complexes that repress genes involved in cell cycle progression, which is a possible explanation for the loss of E2Fs contributing to cancer development [2]. Drugs targeting this pathway using CDK inhibitors are promising [2].

Song et al. [5] found that E2F1 promotes breast cancer metastasis by initiating transcription of the *PRSS22* gene. This gene is upregulated in human breast cancer tissues and expressed at even higher levels in patients with lymph node metastasis [5]. Overexpression and knockdown data reveal that *PRSS22* enhances migration and invasion abilities, making breast cancer cells more aggressive [5]. ANXA1 is the substrate of *PRSS22*, the cleaving of which activates formyl peptide receptor 2 (FPR2)/ERK signaling cascades to contribute to breast cancer progression [5].

Hypoxia-inducible factors

Hypoxia is the lack of oxygen available for tissues to adequately carry out their function. Tumor cells must adapt to hypoxia, as regions of the tumors are often too far from a blood vessel to access the same oxygen concentrations as normal tissues [6]. Hypoxia is associated with increased aggressive tumor behavior, metastasis, and resistance to therapy [7]. Breast cancer cells increase the levels of hypoxia-inducible factors (HIFs) when experiencing hypoxia, and these tumors have an increased risk of metastasis [6]. The *HIF* genes fall under the basic helix-loop-helix (bHLH) + PAS-containing gene family, and their proteins are characterized by the presence of an N-terminal bHLH DNA binding domain upstream of two PAS domains [8]. HIF-1 is a known regulator of processes such as angiogenesis, cell survival, and invasion [9].

Signal transducer and activator of transcription 3 (*STAT3*) is a transcription factor active in over 70% of breast cancers [10]. *STAT3* activates HIF-1α, leading to overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), major signaling proteins that promote angiogenesis [10, 11]. HIFs allow cells to adapt to hypoxic conditions by activating alternate metabolic pathways that are not dependent on oxygen, such as the pentose phosphate pathway, often doing so by targeting genes involved in cell survival, angiogenesis, metabolic reprogramming, immortalization, epithelial-mesenchymal transition (EMT), stem cell maintenance, resistance to radiation and chemotherapy, invasion and metastasis by altering different signaling pathways [6, 7, 9]. The VEGF, PI3K/Akt/mTOR, and MAPK signaling pathways are potential inhibition targets for the treatment of breast cancers [7].

One mouse model study by Liao et al. [9] suggested that HIF-1α is not required for the formation of mammary tumors but does accelerate tumor onset and progression. However, HIFs are necessary for the rapid proliferation of mammary epithelial tumor cells in hypoxic microenvironments [9]. Primary tumors and metastases can react to hypoxia differently, making the study of microenvironments necessary for developing new treatments [9]. A treatment targeting the hypoxic microenvironment of a primary tumor in one way may not be effective for a secondary tumor, and vice versa. In addition, tumors vary from patient to patient, which can impact the treatment's effectiveness.

The clear correlation between HIF presence and metastasis makes them potential prognostic markers for breast cancer. Drugs that block HIFs have promising therapeutic effects as they decrease primary tumor growth, invasion, vascularization, and metastasis [6]. Inhibitors of the HIF-1 pathway include those that impact HIF-1α protein levels, HIF-1 mRNA, HIF-1 dimerization, HIF-1 DNA binding, and HIF-1 transactivation [12]. The HIF-1 pathway is highly activated in TN breast cancer tumors, so they may be particularly effective in these cases, especially since current treatment options work poorly against this type of breast cancer [12].

EMT master transcription factors

EMT is a developmental process used during embryogenesis and utilized by cancers, for tumor progression in which cells lose cell junctions and apical-basal polarity while gaining cell motility and invasive ability to transition from epithelial to mesenchymal cells [11, 13]. EMT occurs in metastatic breast cancer because it increases the migration and invasion capabilities of cancer cells. EMT is a transdifferentiation process involved in wound healing in many organisms [14]. EMT has been evolutionarily conserved and cancer cells have adapted this function to increase stemness and promote metastasis [14].

EMT master regulators, including the zinc finger E-box binding homeobox (Zeb), Twist, and Snail families of transcription factors, are largely responsible for tumor cell dissemination and chemotherapeutic resistance through their regulatory function in the EMT/mesenchymal-epithelial transition (MET) pathways [10, 11]. These transcription factors induce EMT when overexpressed in epithelial cells, often through positive feedback loops and crosstalk [13, 14]. Overexpression of *SNAI1* activates *SNAI2*, *ZEB1/2*, *TWIST1*, and *TCF4*, *SNAI2* activates *TWIST1*, and *ZEB1* and *ZEB2* activate each other [14].

Conditional knockout in human mammary epithelial cells was used in one study to identify *ZEB1/2* as metastasis regulators [14]. In the same study, Dox-inducible short hairpin RNAs (shRNAs) were used to show that suppression of EMT through depletion of *ZEB1/2* blocked spontaneous lung metastasis [14]. *ZEB1* represses the expression of E-cadherin, a cell-cell adhesion protein, and transcription of epithelial polarity genes, allowing for increased metastasis in tumors with high *ZEB1* expression [15]. *ZEB1* downregulates epithelial markers and upregulates mesenchymal markers while also making them more like stem cells, allowing for drug and therapy resistance [13]. The *ZEB* family members both contain C2H2-type zinc fingers, the common DNA-binding motifs binding to paired CAGGTA/G E-box-like elements in the promoters of their target genes [13]. Cancer cells can activate DNA repair and survival signaling pathways to bypass therapies when *ZEB1* increases their stemness, making them more like cancer stem cells [15].

Twist1 promotes malignant tumor transformation by degrading p53 in order to bypass apoptosis and oncogene-induced aging [16]. Crosstalk between the PI3K/Akt and transforming growth factor beta (TGFβ) pathways is enabled by Twist phosphorylation, causing upregulation of the *TGFβ2* gene, an EMT activator [17]. Twist family members are also associated with the EMT-reversal process, MET [17]. In this process, mesenchymal cells regain epithelial characteristics after EMT. MET is important to distant metastases (Figure 1) [16].

The Snail family consists of two members: Snail1/Snail and Snail2/Slug [18]. Snail is a transcriptional repressor of *CDH1*, the E-cadherin gene, which links Snail to EMT as low E-cadherin expression levels are indicative of the transition to the mesenchymal phenotype [18]. Additionally, cells with Snail overexpression experience lower frequencies of apoptosis when exposed to radiation and chemotherapies, and they have increased immunosuppression [18].

HIF-1α is a clear target for treating TN breast cancer, as it has been proven to induce and promote breast cancer metastasis by regulating EMT, degrading extracellular matrix, inducing pre-metastatic niche, and regulating the directional movement of TNBC cells by transcribing integrins [19].

However, Antón-García et al. [20] have found experimental evidence that *SNAI1* and *ZEB1* may not be considered EMT master regulators because TGFβ1-induced EMT occurs independently of either transcription factor.

Other transcription factors

There are a multitude of transcription factors involved in breast cancer, and current research has only explored the mechanisms of a limited few.

SOX family

Sex determining region Y (SRY)-related high-mobility group (HMG) box (*SOX*) genes code for DNA-binding proteins that help regulate cell differentiation, organogenesis, and other developmental processes [21]. The *SOX* family contains more than 20 members in vertebrates, which are classified into eight groups [21]. *SOX* transcription factors are involved in cell determination and regulation of cell plasticity in normal cells, but in cancer cells, these processes are abnormally regulated, leading to the promotion of tumor heterogeneity and metastasis [22]. *SOX4* contributes to breast cancer metastasis by activating the TGFβ pathway and promoting the expression of EMT inducers [21]. *SOX2* expression is positively correlated with tumor size and promotes angiogenesis to enable lymph node metastasis [21, 23]. *SOX9* accumulation in the cytoplasm increased proliferation, migration, and invasion, and targeting this gene showed less metastasis [21]. The *SOX* gene family transcription factors are other potential targets for treatment due to their roles in metastatic processes.

ETS family

The E26 transformation-specific (*ETS*) family is a large transcription factor family consisting of 27 *ETS* genes in humans which can be structurally categorized into 11 subfamilies [24]. The *ETS* family of transcription factors regulates signaling, development, apoptosis, and metastatic processes [24]. Increased

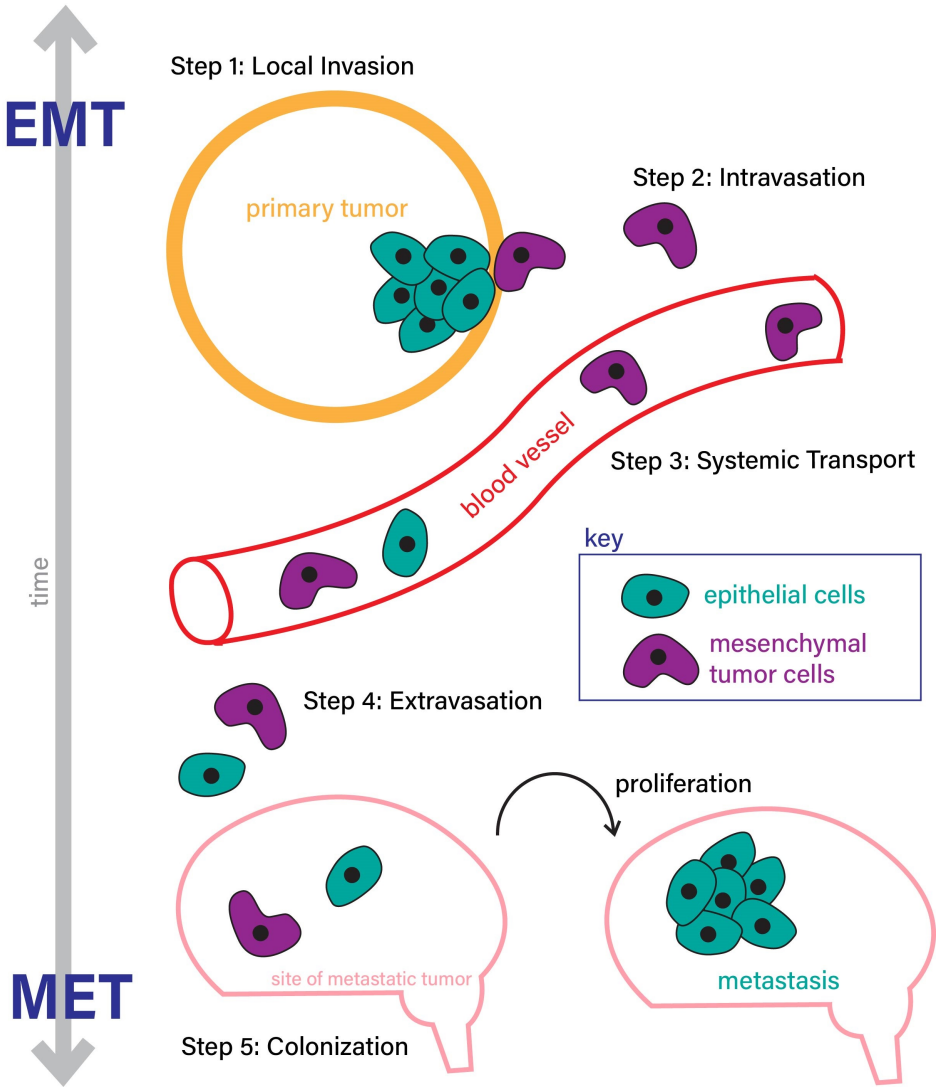

Figure 1. Epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET) processes. EMT occurs through (step 1) local invasion and formation of the initial tumor, (step 2) intravasation to enter the bloodstream, (step 3) systematic transport to a metastatic site, usually another organ, (step 4) extravasation out of the bloodstream, and (step 5) colonization and formation of a metastatic tumor through cell proliferation. MET is the reversal process, which occurs in the same steps in the reverse order as labeled in this figure (steps 5 to 1)

Note. Adapted from "Epithelial–mesenchymal plasticity in carcinoma metastasis" by Tsai JH, Yang J. Genes Dev. 2013;27:2192–206 (https://genesdev.cshlp.org/content/27/20/2192.long). CC BY-NC.

expression of *ETS* transcription factors has been observed in invasive and metastatic breast tumors and indicates poor prognosis [24]. The *ETS* family plays a role in breast cancer metastasis by affecting genes such as *HER2* and *VEGF* that are related to steps in the metastatic process such as proliferation, transformation, migration, invasion, anti-apoptosis, and angiogenesis [24]. A subgroup in the *ETS* family called the *PEA3* group is overexpressed in both human and mouse mammary tumors [25]. *PEA3* overexpression increases invasion and migration and is positively correlated with *HER2/neu* expression in 25–30% of *HER2*-positive breast cancers [24]. *ETS1* overexpresses Long Intergenic Non-protein Coding RNA 1016 (LINC01016), suppressing some ubiquitination degradation in breast cancer cells [26]. *ETS1* is correlated with invasiveness, EMT, and angiogenesis, and *ETS2* is correlated with apoptosis, so these transcription factors also impact breast cancer metastasis through differential regulation of metastatic processes [24].

Yin Yang 1

Yin Yang 1 (*YY1*) is a transcription factor often upregulated in many cancers, including metastatic breast cancer [27]. *YY1* is negatively correlated with the survival of breast cancer patients and positively

correlated with cancer stem cell markers such as *SOX2*, *OCT4*, *BMI1*, and *NANOG*, all of which are related to drug resistance [27, 28]. *YY1* regulates *BRCA1* and *HER2* tumorigenic pathways to promote tumor angiogenesis and metastasis [28]. The main contribution of *YY1* to metastatic breast cancer is its ability to increase cancer stem cell qualities in tumors, which helps enable metastasis.

FoxM1

Forkhead box M1 (FoxM1) is a transcription factor that regulates the cell cycle and mitotic spindle formation in normal cell growth and carcinogenesis by promoting cell motility, invasion, EMT, and metastasis [29]. FoxM1 expression is associated with increased tumor size, lymphovascular invasion, and lymph node metastases [29]. FoxM1 has been implicated in each stage of metastasis by promoting EMT, activating the TGFβ pathway, and modulating the extracellular matrix through the regulation of the other genes [29, 30]. Because of the evident role of FoxM1 in all breast cancer stages and in all breast cancer subtypes, it is a promising potential therapeutic target to block [31, 32].

Bach1

BTB domain and CNC homology 1 (Bach1) is a transcription factor with increased expression in breast cancer cells [33]. Bach1 is a known regulator of heme homeostasis, oxidative stress response, mitochondrial metabolic processes, and the cell cycle [33]. Overexpression of Bach1 promotes migration, invasion, and hypoxia-related pathways [34]. Specifically, in TN breast cancer cells, Bach1 regulates pathways and the expression of genes involved in cellular respiration, affecting the survival of cancer cells [33]. Bach1, like many transcription factors, proves to be a useful target for the treatment and prognosis of metastatic breast cancer.

SIX family

The sineoculis homeobox homolog (*SIX*) family of transcription factors has six members which are important to cell proliferation, differentiation, apoptosis, adhesion, and migration [35]. One study found that expression levels of *SIX1*, *SIX2*, *SIX3*, and *SIX4* were increased in breast cancer cells as compared to low expression in non-cancerous cells [35]. *SIX1* promotes invasion and metastasis by enabling EMT through downregulation of E-cadherin, an epithelial marker, promotes angiogenesis through regulation of *VEGF*, and promotes Ezrin expression, which plays a role in cell adhesion [35, 36]. *SIX2* upregulates *ZEB2* to downregulate E-cadherin, both of which are related to EMT and MET [35]. *SIX1* knockout in animal models has decreased tumor size [36].

RUNX2

The runt-related transcription factor (*RUNX*) family of transcription factors has three members, each with different physiological and developmental roles [37]. *RUNX1* and *RUNX3* act as tumor suppressors in breast cancer cells, while *RUNX2* can act as either a tumor suppressor or an oncogene in cancer cells [37]. Expression levels of *RUNX2* are increased in breast cancer tumors [38]. *RUNX2* is involved in responding to DNA damage, regulating *VEGF*, and in several estrogen signaling pathways and the *TGFβ* pathway [38]. *RUNX2* is important to osteogenesis and bone formation, so it is linked to breast cancer metastasis in the bone as it allows cancer cells to execute osteomimicry and invade bone composition [38].

MYC

The myelocytomatosis (*MYC*) oncogene family consists of three members, *C-MYC*, *L-MYC*, and *N-MYC*, all of which belong to the superfamily of bHLH leucine zipper (bHLHLZ) DNA binding proteins [39]. MYC proteins regulate a wide range of genes involved in several cellular processes, including cell growth, differentiation, apoptosis, angiogenesis, DNA repair, protein translation, immune response, and stem cell formation [39]. These regulatory functions suggest that MYC can contribute to cancer by enhancing cell proliferation, inhibiting cell death, modulating metabolism, promoting angiogenesis, and regulating stem cell formation [39]. Amplification of c-Myc and the activation of pathways downstream are related to high metastatic

ability in breast tumors [40]. Myc-amplification-mediated glutamine-related metabolic pathways are upregulated in the luminal B, *HER2*-positive, and TN breast cancers [40].

KLFs

Kruppel-like factors (KLFs), a subgroup of the *Sp1/KLF* family, contains seventeen members, each with three C2H2-type zinc fingers [41]. KLFs play roles in cell proliferation, apoptosis, EMT, and invasion and are connected to pathways involving *E2F*, *MYC*, and *p53* [41]. Most KLFs are ubiquitously expressed, while others have cell- or tissue-specific expression [41]. KLFs regulate metastatic processes both positively and negatively. KLF8 promotes but KLF6 and KLF9 inhibit changes in the extracellular matrix, KLF8 stimulates and KLF8 and KLF 9 downregulate invasion, KLF4, KLF 5, and KLF17 restrain and KLF8, KLF6-splice variant (SV), and KLF16 promote EMT [41–43]. KLF11 in tumor cells promotes tumor growth [44]. KLF9 represses breast cancer invasion and metastasis by upregulating E-cadherin [42]. KLF16 deletion was found to suppress EMT, migration, and invasion in breast cancer [43].

c-Jun

c-Jun is a protein encoded by the proto-oncogene *JUN* [45]. c-Jun is involved in several processes in breast cancer including proliferation, differentiation, growth, apoptosis, cell migration, and transformation [45]. c-Jun directly binds to and activates at least four genes associated with breast cancer metastasis to the lungs [45]. c-Jun is closely associated with metastasis and acts as both suppressor and oncogene in different situations [46]. c-Jun is also related to glucose metabolism, which may be a mechanism for metastasis based on how c-Jun is related to the expression of glucose transporter protein type 1 (*GLUT1*), a membranous glucose transporter [46]. c-Jun promotes cell growth in breast cancer by interacting with estrogen receptors [47].

Metastatic processes as dictated by transcription factors

Metastasis occurs through invasion, intravasation, transport, extravasation, and colonization [24]. Transcription factors enable these steps through other processes: survival, angiogenesis, and EMT (Figure 2). Transcription factors do not always impact all of these processes, and studying which ones are affected by each transcription factor will give insight into how to implement them in therapeutic strategies.

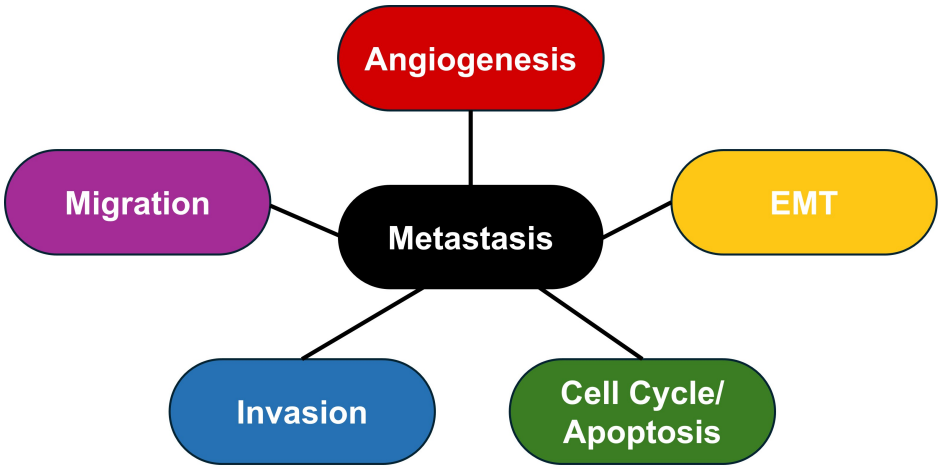

Figure 2. Metastatic processes. The main processes contributing to metastasis are angiogenesis, epithelial-mesenchymal transition (EMT), abnormal regulation of the cell cycle and apoptosis, invasion of tissue, and migration of tumor cells

Survival of tumor cells

Survival of primary tumor cells is crucial to metastasis, especially in the colonization step, as only the cancer cells able to survive in hypoxic conditions, against the human immune system, or against different therapies can go on to form metastases.

E2Fs contribute to tumor cell survival by also promoting cell proliferation by regulating the cell cycle. EMT transcription factors are associated with increased tumor survival and metastatic success because the EMT process often yields cancer stem cells with resistance to chemotherapy, possibly because these cells have a slower cell cycle than the rapidly dividing cells many therapies target [48]. HIFs play a large role in metastasis by providing blood to secondary tumors that would otherwise go through necrosis in deficient blood supply [49].

Angiogenesis and vascularization

Angiogenesis is the development of blood vessels, a process integral to the growth and metastatic capacity of malignant tumors. By increasing angiogenesis, tumors are recruiting their own blood supply to get more oxygen and nutrients to their cells. Vascularization uses angiogenesis to supply oxygen to new areas through blood. HIFs are major transcription factors related to these processes in the cellular response to hypoxia. Activation of the HIF pathway often occurs in breast cancer to stimulate the growth of blood vessels. The concentration of microvessels in a breast cancer sample proves to be an accurate indicator of metastasis or relapse [49].

Angiogenesis in breast cancer tumors results in new vasculature that is disorganized and incomplete compared to angiogenesis in normal tissues [7]. This causes decreased drug delivery and hinders antitumor immune responses, contributing to drug resistance [7].

In terms of metastatic cancer, intravasation and extravasation describe the movement of cancer cells into and out of blood vessels, respectively. These processes are integral to how cancer cells travel through the circulatory or lymphatic system to reach distant tissues. Expression of Zeb1 and Snail1 was found to promote intravasation and transmigration [16].

EMT and migration

Invasion refers to the penetration of neighboring tissues by cancer cells. EMT is one way that cancer cells leave the primary tumor to distant metastatic sites in the body. The transition to mesenchymal phenotype gives tumor cells stem-cell-like qualities. During EMT, the extracellular matrix is degraded to allow for invasion, when cancer cells first leave the primary tumor and enter a neighboring tissue [16]. There are three types of EMT representing different processes, and the regulation of all of them is similar [50]. The main pathways regulating EMT are the Notch, Wnt, Hedgehog (Hh), and *TGFβ* pathways [51]. One crucial EMT process is the loss of E-cadherin, a protein that maintains cell-cell contacts, which is downregulated by transcription factors like Snail, Slug, Ras homolog gene family, member B (RhoB), and *TWIST1* [41].

Snail, Zeb, and Twist family transcription factors promote EMT pathways, making them potential therapeutic targets. Six1 and RunX2 also drive EMT [52]. HIFs transactivate Snail transcription factors and directly regulate Twist and Zeb [53]. *HIF-1α*-induced EMT can be eliminated through inhibiting *ZEB1* [53].

Another effect of EMT is the increased resistance to chemotherapy acquired by breast cancer stem cells in the process as they have increased expression of anti-apoptotic and DNA repair genes [54].

MET, the reverse process of EMT, is important to the colonization step of metastasis to establish secondary tumors [16]. MET at metastatic sites is induced by the re-expression of E-cadherin, giving these secondary tumor cells greater susceptibility to chemotherapy [55].

Targeting transcription factors

Targeting transcription factors can block EMT, immune evasion, resistance, and stem cell properties, and can increase cell death and interfere with autoregulatory pathways in cancer cells [52].

Treatment

The most successful cancer treatment strategy targeting transcription factors so far has been through nuclear hormone receptor ligand binding domains, in other words, molecules that bind to specific receptors [52]. Drugs currently used to treat breast cancer affect the estrogen receptor, androgen receptor, retinoic

acid receptor, and glucocorticoid receptor [52]. The estrogen receptor is a particularly effective target as approximately 75% of breast cancers express it [52]. Widely used current breast cancer therapies include tamoxifen, a selective estrogen receptor modulator, and combination chemotherapy with trastuzumab to target *HER2* and bevacizumab to target VEGF [12].

Targeting protein-protein interactions between transcription factors, co-activators, and co-repressors impacts gene expression [52]. The interaction between *RUNX1* and *ETS1*, for example, occurs for DNA binding [52]. This strategy involves using inhibitors to block the proteins. These inhibitors can be small compounds, peptidomimetics, or stapled helix peptides [32].

Transcription factors are naturally regulated in cells through ubiquitylation and proteasomal degradation [52]. E3 ubiquitin ligases drive these processes [52]. One successful example is an inhibitor of the E3 ubiquitin ligase called von-Hippel Lindau (*VHL*) which interacts with the HIF-1α transcription factor [52]. Deubiquitinases prevent degradation; for example, ubiquitin specific peptidase 10 (*USP10*) protects *SLUG* and *SNAI2* from degradation, and *DUB3* increases *SNAI1* while protecting *TWIST* and *SLUG* [52].

Proteolysis targeting chimeras (PROTACs) can also degrade transcription factors [52]. Using PROTACs involves a ligand that binds to an E3 ligase covalently attached to a ligand that binds to a specific protein, which drives ubiquitylation and subsequent proteasome-mediated destruction [52]. PROTACs are a promising treatment method because they can knock down all functions of a transcription factor through complete degradation that may not be possible with inhibitory substances, which may also require lower dosage and improved efficacy [52].

The binding pockets of transcription factors can be targeted to prevent them from initiation transcription. Some transcription factors involve ligands, so one approach to inhibit these is to develop structural derivatives of the natural ligands for that transcription factor [32]. Most oncogenic transcription factors do not have these ligands, so a more effective approach for those would be to target the DNA-binding pocket of the protein through other protein interactions or direct binding to the DNA [32].

Biomarkers

Biomarkers are measured substances used to evaluate normal processes or responses to a treatment that can be prognostic and predictive [7]. Transcription factors can not only be targeted directly for treatment but they can be evaluated for diagnostic and prognostic purposes as biomarkers. Measuring and comparing levels of transcription factors can allow for correlation between those levels and metastasis, patient survival, etc.

Conclusions

Transcription factors enable invasion, intravasation, transport, extravasation, and colonization of metastasis through other processes such as angiogenesis and EMT, making them a prime target for cancer treatment. Treatment targeting transcription factors is possible because of their roles as master regulators, including E2Fs, HIFs, and EMT master regulators. These transcription factors can also be markers for breast cancer and metastatic prognosis. Several other transcription factors have also been identified to play a role in metastatic breast cancer, but this paper reviews the roles of E2Fs, HIFs, EMT master regulators, *SOX*, *ETS*, *YY1*, FoxM1, Bach1, *SIX*, *RUNX2*, *MYC*, KLFs, and c-Jun.

Transcription factors have diverse and crucial roles in metastatic breast cancer, as well as in every genetic illness. The possibilities for treatment and prevention are vast due to the multitude of transcription factors involved, so research focusing on promising transcription factors should be done, especially because metastasis causes 90 percent of breast cancer deaths [6]. The multitude of transcription factors that target processes integral to breast cancer metastasis and tumor progression provide further insight into the pathways and processes that should be targeted when aiming to treat breast cancer. Most known transcription factors do not have singular or concrete roles and functions, but impact metastasis through several processes (Table 1). Additional transcription factors can be potential treatment targets with a less

direct approach, as there are several that impact cancer progression by regulating more than one related gene.

Table 1. Summary of the discussed metastatic processes of breast cancer affected by various transcription factors

Transcription factor	Metastatic process affected				
	Angiogenesis/Vascularization	EMT/MET	Migration	Invasion	Cell cycle/Apoptosis
E2F	√			√	√
HIF	√	√		√	
EMT master regulators		√	√	√	√
SOX	√	√	√	√	
ETS	√	√	√	√	√
YY1	√				
FoxM1		√	√	√	
Bach1	√		√	√	
SIX	√	√			
RUNX				√	
MYC	√				√
KLFs		√	√	√	√
c-Jun			√		√

EMT: epithelial-mesenchymal transition; MET: mesenchymal-epithelial transition; HIF: hypoxia-inducible factor; *SOX*: sex determining region Y-related high-mobility group box; *ETS*: E26 transformation-specific; *YY1*: Yin Yang 1; FoxM1: forkhead box M1; Bach1: BTB domain and CNC homology 1; *SIX*: sineoculis homeobox homolog; *MYC*: myelocytomatosis; KLFs: Kruppel-like factors; *RUNX*: runt-related transcription factor

Current gaps in research include studies on combination therapies, such as targeting more than one transcription factor at once to increase effectiveness. Further research on tumor microenvironments and tumor heterogeneity in relation to transcription should be conducted because these topics are crucial to understanding therapy resistance in metastatic breast cancer. Since primary and secondary tumors possess different qualities, one transcription factor may only be partially effective for a patient.

The main takeaway is that metastasis is largely controlled by transcription factors, making them a target for the treatment of this deadly condition in breast cancer patients.

Abbreviations

Bach1: BTB domain and CNC homology 1

bHLH: basic helix-loop-helix

CDK: cyclin-dependent kinase

EMT: epithelial-mesenchymal transition

ETS: E26 transformation-specific

FoxM1: forkhead box M1

Her2: human epidermal growth factor receptor 2

HIFs: hypoxia-inducible factors

KLFs: Kruppel-like factors

MET: mesenchymal-epithelial transition

MYC: myelocytomatosis

PROTACs: proteolysis targeting chimeras

RUNX2: runt-related transcription factor 2

SIX: sineoculis homeobox homolog

SOX: sex determining region Y-related high-mobility group box

TGFβ: transforming growth factor beta

TN: triple-negative

VEGF: vascular endothelial growth factor

YY1: Yin Yang 1

Zeb: zinc finger E-box binding homeobox

Declarations

Author contributions

SM: Conceptualization, Investigation, Visualization, Writing—original draft, Writing—review & editing. CM: Conceptualization, Funding acquisition, Supervision. YL: Project administration, Validation, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

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References

1. Park M, Kim D, Ko S, Kim A, Mo K, Yoon H. Breast Cancer Metastasis: Mechanisms and Therapeutic Implications. Int J Mol Sci. 2022;23:6806. [DOI] [PubMed] [PMC]
2. Johnson J, Thijssen B, McDermott U, Garnett M, Wessels LF, Bernards R. Targeting the RB-E2F pathway in breast cancer. Oncogene. 2016;35:4829–35. [DOI] [PubMed] [PMC]
3. Hollern DP, Honeysett J, Cardiff RD, Andrechek ER. The E2F transcription factors regulate tumor development and metastasis in a mouse model of metastatic breast cancer. Mol Cell Biol. 2014;34:3229–43. [DOI] [PubMed] [PMC]
4. Liu ZL, Bi XW, Liu PP, Lei DX, Wang Y, Li ZM, et al. Expressions and prognostic values of the *E2F* transcription factors in human breast carcinoma. Cancer Manag Res. 2018;10:3521–32. [DOI] [PubMed] [PMC]

5. Song L, Li H, Ma RR, Liu S, Zhang GH, Guo XY, et al. E2F1-initiated transcription of PRSS22 promotes breast cancer metastasis by cleaving ANXA1 and activating FPR2/ERK signaling pathway. Cell Death Dis. 2022;13:982. [DOI] [PubMed] [PMC]
6. Gilkes DM, Semenza GL. Role of hypoxia-inducible factors in breast cancer metastasis. Future Oncol. 2013;9:1623–36. [DOI] [PubMed] [PMC]
7. de Heer EC, Jalving M, Harris AL. HIFs, angiogenesis, and metabolism: elusive enemies in breast cancer. J Clin Invest. 2020;130:5074–87. [DOI] [PubMed] [PMC]
8. Graham AM, Presnell JS. Hypoxia Inducible Factor (HIF) transcription factor family expansion, diversification, divergence and selection in eukaryotes. PLoS One. 2017;12:e0179545. [DOI] [PubMed] [PMC]
9. Liao D, Corle C, Seagroves TN, Johnson RS. Hypoxia-inducible factor-1α is a key regulator of metastasis in a transgenic model of cancer initiation and progression. Cancer Res. 2007;67:563–72. [DOI] [PubMed]
10. Hegde M, Daimary UD, Kumar A, Chinnathambi A, Alharbi SA, Shakibaei M, et al. STAT3/HIF1A and EMT specific transcription factors regulated genes: Novel predictors of breast cancer metastasis. Gene. 2022;818:146245. [DOI] [PubMed]
11. Ell B, Kang Y. Transcriptional control of cancer metastasis. Trends Cell Biol. 2013;23:603–11. [DOI] [PubMed] [PMC]
12. Liu ZJ, Semenza GL, Zhang HF. Hypoxia-inducible factor 1 and breast cancer metastasis. J Zhejiang Univ Sci B. 2015;16:32–43. [DOI] [PubMed] [PMC]
13. Wu HT, Zhong HT, Li GW, Shen JX, Ye QQ, Zhang ML, et al. Oncogenic functions of the EMT-related transcription factor ZEB1 in breast cancer. J Transl Med. 2020;18:51. [DOI] [PubMed] [PMC]
14. Addison JB, Voronkova MA, Fugett JH, Lin CC, Linville NC, Trinh B, et al. Functional Hierarchy and Cooperation of EMT Master Transcription Factors in Breast Cancer Metastasis. Mol Cancer Res. 2021; 19:784–98. [DOI] [PubMed] [PMC]
15. Zhang P, Sun Y, Ma L. ZEB1: at the crossroads of epithelial-mesenchymal transition, metastasis and therapy resistance. Cell Cycle. 2015;14:481–7. [DOI] [PubMed] [PMC]
16. Tsai JH, Yang J. Epithelial–mesenchymal plasticity in carcinoma metastasis. Genes Dev. 2013;27: 2192–206. [DOI] [PubMed] [PMC]
17. Tang H, Massi D, Hemmings BA, Mandalà M, Hu Z, Wicki A, et al. AKT-ions with a TWIST between EMT and MET. Oncotarget. 2016;7:62767–77. [DOI] [PubMed] [PMC]
18. de Herreros AG, Peiró S, Nassour M, Savagner P. Snail family regulation and epithelial mesenchymal transitions in breast cancer progression. J Mammary Gland Biol Neoplasia. 2010;15:135–47. [DOI] [PubMed] [PMC]
19. Liu Q, Guan C, Liu C, Li H, Wu J, Sun C. Targeting hypoxia-inducible factor-1alpha: A new strategy for triple-negative breast cancer therapy. Biomed Pharmacother. 2022;156:113861. [DOI] [PubMed]
20. Antón-García P, Haghighi EB, Rose K, Vladimirov G, Boerries M, Hecht A. TGFβ1-Induced EMT in the MCF10A Mammary Epithelial Cell Line Model Is Executed Independently of SNAIL1 and ZEB1 but Relies on JUNB-Coordinated Transcriptional Regulation. Cancers (Basel). 2023;15:558. [DOI] [PubMed] [PMC]
21. Grimm D, Bauer J, Wise P, Krüger M, Simonsen U, Wehland M, et al. The role of SOX family members in solid tumours and metastasis. Semin Cancer Biol. 2020;67:122–53. [DOI] [PubMed]
22. Liu Y, Guo W. SOX factors as cell-state regulators in the mammary gland and breast cancer. Semin Cell Dev Biol. 2021;114:126–33. [DOI] [PubMed] [PMC]
23. Mehta GA, Khanna P, Gatza ML. Emerging Role of SOX Proteins in Breast Cancer Development and Maintenance. J Mammary Gland Biol Neoplasia. 2019;24:213–30. [DOI] [PubMed] [PMC]
24. Kar A, Gutierrez-Hartmann A. Molecular mechanisms of ETS transcription factor-mediated tumorigenesis. Crit Rev Biochem Mol Biol. 2013;48:522–43. [DOI] [PubMed] [PMC]

25. de Launoit Y, Chotteau-Lelievre A, Beaudoin C, Coutte L, Netzer S, Brenner C, et al. The PEA3 Group of ETS-related Transcription Factors. In: Mol JA, Clegg RA, editors. Biology of the Mammary Gland. Boston, MA: Springer US; 2002. pp. 107–16. [DOI] [PubMed]
26. Sun Y, Zhang H, Ma R, Guo X, Zhang G, Liu S, et al. ETS-1-activated LINC01016 over-expression promotes tumor progression via suppression of RFFL-mediated DHX9 ubiquitination degradation in breast cancers. Cell Death Dis. 2023;14:507. [DOI] [PubMed] [PMC]
27. Kaufhold S, Garbán H, Bonavida B. Yin Yang 1 is associated with cancer stem cell transcription factors (SOX2, OCT4, BMI1) and clinical implication. J Exp Clin Cancer Res. 2016;35:84. [DOI] [PubMed] [PMC]
28. Guo Q, Wang T, Yang Y, Gao L, Zhao Q, Zhang W, et al. Transcriptional Factor Yin Yang 1 Promotes the Stemness of Breast Cancer Cells by Suppressing miR-873-5p Transcriptional Activity. Mol Ther Nucleic Acids. 2020;21:527–41. [DOI] [PubMed] [PMC]
29. Saba R, Alsayed A, Zacny JP, Dudek AZ. The Role of Forkhead Box Protein M1 in Breast Cancer Progression and Resistance to Therapy. Int J Breast Cancer. 2016;2016:9768183. [DOI] [PubMed] [PMC]
30. Zhang YL, Ma Y, Zeng YQ, Liu Y, He EP, Liu YT, et al. A narrative review of research progress on FoxM1 in breast cancer carcinogenesis and therapeutics. Ann Transl Med. 2021;9:1704. [DOI] [PubMed] [PMC]
31. O'Regan RM, Nahta R. Targeting forkhead box M1 transcription factor in breast cancer. Biochem Pharmacol. 2018;154:407–13. [DOI] [PubMed] [PMC]
32. Lambert M, Jambon S, Depauw S, David-Cordonnier MH. Targeting Transcription Factors for Cancer Treatment. Molecules. 2018;23:1479. [DOI] [PubMed] [PMC]
33. Padilla J, Lee J. A Novel Therapeutic Target, BACH1, Regulates Cancer Metabolism. Cells. 2021;10:634. [DOI] [PubMed] [PMC]
34. Liang Y, Wu H, Lei R, Chong RA, Wei Y, Lu X, et al. Transcriptional network analysis identifies BACH1 as a master regulator of breast cancer bone metastasis. J Biol Chem. 2012;287:33533–44. [DOI] [PubMed] [PMC]
35. Xu HX, Wu KJ, Tian YJ, Liu Q, Han N, He XL, et al. Expression profile of SIX family members correlates with clinic-pathological features and prognosis of breast cancer: A systematic review and meta-analysis. Medicine (Baltimore). 2016;95:e4085. [DOI] [PubMed] [PMC]
36. Blevins MA, Towers CG, Patrick AN, Zhao R, Ford HL. The SIX1-EYA transcriptional complex as a therapeutic target in cancer. Expert Opin Ther Targets. 2015;19:213–25. [DOI] [PubMed] [PMC]
37. Chimge NO, Frenkel B. The RUNX family in breast cancer: relationships with estrogen signaling. Oncogene. 2013;32:2121–30. [DOI] [PubMed] [PMC]
38. Wysokinski D, Blasiak J, Pawlowska E. Role of RUNX2 in Breast Carcinogenesis. Int J Mol Sci. 2015;16:20969–93. [DOI] [PubMed] [PMC]
39. Duffy MJ, O'Grady S, Tang M, Crown J. MYC as a target for cancer treatment. Cancer Treat Rev. 2021;94:102154. [DOI] [PubMed]
40. Wang L, Zhang S, Wang X. The Metabolic Mechanisms of Breast Cancer Metastasis. Front Oncol. 2021;10:602416. [DOI] [PubMed] [PMC]
41. Zhang J, Li G, Feng L, Lu H, Wang X. Krüppel-like factors in breast cancer: Function, regulation and clinical relevance. Biomed Pharmacother. 2020;123:109778. [DOI] [PubMed]
42. Bai X, Jiang X, Liu Y, Wang Y, Jiang X, Song G, et al. Krüppel-like factor 9 upregulates E-cadherin transcription and represses breast cancer invasion and metastasis. Am J Cancer Res. 2021;11:3660–73. [PubMed] [PMC]
43. Bang S, Li J, Zhang M, Cui R, Wu X, Xin Z, et al. The Clinical Relevance and Function of Krüppel-Like Factor 16 in Breast Cancer. Cancer Manag Res. 2020;12:6373–83. [DOI] [PubMed] [PMC]

44. Lin L, Pfender K, Ditsch N, Kuhn C, Rahmeh M, Peng L, et al. KLF11 is an independent negative prognostic factor for breast cancer from a cohort study and induces proliferation and inhibits apoptosis in vitro. Breast Cancer. 2023;30:758–71. [DOI] [PubMed] [PMC]
45. Shao W, Li S, Li L, Lin K, Liu X, Wang H, et al. Chemical genomics reveals inhibition of breast cancer lung metastasis by Ponatinib via c-Jun. Protein Cell. 2019;10:161–77. [DOI] [PubMed] [PMC]
46. Zhu P, Liu G, Wang X, Lu J, Zhou Y, Chen S, et al. Transcription factor c-Jun modulates GLUT1 in glycolysis and breast cancer metastasis. BMC Cancer. 2022;22:1283. [DOI] [PubMed] [PMC]
47. Jiang C, Zhu Y, Chen H, Lin J, Xie R, Li W, et al. Targeting c-Jun inhibits fatty acid oxidation to overcome tamoxifen resistance in estrogen receptor-positive breast cancer. Cell Death Dis. 2023;14:653. [DOI] [PubMed] [PMC]
48. Chang JC. Cancer stem cells: Role in tumor growth, recurrence, metastasis, and treatment resistance. Medicine (Baltimore). 2016;95:S20–5. [DOI] [PubMed] [PMC]
49. Madu CO, Wang S, Madu CO, Lu Y. Angiogenesis in Breast Cancer Progression, Diagnosis, and Treatment. J Cancer. 2020;11:4474–94. [DOI] [PubMed] [PMC]
50. Wang Y, Zhou BP. Epithelial-mesenchymal transition in breast cancer progression and metastasis. Chin J Cancer. 2011;30:603–11. [DOI] [PubMed] [PMC]
51. Takebe N, Warren RQ, Ivy SP. Breast cancer growth and metastasis: interplay between cancer stem cells, embryonic signaling pathways and epithelial-to-mesenchymal transition. Breast Cancer Res. 2011;13:211. [DOI] [PubMed] [PMC]
52. Bushweller JH. Targeting transcription factors in cancer — from undruggable to reality. Nat Rev Cancer. 2019;19:611–24. [DOI] [PubMed] [PMC]
53. Gilkes DM. Implications of Hypoxia in Breast Cancer Metastasis to Bone. Int J Mol Sci. 2016;17:1669. [DOI] [PubMed] [PMC]
54. da Silveira WA, Palma PVB, Sicchieri RD, Villacis RAR, Mandarano LRM, Oliveira TMG, et al. Transcription Factor Networks derived from Breast Cancer Stem Cells control the immune response in the Basal subtype. Sci Rep. 2017;7:2851. [DOI] [PubMed] [PMC]
55. Demirkan B. The Roles of Epithelial-to-Mesenchymal Transition (EMT) and Mesenchymal-to-Epithelial Transition (MET) in Breast Cancer Bone Metastasis: Potential Targets for Prevention and Treatment. J Clin Med. 2013;2:264–82. [DOI] [PubMed] [PMC]