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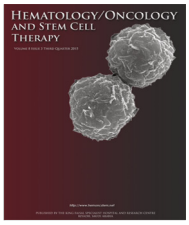

REVIEW ARTICLE

Molecular mediators of breast cancer metastasis

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Relapse

Abstract
Breast cancer has the highest incidence rate of malignancy in women worldwide. A major clinical challenge faced by patients with breast cancer treated by conventional therapies is frequent relapse. This relapse has been attributed to the cancer stem cell (CSC) population that resides within the tumor and possess stemness properties. Breast CSCs are generated when breast cancer cells undergo epithelial-mesenchymal transition resulting in aggressive, highly metastatic, and invasive phenotypes that exhibit resistance towards chemotherapeutics. Metastasis, a phenomenon that aids in the migration of breast CSCs, occurs through any of three different routes: hematogenous, lymphatic, and transcoelomic. Hematogenous dissemination of breast CSCs leads to metastasis towards distant unrelated organs like lungs, liver, bone, and brain causing secondary tumor generation. Activation of metastasis genes or silencing of metastasis suppressor genes often leads to the advancement of metastasis. This review focuses on various genes and molecular factors that have been implicated to regulate organ-specific breast cancer metastasis by defying the available therapeutic interventions.

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Contents

Introduction

Cancer is a heterogeneous disease characterized by uncontrolled growth and spread of malignant cells harboring genetic or epigenetic alterations. These cells are capable of evading the host immune response and invading other distant organs where they form secondary tumors by the process known as metastasis [1]. Globally, breast cancer is the most commonly diagnosed malignancy causing the highest number of cancer-related deaths among women [2]. Based on the expression of hormone receptors, namely estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), breast cancer can be classified into four molecular subtypes: Luminal A (ER^+/PR^+), Luminal B ($ER^+/PR^+/HER2^{-/+}/Ki67^+$), HER2 overexpressing ($ER^-/PR^-/HER2^+$), and basal-like ($ER^-/PR^-/HER2^-$) [3]. Among these, basal-like, or triple-negative breast cancers (TNBCs), lack the expression of all three hormonal receptors and cannot be efficiently targeted by hormonal therapy. These TNBCs are very aggressive and exhibit poor prognosis [4]. Patients suffering from TNBCs exhibit early risk of relapse as well as a low survival rate when compared with non-TNBC patients. This relapse is attributed to the subpopulation of cells possessing the tumor-initiating properties, residing within the tumor, known as breast cancer stem cells (CSCs) [5]. The generation of these CSCs has been explained by the CSC model suggesting that a small subset of cells within the tumor is responsible for maintaining tumorigenesis and establishing cellular heterogeneity [6]. CSC hypothesis suggests that epithelial cancer cells tend to lose their apical-basal polarity and gain mesenchymal phenotype, exhibiting more metastatic and invasive properties and thereby leading to the generation of CSCs. This phenomenon has been termed as epithelial-mesenchymal transition (EMT), regulated by various transcription factors (TFs), which are referred to as EMT-TFs [7]. CSCs possess stemness property-the ability to self-renew and proliferate asymmetrically leading to the generation of a cancer cell and a CSC [8]. The characteristic features exhibited by breast CSCs are aggressiveness, resistance to conventional chemotherapeutics, highly metastatic, and invasive phenotypes [9]. This review focuses on the latest studies on breast cancer metastasis, how it is regulated by various molecular factors, and how it can be targeted by treatments that are being developed.

Metastasis: A key phenomenon for cancer relapse

Metastasis, a multistep process, involves the EMT-mediated generation of aggressive CSCs that degrade the extracellular matrix (ECM) and adhere to the substratum, followed by

Table 1 Percent Incidence and the Predominant Breast Cancer Subtype Responsible for Breast Cancer Metastasis.

Metastatic site	Percent incidence (%)	Predominant breast cancer subtype
Lungs	21—32 [28]	Basal-like [19]
Bone	30—60 [28]	Luminal [23]
Liver	15—32 [28]	Luminal-A and HER2$^+$ [27]
Brain	4—10 [28]	Basal-like and HER2$^+$ [28]

HER2 - Human Epidermal Growth Factor Receptor 2.

intravasation into the blood or lymphatic vessels, wherein they survive by resisting anoikis, evade the immune responses, and invade distant organs [10]. Once these CSCs reach the secondary site, they revert to epithelial cell phenotype by a phenomenon called mesenchymal-epithelial transition (MET) and colonize to generate secondary tumors. Metastasis occurs through any of the three different routes-blood, lymphatic systems, and body cavities which are termed as hematogenous, lymphatic, and transcoelomic routes, respectively [11].

Breast cancer metastasis

The metastatic spread of cancer cells depends on various factors such as anatomy, physiology, and molecular features of the primary tumor. In most cases, tumor cell dissemination predominantly occurs by a hematogenous route. However, in the case of breast tumors, the lymphatic system is preferentially utilized for tumor cell dissemination. The aggressiveness of cancer depends on the lymph node metastasis that is associated with poor prognosis [12]. Lymph node invasion is governed by the location of the tumor within the breast. Tumor cells progress towards the sentinel lymph node from the primary tumor site and exit from the efferent lymphatic system. However, the direct route from lymph nodes to the metastatic organs has not yet been identified. Reports indicate that during the early stages of breast cancer, malignant tumor cells disseminate through blood [13] to the bone, lung, liver, and brain [14]. Over 90% of breast cancer-related deaths are due to secondary tumors in a distant organ, thus emphasizing the severity of metastasis [15]. The expression of certain molecular mediators at the primary site as well as the metastatic site determines the metastasis of malignant cells to a particular organ. For example, vascular endothelial growth factor A (VEGF A) secretion from the primary tumor is a signal to demarcate the metastatic microenvironment. Studies have revealed that the expression of the chemokine receptor CXCR4 in the liver, lung, and bone facilitates the dissemination of primary breast cancer cells towards the secondary site, while its silencing suppresses metastasis [16]. Interestingly, breast cancer metastasis to different tissues is also dependent upon the molecular subtypes of breast cancer (Table 1). In this review, we have elaborated on the hematogenous dissemination of breast cancer cells to various organs.

Breast to lung metastasis

Metastatic breast cancers majorly metastasize to lung or bone [17]. Reportedly, 60% of deaths in the case of metastatic breast cancers are due to lung metastasis, and the patient survival rate is as less as 25 months [18]. Clinical studies conducted by Luck et al. [19] revealed that lung metastasis is relatively more prominent in TNBC patients than in non-TNBC patients, although few cases have been also reported in the latte. Epidermal growth factor receptor (EGFR) expression has been strongly correlated with lung metastasis as the case studies reveal that 75.8% of patients who have shown lung as their primary metastatic site were positive for EGFR or HER2 [20]. Further studies on the chances of breast cancer metastasis to lungs have revealed that the metastasis rate was also high in the case of luminal B breast cancer patients following the highest rate observed in TNBC patients. HER2$^+$ and luminal A are the least common subtypes with a 13.3% and 6.7% probability, respectively, of displaying lung metastasis [21]. The development of lung metastases in patients with known malignancies indicates disseminated disease and places the patient in stage IV in TNM (tumor, node, and metastasis) staging systems.

Breast to bone metastasis

Bone has been regarded as another common metastatic site for breast cancers contributing to 30—60% of breast cancer metastasis. Bone metastasis was observed to be predominant among patients diagnosed with luminal type of breast cancers [22]. A case study on breast cancer metastasis revealed that the chances of bone metastasis were highest in the case of luminal A followed by luminal B and HER2$^+$ breast cancer patient groups, and the least was observed in the case of TNBC patients [23]. A case study disclosed that tumors expressing SNAI1, a known EMT-TF, exhibited bone metastasis in 87 out of 145 (60%) patients with SNAI1-positive tumors [20]. The life expectancy has been reported to be as low as 24—26 months after the advent of breast cancer bone metastasis [24]. The prognosis of breast cancer metastasis into bone has been reported in patients with severe pain, reduced mobility, hypercalcemia, osteolysis, and bone fractures. In some cases, spinal cord compression and bone marrow aplasia also occur eventually resulting in morbidity [25].

Breast to liver metastasis

Liver metastasis, the third most common site for breast cancer metastasis, constitutes 15—32% of metastatic breast cancers [26]. Detection of the first distant recurrence in the liver was associated with the absence of SNAI1 expression in the breast tumor. The liver was the first distant metastatic site in 28 (19.3%) of the 145 women with SNAI1-positive cancer compared with 25 (36.2%) of the 69 women whose breast tumor did not express SNAI1 [20]. Among the various molecular subtypes, luminal A and HER2$^+$ exhibit predominant liver metastasis as compared with other subtypes of breast cancer [27]. Although

Table 2 Molecular Mediators as Breast Cancer Metastasis Activators.

Metastasis activators	Role	Potential therapeutic strategy
Growth factors		
TGF-β	Bone metastasis	TGF-β pan-neutralizing mAbs: 1D11, 2G7 along with doxorubicin treatment
PDGF	Bone and lung metastasis	PDGF mAbs
IL-1	Bone and lung metastasis	Combinatorial therapy of mAbs - PDR001, CJM112, Ilaris and EGFR tyr kinase inhibitor EGF816
BMP	Induce tumorigenesis, metastasis, and invasion	Soluble decoy receptors of the ligand-binding domains of BMP receptors
CXCL1	Lung metastasis	CXCl1 mAbs
Receptors		
PDGFRβ	Lung metastasis	PDGFRβ mAb: IMC-2C5
EGFR	Brain metastasis	Panitumumab with 5-fluorouracil, epidoxorubicin, and cyclophosphamide followed by docetaxel
CXCR4	Lung and liver metastasis	AMD3100 or Plerixafor
Integrins	αvβ3 - lung metastasis αvβ5 - liver metastasis	Integrin signaling specific antibodies, peptides, peptidomimetics, and other antagonists
Notch	Bone metastasis	miR-34a along with Paclitaxel and Adriamycin
Transcription factors		
TWIST1	Lungs metastasis	Harmine, inhibitor of TWIST1
ID1	Lungs metastasis	Small molecule inhibitors against ID1
ECM proteins		
VCAM-1	Lung & bone metastasis	Targeting integrins - VLA-4/α4β1 with mAbs to inhibit interaction with VCAM-1
VCAN	Lung metastasis	Knockdown of versican
Other factors		
PDK1	Liver metastasis	Small molecule inhibitors against PDK1
COX-2	Brain metastasis	Non-steroidal anti-inflammatory drugs (NSAIDs)
miRNAs	miR-19a and miR-141 - brain metastasis	Oligonucleotides targeting mature miRNA
Wnt/β-catenin	Lung metastasis	PORCN inhibitors, WNT ligand antagonists, and FZD antagonists/ mAbs

TGFβ - Transforming Growth Factor beta; PDGF - Platelet-derived Growth Factor; IL-1 - Interleukin 1; BMP - Bone Morphogenic Protein; CXCL1 - C-X-C motif chemokine ligand 1; PDGFRβ - PDGF Receptor beta; EGFR - Epidermal Growth Factor Receptor; CXCR4 - C-X-C chemokine receptor type 4; ID1 - Inhibitor of Differentiation 1; VCAM-1 - Vascular Cell Adhesion Molecule 1; VCAN - Versican; PDK1 - Pyruvate Dehydrogenase Kinase 1; COX-2 - Cycloxygenase 2; miRNAs - Micro Ribo Nucleic Acids; Wnt - Wingless-related integration site.

the TNBC patients show fewer chances of liver metastasis, the worst prognosis of liver metastasis has been also reported in these patients. Liver metastasis has been reported to be least in the case of luminal B breast cancer patients [21].

Breast to brain metastasis

Brain, although considered to be the most uncommon metastatic site for breast cancer, constitutes 4–10% of cases [28]. Basal-like and HER2$^+$ breast cancer subtypes exhibit a high extent of brain metastasis compared with other molecular subtypes of breast cancer. Luminal breast cancer patients exhibit the least cases of brain metastasis [21]. Expression of genes like nestin, prominin-1, CK5, and α-SMA in the breast tumor has been correlated with brain metastasis. The patient survival rate has been reported to be as less as 2 months after the development of brain metastases [29].

Molecular factors responsible for breast cancer metastasis

Preclinical studies and its clinical correlates from the pathological studies in the patient tumor samples have implicated the predominant role of various genes and molecular factors responsible for metastasis of breast cancer. Reports suggest that while the expression of specific genes was critical for the breast cancer cells or CSCs at the primary tumor site, breast, there are genes that are often expressed by the cells at the distant organs/tissues (secondary site) that drive these breast CSCs to migrate/metastasize towards the secondary site to form secondary tumors.

The main focus of the present review was to identify these molecular genes/factors that play a key role in the migration/metastasis of breast CSCs to distant secondary sites. These molecular genes/factors can be broadly classified into two categories: (a) metastasis activators and (b)

metastasis suppressors. Overexpression of metastasis activators and/or silencing of metastasis suppressors promotes the metastasis of cancer cells.

Metastasis activators

This class of metastasis modulators can be subdivided into five subcategories: (a) growth factors, (b) receptors, (c) TFs, (d) ECM proteins, and (e) other factors (Table 2).

Growth factors

This is the major class of molecular genes/factors that code for the proteins which promote various cellular activities like proliferation, differentiation, and migration. The growth factors that are reported to be involved in breast cancer metastasis includes the following.

Transforming growth factor-β. Transforming growth factor-β (TGF-β), a unique cytokine, acts as both tumor suppressor as well as an activator [30]. In the early stage of breast cancer, TGF-β acts as a tumor suppressor but as cancer progresses towards the advanced stage, it facilitates tumor metastasis, and the suppressive function of TGF-β gets restricted as the tumor-suppressive pathway gets deactivated [31]. Induction of metastasis through TGF-β facilitates the activation of Smads that in turn promote the expression of various other cytokines, thereby leading to breast cancer metastasis and invasion [31]. The upregulation of TGF-β expression at bone leads to breast cancer metastasis towards bone [32]. TGF-β activation led to the induction of Jagged1, a Notch signaling pathway mediator that marks the onset of EMT [33]. An osteolytic outcome was observed in the case of TGF-β-mediated breast cancer metastasis [34]. The cross-talk between TGF-β and various other signaling cascades also plays a dominant role in breast cancer metastasis (Fig. 1). For example, TGF-β transcriptional activation was observed to be downregulated during the Hippo pathway activation by RAS effector and Hippo kinase scaffold, RASSF1A. RASSF1A limits the nuclear translocation of the YAP1/SMAD2 complex, thereby downregulating TGF-β transcriptional activation [35]. The cross-talk between TGF-β-Wnt, unlike TGF-β-Hippo, is known to promote breast cancer metastasis. The upregulated expression of Wnt ligands and receptors has been directly correlated with poor clinical outcome. Most importantly, high Wnt7a expression is associated with reduced overall and

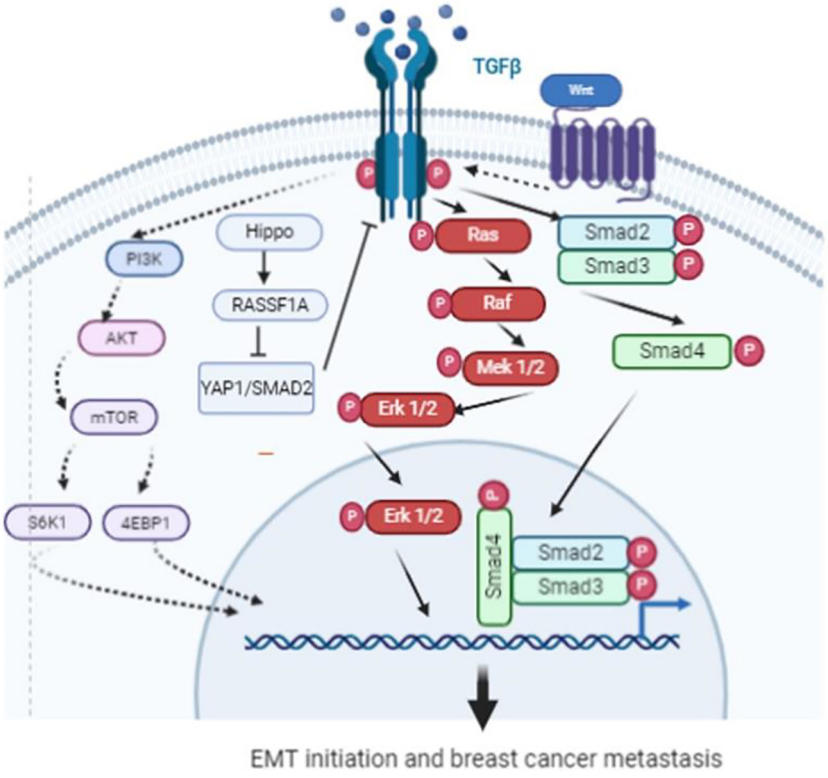

Fig. 1 Transforming growth factor-β (TGF-β) signaling cross-talk with various other pathways that leads to breast cancer metastasis. TGF-β induction-mediated activation of Smads in turn promotes the expression of various other cytokines leading to breast cancer metastasis and invasion. Hippo pathway activation by RASSF1A can downregulate the activation of TGF-β, while the Wnt pathway activates the TGF-β-mediated breast cancer metastasis. The cross-talk between TGF-β-PI_3K as well as TGF-β-EGFR/RAS also promotes breast cancer metastasis. PI3K - Phospoinositide 3-kinase; AKT - Protein Kinase B; mTOR - Mechanistic Target of Rapamycin; S6K1 - Ribosomal Protein S6 Kinase Beta-1; 4EBP1 - Eukaryotic Translation Initiation Factor 4E Binding Protein 1; RASSF1A - Ras Association Domain Family Member 1A; YAP1 - Yes-associated Protein 1; RAS - Rat Sarcoma, Smad - Small mothers against decapentaplegic; Raf - Rapidly Accelarated Fibrosarcoma; Mek1/2 - Mitogen-activated Protein Kinase/Extracellular Signal-Regulated Kinase 1/2 (Erk 1/2); Wnt - Wingless-related Integration Site; EGFR - Epidermal Growth Factor Receptor.

metastasis-free survival of breast cancer patients. Wnt7a expression in breast cancer cells leads to the activation of fibroblasts into cancer-associated fibroblasts (CAFs) that facilitate tumor invasion and metastasis in a TGF-β signaling-dependent pathway [36]. In breast cancer cells, TGF-β-mediated phosphatidylinositol 3-kinase (PI_3K)/AKT pathway regulation led to the activation of downstream signaling molecules like mTOR, P70S6K, and 4E-BP1. The TGF-β-PI_3K/AKT cross-talk has led to the induction of EMT, cell migration, tumor metastasis, and cell differentiation. In the case of HER2-expressing breast cancer cells, TGF-β treatment-mediated AKT activation has led to enhanced cell migration [37]. This axis also has a key role in EMT initiation along with breast cancer metastasis. Studies have shown that the interplay between the TGF-β pathway and EGFR/RAS also facilitates EMT induction during breast cancer metastasis [38].

Platelet-derived growth factor. Platelet-derived growth factor (PDGFs) play a crucial role in cellular functions like cell proliferation and migration of numerous cell types. The aberrations in PDGF/PDGF receptor (PDGFR) signaling are implicated in diseases like cancer [39]. PDGF signaling results in breast cancer metastasis to bone. Reports suggest a strong correlation of TGF-β as well as PDGF expression in facilitating breast cancer metastasis to bone and lung [40]. In the case of breast cancers, PDGF-C binds and activates its cognate receptor that leads to tyrosine kinase pathway activation. This mediates fibroblast activation, secretion of a variety of cytokines, and formation of the cellular microenvironment. Activated fibroblasts, known as CAFs, secrete SDF-1/CXCR4 that promotes tumor metastasis. CAFs also facilitate tumor growth and metastasis by secreting cytokines such as hepatocyte growth factor, epidermal growth factor, basic fibroblast growth factor, and insulin-like growth factor. Overexpression of PDGF-D led to increased proliferation, decreased apoptosis, and induction of CXCR4 expression which promoted tumor growth and lymph node metastasis. PDGF-BB upregulates the expression of Il-33 that promotes metastasis through the recruitment of tumor-associated macrophages (TAMs). Pharmacological inhibition of the IL-33-ST2 signaling by a soluble ST2 significantly inhibited TAMs and metastasis. Genetic deletion of host IL-33 in mice blocked PDGF-BB-induced TAM recruitment and metastasis. PDGF signaling led to osteoblastic metastases, a type of bone metastasis, where the invaded breast cancer cells cause the proliferation of bone cells that increases bone density, ultimately leading to bone sclerosis [41].

Interleukin-1. Interleukin-1 (IL-1), the most potent cytokine, belongs to a large family of proteins comprising 11 different cytokines. Of these, IL-1β expression has been correlated with breast cancer relapse by metastasis into bone and generation of bone tumors [42]. Nutter et al. [43] have shown that MDA-IV, a breast cancer cell line that specifically infiltrates mouse bone, expresses high levels of IL-1β. Genome-wide mRNA expression array of human breast cancer suggested a positive correlation between IL-1B, osteoprotegerin (OPG), and CCL2. IL-1B upregulates OPG via p38 and p42/22 mitogen-activated protein kinase (MAPK) signaling pathway and induces OPG secretion, which also associates with macrophage infiltration in primary breast tumors. Inhibition of OPG in breast cancer cell lines showed reduced invasion and metastasis. Thus, the interplay between IL-1B and OPG plays a crucial role in mediating breast cancer metastasis. Inhibition of IL-1R signaling efficaciously reduced breast cancer metastasis into bone [44]. IL-1 also promotes breast cancer metastasis to the lung [45]. Studies conducted on the murine spontaneous mammary tumor model MMTV-PyMT lacking functional caspase-1 and NLRP3 in combination with pharmacological treatment to inhibit IL-1R resulted in the inhibition of inflammasome and IL-1 signaling. This led to reduced primary tumor growth, lung metastasis, and myeloid cell infiltration.

Bone morphogenetic protein. Bone morphogenetic protein (BMP3), also known as osteogenin, has been widely known for its role in osteogenesis and bone turnover [46]. Tumor development and progression are associated with genetic defects in BMP3 [47]. It activates the smad-dependent pathway during the BMP-mediated tumorigenesis [48]. Interestingly, smad-independent signaling pathways via p38 and JNK signaling have also been reported in breast cancer [49]. Other than BMP3, BMP2 and BMP4 are also known to induce tumorigenesis, metastasis, and invasion [50]. BMP2 may contribute to the invasiveness of tumor cells via induction of the ECM glycoprotein Tenascin-W in the tumor surrounding stroma. Overexpression of Tenascin-W in the stroma of breast cancer promotes invasion and migration of cancer cells through an interaction with α8 integrin. *In vitro* and *in vivo* studies suggest that BMP4 treatment results in increased invasion and migration.

C-X-C motif chemokine ligand 1. TAMs secrete C-X-C motif chemokine ligand 1 (CXCL1), which not only has a prominent role in EMT induction but also facilitates the migration and invasion of aggressive breast cancer cells [51]. It acts as a ligand for its cognate receptor, CXCR2, and the CXCL1/CXCR2 signaling promotes the migration and invasion ability of malignant cells [52]. The molecular mechanism of this signaling suggests that CXCL1 induces SOX4-mediated metastasis via NF-κB activation [53]. CXCL1 expression is associated with an increase in the aggressiveness of circulating breast tumor cells as well as lung relapse in breast tumors. CXCL1/2 from breast cancer cells recruits myeloid producers of S100A8/9, which in turn promote breast cancer metastasis.

Receptors

Platelet-derived growth factor receptor β. Platelet-derived growth factor receptor β (PDGFRβ) belongs to the family of receptor tyrosine kinases and is widely known for regulating cellular functions like proliferation, angiogenesis, migration, and invasion [54]. TGF-β acts as one of the upstream modulators of PDGFRβ that facilitates EMT induction [55]. PDGFRβ has been observed to be upregulated in breast cancers and results in poor prognosis [56]. It acts as a biomarker for TNBCs whose activation leads to the induction of PI_3K signaling (Fig. 2) [57]. Studies have suggested the activation of PDGFRβ signaling with the facilitation of breast cancer metastasis to the lung [58].

Epidermal growth factor receptor. Elevated level of EGFR is associated with the aggressiveness of TNBCs [59]. Report-

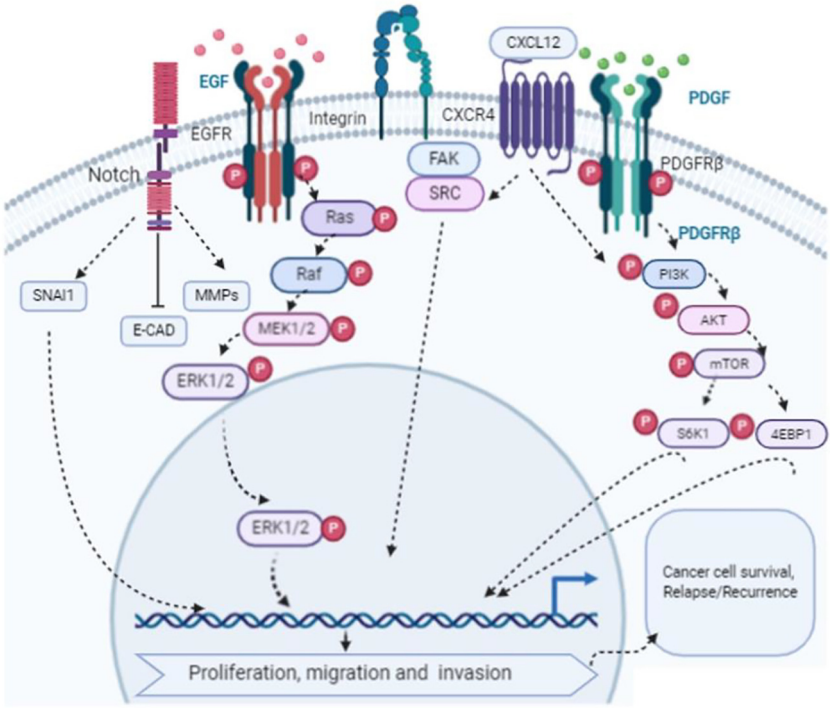

Fig. 2 Signaling pathways that mediate cancer cell proliferation, migration, and invasion. PDGFRβ activation-induced PI_3K signaling in aggressive breast cancers ultimately facilitates metastasis of breast tumors. Metastatic induction through ERK/PI_3K signaling was observed in the case of EGFR activation by EGF. Integrins signaling can activate downstream signaling intermediates like FAK and SRC which promote breast cancer metastasis. Upon CXCL12 binding onto CXCR4, several pathways get activated like PI_3K/AKT and FAK/SRC that will cause tumor cell dissemination. EGF - Epidermal Growth Factor; MMPs - Matrix metalloproteinases; E-CAD - E-cadherin; FAK - Focal Adhesion Kinase; SRC - Steroid Receptor Co-Activator; CXCL12 - C-X-C motif chemokine 12; CXCR4 - C-X-C chemokine receptro type 4; PDGF - Platelet-derived Growth Factor; PDGFRβ - PDGF Receptor beta.

edly, 15—30% of breast carcinomas that express high levels of EGFR exhibit poor prognosis [60], while 15—35% of the invasive breast cancers that express high levels of HER2 result in a marked decrease in the patient's survival [61]. Studies suggest that both EGFR and HER2 contribute to breast cancer metastasis to the brain [62]. Interestingly, EGFR expression in the nuclear compartment of the breast cancer cells led to the upregulation of cyclooxygenase 2 (COX-2), which in turn facilitates its transgression of the blood—brain barrier [63].

CXC chemokine receptor 4. CXCL12/CXCR4 axis has been reported to help in the development of primary breast tumorigenesis as well as plays a crucial role in secondary tumor formation by aiding the metastasis of breast cancer cells [64]. Xu et al. suggested that elevated expression oof CXCR4 in breast cancer cells led to metastasis to lung and liver [64]. At secondary tumor sites, CXCL12 acts as a chemoattractant for breast cancer cells expressing its cognate receptor, CXCR4, leading to migration and homing of breast cancer cells [65]. This CXCR4/CXCL12 axis, in turn, activates downstream signaling pathways like MAPK, PI_3K, and focal adhesion kinase that ultimately enhance the migration and invasion abilities [66]. In case of bone metastasis, this axis enables the Src/AKT pathway that helps in proliferation of cancer cells within the secondary tumor site in bone [67].

Integrins. These are transmembrane receptors that participate in cell—cell adhesion and are primarily composed of two subunits, α and β [68]. Among the various known integrins, αvβ3 expression is associated with malignant breast tumors facilitating tumor angiogenesis [69]. In the case of invasive as well as metastatic tumors, αvβ3 plays a crucial role in aiding distant metastases [70]. Reports suggest a mechanistic role of αvβ3 in breast cancer metastases to the lung. Integrin αvβ5 has been also reported to aid breast cancer metastasis to the liver [71].

Notch receptors. Increased expression of Notch1 or Jagged1 has been correlated with poor survival of breast cancer patients. Interestingly, expression of Slug was also observed to be increased with overexpression of Jagged1 or Notch1 in human breast cancers. Studies suggest that Notch activation by Jagged1 induces Slug expression as well as repression of the epithelial marker protein, E-cadherin, leading to EMT in breast epithelial cells. It was observed that inhibition of Notch signaling in the case of Slug-positive/E-cadherin—negative human breast cancer xenografts led to reduced primary tumor growth and distant metastases [72]. Activation of Notch signaling due to loss of Numb, a clathrin-associated sorting protein that modulates Notch signaling, resulted in EMT induction and acquisition of stem cell-like properties in TNBCs leading to early relapse and metastasis [73]. Notch1 facilitates breast cancer metastasis by activating

matrix metalloproteases like MMP-2 and MMP-9 as well as urokinase-type plasminogen activator (uPA), a target of Notch signaling that aids in ECM degradation. uPA expression is associated with poor clinical outcome and a high risk of metastasis that causes breast cancer recurrence. Studies show that Notch1 silencing decreased the uPA levels, whereas a positive correlation was observed in case of jagged1 and uPA. Upon uPA binding, plasminogen gets converted to plasmin, and uPA along with MMPs degrade ECM that facilitates tumor cell metastasis [74]. Notch is also reported to act indirectly via promoting the binding of hypoxia-inducible factor 1alpha (HIF-1α) to lysyl oxidase (LOX) promoter. This aids in the stabilization of Snail-1 and tissue inhibitor of metalloproteinase 4 syntheses, thus promoting EMT and metastasis [75]. A positive correlation between LOX expression and ER-negative in breast cancers is associated with bone metastasis [76].

Transcription factors

TWISt1. It belongs to the basic helix loop helix (bHLH) family of TFs that gets activated in the dimerized form [77]. It usually forms homo- or heterodimers with other TFs, such as E2A and E12, which ultimately decides the fate of the target genes expression-repression or activation. TWIST1 recognizes the consensus sequence, *CANNTG*, known as E-box on the promoter region of its target genes [78]. TWIST1 promotes breast cancer metastasis by upregulating the expression of PDGFR α (PDGFRα) and Jagged1 which facilitate in ECM degradation as well as invadopodia formation [79]. Foxa1 repression by TWIST1 enables migration, invasion, and metastasis of breast cancer cells [80]. TWIST1 has been also reported to be involved in the repression of luminal gene expression and induction of basal phenotype [68]. TWIST1 has been shown to impart breast cancer metastasis to the lungs [81].

Inhibitor of DNA binding 1. Inhibitor of DNA Binding 1 (ID1) also belongs to the bHLH family of TFs and has been shown to form heterodimers with other bHLH family members, including TWIST1, Hey1, or HIF-1 [82]. It plays a key role in transcriptional regulation of genes that participate in regulating several cellular activities like proliferation, differentiation, angiogenesis, and senescence [83]. In the case of metastatic tumors, ID1 facilitates cancer cell invasion and metastasis [84]. ID1 particularly mediates the breast cancer metastasis to lungs by interacting with TFAP2A and eventually suppressing S100A9 expression, leading to RhoC activation. S100A9, a calcium-binding protein, either suppresses or promotes metastasis depending on the cellular context, its expression level, and post-translational modifications. Suppression of S100A9 and activation of the RhoC pathway leads to cell migration, invasion, and metastasis phenotypes [85].

Extracellular matrix proteins

ECM not only provides physical support to the cellular constituents but also initiates crucial biochemical and biomechanical cues that are required for tissue morphogenesis, differentiation, and homeostasis [86]. Besides these, the phenomenon of cellular adhesion has been known to be regulated by ECM receptors, such as integrins, discoidin domain receptors, and syndecans [87]. The dynamic changes in the ECM lead to the migration of cells [88].

Vascular cell adhesion molecule-1. Vascular cell adhesion molecule-1 (VCAM-1), a membrane protein expressed by cytokine-activated endothelium [89], mediates leukocyte-endothelial cell adhesion, recruitment of leukocytes to the site of inflammation, and signal transduction. It promotes resistance to apoptosis of breast cancer cells, tumor neovascularization, invasion, and metastasis [90]. VCAM-1 expressed in breast cancer cells elicits the activation of PI_3K—AKT signaling and helps in breast cancer metastasis to lungs [91]. Interestingly, overexpression of VCAM-1 is associated with bone metastasis of breast cancer, and its silencing led to the prevention of metastasis to two of the main sites, lungs and bone [92].

Versican. Versican (VCAN) constitutes a major part of ECM and binds to hyaluronic acid. VCAN plays a central role in tissue morphogenesis, promotes tumor progression, and enhances metastasis [93]. Elevated levels of VCAN signified poor patient survival and prognosis in most of the cancers, including breast cancer [94]. It usually serves as a metastatic biomarker and aids in the lung metastasis of aggressive breast cancers [95].

Other factors

There are other breast cancer metastatic genes which have been reported to indirectly exert their effect on metastasis of breast cancers. PDK1 and COX-2 have been implicated in breast cancer metastasis to the liver and brain, respectively [96]. MicroRNA miR-19a has been also implicated in promoting metastasis of aggressive breast tumors to the brain [97]. miR-141 promoted brain metastasis of aggressive breast cancer cell lines, thus exhibiting a greater commitment to the mesenchymal phenotype [98]. Wnt/β-catenin signaling contributes to EMT and breast cancer metastasis in TNBC patients with a greater risk of lung metastasis. Genetic, pharmacological, and functional studies have revealed that attenuation of β-catenin transcriptional activity abrogated metastasis-associated phenotypes in TNBC cells [99].

Metastasis suppressors

Metastasis suppressors can be classified as: (a) developmentally regulated GTP binding protein 1 (DRG-1), (b) nucleoside diphosphate kinase (Nm23), (c) breast cancer metastasis suppressor 1 (BRMS1), (d) Ras homolog family member B (RhoB), (e) Raf kinase inhibitory protein (RKIP), (f) CD82, (g) Deleted in liver cancer 1 protein (DLC-1), (h) Kisspeptin-1 (KISS-1), (i) Myc, (j) E-cadherin, and (k) miRNAs (Table 3).

Developmentally regulated GTP binding protein 1

DRG-1 is a microtubule polymerase that catalyzes the conversion of GTP to GDP. Loss of its expression results in a more aggressive, metastatic phenotype, while a low level of DRG-1 expression was observed to be associated with more advanced and poorly differentiated tumors in breast cancer patients. The expression of DRG-1 is regulated by the known tumor suppressors, p53 and PTEN. Immunohisto-

Table 3 Molecular Mediators as Breast Cancer Metastasis Suppressors.

Metastasis suppressors	Role
DRG-1	Increases E-cadherin expression levels and decreases migratory and invasive potential
Nm23	Suppresses metastasis by regulating Smoothened and pleiotrophin
BRMS1	Inhibits migration, invasion, and promotes anoikis
RhoB	Decreases lung, liver, and lymph node metastasis
RKIP	Blocks angiogenesis, local invasion, intravasation, colonization of tumor cells, and reduces metastasis
KAI1/CD82	Inhibits colonization, reduces invasion, and metastasis
DLC-1	Reduces migration, invasion, and suppresses lung metastases
KISS1	Suppresses metastasis by preventing NF-κB binding to the promoters of pro-metastatic genes
MYC	Inhibits metastases to liver and lungs by repressing αvβ3 integrin
E-cadherin	Suppresses breast cancer bone metastases
miR-146	Promotes BRMS1-mediated metastasis suppression
miR-335 and −206	Decreases lung and bone metastasis
miR-142-3p	Reduces the cell migration ability of breast cancer cells
miR-17-5p	Reduces lung metastasis
miR-1179	Suppresses the growth and metastasis of breast cancer cells
miR-21	Decreases the invasive and/or metastatic phenotypes of tumors
miR-3178	Inhibits metastasis by blocking Notch1-induced EMT
miR-9	Reduces metastatic behaviors in TNBC by targeting Notch1

DRG-1 - Developmentally-regulated GTP binding Protein 1; Nm23 - Nucleoside diphosphate Kinase 23; BRMS1 - Breast Cancer Metastasis Suppressor 1; RhoB - Ras Homolog Family Member B; RKIP - Raf Kinase Inhibitory Protein; KAI1 - Kangai 1; CD82 - Cluster of Differentiation 82; DLC-1 - Deleted in Liver Cancer 1; KISS1 - Kisspeptin 1; MYC - MYC Protoncogene, Basic Helix Loop Helix Transcription Factor; miR - Micro ribo nucleic acids.

chemical studies have revealed an identical staining pattern between PTEN and DRG-1 expression in breast cancer [100]. DRG-1 expression is associated with improved survival rate of breast cancer patients. *In vitro* studies revealed that ectopic expression of DRG-1 in MDA-MB-468 cells led to an increased E-cadherin expression levels and decreased migratory and invasive potential [101]. Its role as a metastasis suppressor might not be limited to regulating the expression of E-cadherin, and understanding its molecular targets will eventually help in deciphering its role as a metastasis suppressor.

Nucleoside diphosphate kinase

Nm23, also referred to as NME/NME1, was the first metastasis suppressor gene to be identified and characterized in breast cancer cells. *In vitro* studies have suggested that overexpression of Nm23 decreases the metastatic and malignant properties of breast cancer cells [102]. It also plays a key role in suppressing metastasis by regulating various proteins like Smoothened and pleiotrophin that contribute to metastasis.

Breast cancer metastasis suppressor 1

Reports suggest that BRMS1 acts as a metastasis suppressor in breast cancer cells. It inhibits migration and invasion, and promotes anoikis, without affecting the cancer cells growth *in vitro* or *in vivo* [103]. Recent studies have revealed that the enforced expression of BRMS1 in various human breast cancer cell lines led to decreased migratory potential and PI_3K activity *in vitro* and exhibited reduced metastasis *in vivo*.

Ras homolog family member B

Although RhoB is dispensable during normal development, it mediates apoptosis in neoplastically transformed cells. In mice, ectopic expression of RhoB exhibited decreased lung, liver, and lymph node metastasis. However, its silencing did not affect the metastasis [104]. Its expression is positively correlated with patient survival. Literature suggests that aggressive tumors exhibiting poor prognosis have lost the expression of RhoB.

Raf kinase inhibitory protein

RKIP is known to act as a metastasis suppressor in multiple solid tumors including breast by binding to Raf-1 and thus inhibiting the Raf-induced ERK—MAPK signaling. Overexpression of RKIP depicted a decrease in the invasive potential of breast cancer cells, while the proliferation of these cells remained unaltered [105]. *In vivo* studies suggested that enforced expression of RKIP blocked various steps involved in metastasis such as angiogenesis, local invasion, intravasation, and colonization of tumor cells [105,106]. A negative correlation was observed between RKIP expression and prognosis of breast cancer patients.

KAI1/Cd82

It is a membrane glycoprotein belonging to the tetraspanin family which serves as a metastatic suppressor in breast cancer [107]. Ectopic expression of KAI1 in breast cancer cells led to poor colonization in soft agar, reduced invasion, and metastasis [108]. A strong correlation was observed between p53 and KAI1, and the loss of these two proteins is associated with poor survival.

Deleted in liver cancer 1 protein

DLC-1, a GTPase activating protein, acts as a switch between the active GTP-bound state and the inactive GDP-bound state of Rho proteins. *In vitro* studies have demonstrated that ectopic expression of DLC-1 in the MDA-MB-435 breast cancer cell line resulted in reduced migration, invasion, and significantly suppressed lung metastases [109].

Kisspeptin-1

KISS1 was identified to act as a metastasis suppressor gene in melanomas and breast carcinomas without affecting tumorigenicity. Its expression is found to be downregulated in secondary tumor sites during breast cancer metastasis [110]. Kiss1 prevents NF-κB binding to the promoters of pro-inflammatory and pro-metastatic genes, thus suppressing metastasis.

Myc xxx

It is a pleiotropic TF that plays a role in cell cycle progression, apoptosis, and cellular transformation. It was interesting to observe that overexpression of *Myc* led to suppressed migration and invasion of cancer cells *in vitro* [111]. *In vivo* studies also demonstrated that *Myc* overexpression inhibited metastases to liver and lungs due to the repression of αvβ3 integrin [111]. Another study revealed that either genetic or pharmacological inhibition of Myc synergized to increase TGF-β-induced metastasis.

E-cadherin

E-cadherin is a calcium-dependent cell—cell adhesion glycoprotein that serves as an epithelial marker. Mutations in this gene are correlated well with various tissue-specific cancers, including breast cancer. Loss of function of this gene contributes to cancer progression by increasing proliferation, invasion, and/or metastasis. Clinicopathological studies have demonstrated reduced E-cadherin expression favoring dissemination, a characteristic feature of advanced-stage cancers. A negative correlation has been observed between the expression of E-cadherin and the aggressiveness of cancer [112]. However, recent studies have demonstrated that this negative correlation is context-dependent and varies with the type of breast cancer. In invasive ductal carcinoma, E-cadherin promotes metastasis, whereas in invasive lobular carcinoma it acts as a metastasis suppressor [113].

miRNAs

miRNAs play a unique role in metastasis; while overexpression of few miRNAs promotes metastasis, enforced expression of certain miRNAs leads to suppression of metastasis. miR-146 plays a key role in the regulation of inflammation as well as BRMS1-mediated metastasis suppression. A significant decrease in the expression levels of EGFR along with reduced invasion, migration, and lung metastasis was observed with overexpression of miR-146a/b in MDA-MB-231 cells [114]. Expression levels of miR-335 and −206 were gradually lost with increasing metastatic potential in human breast cancer cells. Enforced expression of these miRs in cancer cells decreased lung and bone metastasis but did not affect the primary tumor size. miR-335 regulates the expression of SOX4 and tenascin C and thus suppresses the metastasis [115]. Studies depict a negative correlation between miR-142-3p and the cell migration ability in breast cancer cells. Suppression of miR-142-3p expression led to enhanced expression of various proteins like zinc finger E-box binding homeobox 1 and Ras-related C3 botulinum toxin substrate 1 which facilitated the development of an invasive phenotype. Recent literature suggested that overexpression of miR-142-3p led to the silencing of Bach-1, MMP9, CXCR4, and VEGFR protein expression in breast cancer cells [116]. Recent studies have demonstrated the novel antimetastatic function of miR-17-5p. While silencing of miR-17-5p led to increased expression of various pro-metastatic genes and enhanced lung metastasis, intratumoral administration of miR-17-5p mimic significantly reduced lung metastasis. This antimetastatic gene has potential prognostic values and serves as a therapeutic target to prevent metastasis of basal-like breast tumors [117]. Clinicopathological analysis revealed that decreased miR-1179 expression in breast cancer was correlated with advanced clinical stage and lymph node metastasis. Upregulated miR-1179 regulates the expression of Notch1, Notch4, and their downstream modulators, Hes1, thus suppressing the growth and metastasis of breast cancer cells [118]. Overexpression of miR-21 increases MMP-9 activity in MDA-MB-231, thus reducing the invasive and/or metastatic phenotypes of tumors, whereas the loss of miR-21 expression reduced migration and invasion ability of these cells [119]. miR-3178, a prognostic factor, particularly in TNBC, and its ectopic overexpression can inhibit metastasis by blocking Notch1-induced EMT [120]. Similarly, antimetastatic miRNA, miR-9, can reduce metastatic behaviors in TNBC by targeting Notch1 [121].

Therapeutic implications of molecular targets in breast cancer metastasis

Presently, therapeutics available to treat metastatic breast tumor are limited. Lapatinib, a small-molecule inhibitor of HER2 and EGFR was the first FDA-approved tyrosine kinase inhibitor indicated for use in metastatic breast tumor patients. However, the most common toxicities like diarrhea and hand-foot syndrome were associated with its use [122]. Clinical practice of combinatorial therapies with targeted monoclonal antibodies (mAbs) and chemo- or radiotherapies has resulted in profoundly increased survival with HER2-positive breast cancer, which is otherwise associated with poor prognosis. Also, the use of HER2-directed combinational therapies with bisphosphonates for breast cancer metastasis to bone has been the mainstay of treatment strategies [123]. With the present knowledge of various molecular factors that induce breast cancer metastasis, it becomes pertinent to explore the plausible therapeutics targeting breast cancer metastasis. Preclinical studies identified TGF-β as a molecular factor responsible for bone metastasis of breast tumors which was efficiently blocked by pan-neutralizing mouse mAbs, 1D11 and 2G7. Treatment of mice with 1D11 following orthotopic injections of 4 T1 breast cancer cells suppressed metastasis to lungs [124]. The use of recombinant Fc-fusion proteins has been shown to reduce breast cancer metastases in animal models. In a xenograft model of intracardiac inoculated

MDA-MB-231 human breast cancer cells, SD-208 significantly inhibited the size of osteolytic lesions, bone metastatic growth, and survival. Furthermore, SD-208 treatment in mice with already established bone metastases inhibited further tumor growth and formation of osteolytic lesions [125]. TGF-β inhibition along with doxorubicin treatment led to successful suppression of breast cancer growth and metastasis in a preclinical model [126].

Similarly, mAbs directed against PDGF or PDGFR have been evaluated for their potential efficacy in delaying or mitigating tumor development. IMC-3G3 and IMC-2C5 are mAbs that specifically bind with high affinity to human PDGFRα and PDGFRβ, respectively, and block PDGF ligand binding and receptor activation [127]. These receptors have been also inhibited using PDGF receptor kinase inhibitors, such as imatinib, sunitinib, sorafenib, pazopanib, and nilotinib. Despite robust preclinical data, imatinib has proven ineffective in Phase I and II clinical trials in patients. A Phase II clinical trial showed that PDGFR inhibition with tandutinib was associated with accelerated disease progression, hypothesizing that PDGF contributes to the homeostasis of bone metastases [128].

Presently, a promising therapeutic strategy targeting metastatic breast cancer using an IL-1 receptor antagonist, Anakinra (Nbib1802970), is being explored alone or in combination with chemotherapeutic agents like Cisplatin, antiresorptive agents like anti-RANKL mAb or mTOR inhibitor Everolimus in clinical trials [129]. Phase I clinical trial of PDR001 in combination with CJM112, EGF816, Ilaris (Canakinumab) has proven to be effective against TNBC [129].

EGFR has been correlated with aggressive breast cancer phenotype. High expression in breast CSCs makes it a preferred therapeutic target for inhibiting breast CSC metastasis and the recurrence of cancer. Small molecule tyrosine kinase inhibitors like gefitinib and erlotinib are known EGFR blockers that bind to the ATP binding site of EGFR thus abrogating EGFR signaling [130]. Gefitinib and erlotinib administration exhibited not only some mild side effects like rash, diarrhea, muscle pain, joint pain, and cough but also serious side effects like lung problems, kidney problems, liver failure, and stroke. Manupati et al. [59] demonstrated that attenuation of EGFR signaling led to a reversal of EMT or the induction of MET in breast CSCs, along with increased responsiveness to chemotherapeutics when simultaneously treated with doxorubicin and EGFR inhibitors. Phase II trial in patients with advanced breast cancer showed that cetuximab, a mAb, improved the overall response rate only in patients with TNBC. Panitumumab, an antibody targeting EGFR, in combination with 5-fluorouracil, epidoxorubicin, and cyclophosphamide followed by docetaxel for neoadjuvant therapy exhibited a greater potency against TNBC in Phase II clinical trials [131].

CXCR4, another important therapeutic target was blocked using inhibitors, AMD3100 or Plerixafor, which decreased the metastatic potential in preclinical animal models of breast cancer by inhibiting CXCR4/CXCL12 signaling axis and holds great promise towards antibreast cancer therapy [132]. Baohuoside I, a component of *Epimedium koreanum*, could successfully downregulate the CXCR4 expression that ultimately decreased CXCL12-induced invasion of breast cancer cells leading to suppression of breast cancer metastasis [133]. Preclinically, the CXCR4-CXCL12 axis that promotes breast cancer metastasis to bone was experimentally interrupted by AMD3100, an antagonist, that eventually led to a decrease in the invasiveness and metastasis of breast cancer cells [134].

Inhibition of Notch signaling via knockdown of Notch3 or treatment with a GSI markedly decreased breast cancer metastasis to bone. In metastatic breast cancer cells, overexpression of miR-34a significantly increases the protein level of tumor suppressor gene p53 and decreases the expression of Notch1, thereby inhibiting cell proliferation, invasion, and inducing apoptosis [135]. Additionally, miR-34a can sensitize metastatic breast cancer cells to Paclitaxel and Adriamycin partly by downregulating Notch1 expression. Treatment with nonsteroidal anti-inflammatory drugs may upregulate Nm23 expression, thus inhibiting Notch/HES1 and reducing circulating tumor cells that contribute to metastasis. KiSS1 encodes an active peptide, metastin, which only affects secondary tumor sites but not primary lesions [136].

Conclusion and future perspective

Among the various tissue-specific cancers, breast cancer remains one of the most common causes of death among women across the globe. Relapse poses the greatest threat to breast cancer patients who have undergone various conventional therapies. Metastasis has been considered as the root cause of relapse of cancer, which ultimately diminishes the overall disease-free survival and prognosis in patients. The major organs in the body that home the breast cancer metastatic cells include the lungs, liver, bone, and brain. Studies suggest that the metastasis of breast tumor cells exhibiting specificity to these organs was majorly dependent upon the breast cancer subtypes and confirmed by specific molecular cues that were observed at the primary site (breast) and/or secondary metastatic sites. Our critical analysis of the existing literature led us to identify that interplay between specific receptor-ligand axis, or growth factor receptors activation, or involvement of specific TFs, and/or ECM proteins activation at the primary and secondary tumor sites are the key factors for breast cancer metastasis. PDGFRβ, EGFR, and TGF-β-induced signaling form the basis of breast cancer metastasis that in turn activates several signaling cascades like PI_3K/AKT, ERK1/2, and Smad pathways. TFs like TWIST1 and ID1 either directly bind to DNA or form dimer with other TFs that bind to DNA and contribute to breast cancer metastasis by activating/silencing their downstream targets. ECM proteins like VCAM-1 and VCAN contribute to bone and lung metastasis of breast tumors. Metastasis is not only contributed by activators but also due to the silencing of metastatic suppressors. Over the years, many metastatic suppressors have been identified whose repression has led to the activation of pro-metastatic genes thus contributing to metastasis. Several miRNAs have been explored for their antimetastatic properties which regulate various downstream targets. These might have multiple targets and can be further investigated to get a better understanding of their antimetastatic properties. Another fascinating fact is that miRNAs can be classified as both activators and suppressors making them a novel tar-

get for breast cancer metastasis. All these molecular factors have been extensively evaluated using preclinical orthotopic-xenograft models which correlated well with clinical-pathological studies, thus necessitating further clinical investigations for the development of efficacious therapeutics. Targeting these metastatic genes/factors and their downstream signaling pathways will lead to the generation of efficacious therapeutics that will not only regress the metastatic tumor growth in breast cancer patients but also prevent the relapse of cancers. Research on this area can indeed aid in increasing efficacy and overcome the relapse of breast cancers at secondary sites, thereby increasing the patient survival rate.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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