Biochemical and Biophysical Research Communications 453 (2014) 112–116

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Mini Review

Breast cancer stem cells, EMT and therapeutic targets

Srishti Kotiyal, Susinjan Bhattacharya *

Department of Biotechnology, Jaypee Institute of Information Technology, A-10, Sector-62, Noida, UttarPradesh, India

ARTICLE INFO

Article history:
Received 13 September 2014
Available online 26 September 2014

Keyword:
BCSC
EMT signalling pathways
Therapeutic targets
miRNA

ABSTRACT

A small heterogeneous population of breast cancer cells acts as seeds to induce new tumor growth. These seeds or breast cancer stem cells (BCSCs) exhibit great phenotypical plasticity which allows them to undergo "epithelial to mesenchymal transition" (EMT) at the site of primary tumor and a future reverse transition. Apart from metastasis they are also responsible for maintaining the tumor and conferring it with drug and radiation resistance and a tendency for post-treatment relapse. Many of the signaling pathways involved in induction of EMT are involved in CSC generation and regulation. Here we are briefly reviewing the mechanism of TGF-β, Wnt, Notch, TNF-α, NF-κB, RTK signalling pathways which are involved in EMT as well as BCSCs maintenance. Therapeutic targeting or inhibition of the key/accessory players of these pathways could control growth of BCSCs and hence malignant cancer. Additionally several miRNAs are dysregulated in cancer stem cells indicating their roles as oncogenes or tumor suppressors. This review also lists the miRNA interactions identified in BCSCs and discusses on some newly identified targets in the BCSC regulatory pathways like SHIP2, nicastrin, Pin 1, IGF-1R, pro-inflammatory cytokines and syndecan which can be targeted for therapeutic achievements.

1. Introduction

Breast cancer (BC) is one of the leading cause of cancer-related deaths in women worldwide [1]. It has now been established that a heterogeneous population of cancer stem cells (CSCs) is responsible for tumor initiation and maintenance [2]. These CSCs are responsible for metastatic growth in breast cancer which contributes to majority of the breast cancer related morbidity and mortality. Breast CSCs (BCSC) cause treatment relapse as they have higher chemo resistance and migratory potential than differentiated, non-tumorigenic, breast cancer cells [3]. Human epithelial mammary cells give rise to BCSCs by an Epithelial to Mesenchymal transition (EMT) induced Ras-MAPK pathway activation [2]. EMT is a process by which epithelial cells attain a mesenchymal phenotype, allowing them to break free from the primary tumor site and metastasize at distant sites. EMT signaling is involved in development and maintenance of BCSCs. Therefore for targeted therapeutic achievement of BCSCs we need to have more understanding of EMT signaling and also identify targets within these pathways [4].

2. Developmental states of BSCSs characterized by expression of distinct CSC markers

BCSCs exist in two distinct development states and transit between them reversibly due to their property of cell plasticity [5]. The first state is the mesenchymal-like (epithelial–mesenchymal transition [EMT]) state in which BCSCs express cell surface marker profile $CD24^{-}$ $CD44^{+}$. They are mainly quiescent and are localized at the tumor-invasive edge adjacent to the tumor stroma [6]. The second state is the epithelial-like (mesenchymal–epithelial transition [MET]) state in which they express the de-toxifying enzyme, aldehyde dehydrogenase (ALDH). These BCSCs are proliferative, and more centrally located [6]. BCSCs possessing both the CSC markers ($CD24^{-}$ $CD44^{+}$ and $ALDH^{+}$) show the greatest tumor-initiating capacity [6].

3. Key signaling pathways involved in induction of EMT and further development of breast CSCs

EMT induction in cancer involves an intricate network of multiple signalling pathways (Fig. 1), including TGF-β, Wnt, Notch, NF-κB and ERK/MAPK pathways [7].

- *Wnt signaling pathway:* Wnt signaling activates and stabilizes the downstream signaling molecule β-catenin leading to its

* Corresponding author.
E-mail address: s.bhattacharya@jiit.ac.in (S. Bhattacharya).

http://dx.doi.org/10.1016/j.bbrc.2014.09.069
0006-291X/

accumulation and translocation into the nucleus to regulate the transcription of Wnt target genes [8]. This leads to subsequent Snail accumulation and E-cadherin down-regulation causing development of EMT. In human breast cancer cells, canonical Wnt signaling induces the expression of intracellular protein Axin 2 to stabilize the Snail, thereby inducing EMT [9]. In the non-canonical Wnt/β-catenin pathway, Wnt signaling activates the ERK1/2 pathway which activates β-catenin via RTK-PI3K/Akt pathway [8].

- *TNF-α/NF-κB signalling pathway:* Tumour necrosis factor-α (TNF-α), a pro-inflammatory cytokine involved in inflammation, immunity, cellular homeostasis and tumour progression is involved in all the steps of tumorigenesis in many cancers [8]. It activates NF-κB which induces transcription of factors associated with EMT, such as Snail, Slug, Twist, ZEB1 and ZEB2 [10]. In the classical TNF-α/NF-κB activation pathway, TNF-α stabilizes Snail [11] and also increases its transcription by binding to its promoter.
- *Notch signaling pathway:* The Notch signaling pathway maintains a balance between cell proliferation, differentiation and apoptosis & plays an important role in determining cell fate and maintaining progenitor cell population. Notch signaling requires coordination with other signals to promote EMT. TGF-β increases Notch activity through Smad3, subsequently promoting Slug expression which suppresses E-cadherin [12]. Slug-induced EMT is accompanied by activation of β-catenin and anoikis-resistance. Wnt and Notch pathways also show cross-linking wherein Wnt1-transformed cells show increased Notch signaling which is also needed for the tumorigenic phenotype [8,13].
- *Transforming growth factor-β (TGF-β) signaling:* In early stages of tumor growth, TGF-β suppresses tumors while during tumor progression, the EMT response is retained or even increased while a decline in the growth inhibitory response to TGF-β is seen [8]. Reduction of TGF-β signaling in tumor cells is accompanied by increased secretion of the TGF-β ligand which functions independently to increase tumorigenesis and metastasis [14]. TGF-β and its receptors regulate transcription of various EMT regulators, including Snail, Slug and Twist [8]. Cross-talk of TGF-β with other signaling pathways like Notch, Wnt/β-catenin, nuclear factor (NF)-κB and receptor tyrosine kinases (RTKs) is involved in induction of EMT which further helps in maintaining the mesenchymal phenotype of metastatic tumor cells [8].
- Receptor Tyrosine kinase signalling pathway (RTK): The RTKs have been shown to contribute to EMT and tumor cell invasion [8]. The activation of RTKs and their downstream signalling effectors such as MAPK or PI3K is crucial for an increased rate of cell proliferation in epithelial cells. Signalling via either MAPK or PI3K along with TGF-β is also necessary and sufficient to regulate EMT [15]. RTK activated pathway also crosstalk with Wnt and EGFR pathways [8].

In the mammary glands, signalling pathways such as Hedgehog (Hh), Wnt/β-catenin, and Notch play important role in embryogenesis, organogenesis and maintenance of tissues in adults by regulating the balance between self-renewal and differentiation of stem cells [16]. CSCs hijack these mechanisms to induce tumor formation. Specific targeting of those cells which have the potential to metastasize will be an important aspect in BCSC research, as this causes majority of the cancer fatalities.

4. Therapeutic targets

These pathways in BCSCs have highlighted a list of the therapeutic targets that regulate EMT and stem cell characteristics. Although a detailed discussion on all the targets is not possible within the limits of this review, but a few of these have been discussed below.

- *IGF-1R:* Insulin-like growth factor-1 receptor (IGF-1R) can activate the PI3K/Akt/mTOR pathway upon stimulation by insulin-like growth factor-1 (IGF-1). Expression of phosphorylated IGF-1R is greater in BCSCs than in non-BCSCs from xenografts of human breast cancer [17]. IGF-1R-expressing cells display features of cancer stem/progenitors such as mammosphere formation *in vitro* and tumorigenicity *in vivo*, both of which are suppressed by IGF-1R knockdown. Picropodophyllin (inhibitor of IGF-1R) suppresses phospho-Akt^{Ser473} and preferentially decreases ALDH^{+} BCSC populations of human breast cancer cells [17]. Furthermore, picropodophyllin inhibits the capacity of CD24^{-} CD44^{+} BCSCs to undergo the epithelial–mesenchymal transition process with downregulation of mesenchymal markers (vimentin, twist and N-cadherin) [17]. Inhibitors of signal molecules downstream of IGF-1R including PI3K/Akt/mTOR also reduce the ALDH^{+} population of breast cancer cells. Therefore

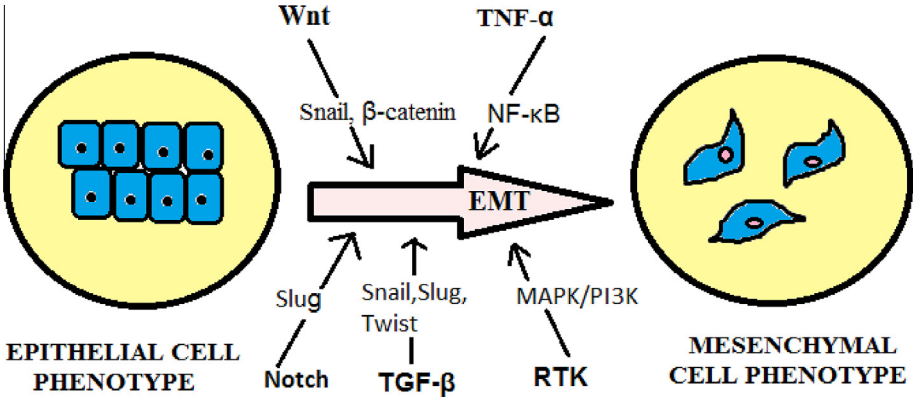

Fig. 1. Signalling pathways involved in induction of EMT and generation of BCSCs. The figure on left represents cells with an epithelial phenotype while the figure on right represents cells with a mesenchymal phenotype. TGF-β and its receptors regulate transcription of various EMT regulators, including Snail, Slug and Twist. They cross-talk with other signaling pathways like Notch, Wnt/β-catenin, nuclear factor (NF)-κB and receptor tyrosine kinases (RTKs) to induce EMT. Activation of RTK and its downstream effector Ras activates the MAPK/PI3K cascade and promotes the breast tumour cell EMT in association with TGF-β signalling. The Wnt pathway works Snail and β-catenin stabilization which promotes EMT. Activation of Notch signalling activates promotes SLUG expression and induces EMT. SLUG induced EMT is also accompanied with activation of β-catenin which induces resistance to anoikis and contributes to breast cancer metastasis. TNF-α activates NF-κB which promotes the expression of several EMT-associated transcription factors. Cross talk in these pathways leads to induction of EMT.

studies establish IGF-1R as a marker of stemness, and IGF-1R and its downstream PI3K/Akt/mTOR pathway provide attractive therapeutic targets against BCSCs.

- *Pin1:* Propyl-isomerase Pin1 is a pivotal regulator which acts downstream of miR-200c and promotes BCSC expansion, invasiveness and tumorigenicity. Pin1 silencing in primary breast cancer cells isolated from clinical samples inhibited the expansion, self-renewal activity and tumorigenesis of BCSCs *in vitro* and *in vivo* [18]. It is a key target of miR-200c which is a critical regulator of breast cancer stem-like cells. Pin1 overexpression increases the growth and tumorigenicity of BCSCs, triggers EMT while its inhibition reduces the abundance and self renewal activity of BCSC [18]. Moderate overexpression of miR-200c-resistant Pin1 rescued the BCSC defect in miR-200c expressing cells [19]. Hence, Pin1 is a suggestive therapeutic target to control BCSC growth.
- *Nicastrin:* γ-Secretase (GS) is multiprotein enzyme complex, composed of presenilin 1 (PS1), nicastrin (NCT), anterior pharynx-defective phenotype 1 (APH-1), and the PS enhancer 2 (PEN-2) [20]. GS is responsible for the intramembranous cleavage and activation of various type-I membrane proteins such as Notch, CD44, HER4, etc., [21]. Unusual activation of these substrates has been implicated in tumorigenesis, metastasis, and development of resistance to existing treatment regimens in oncology [21]. Nicastrin (NCT) is a vital component of the γ-secretase (GS) enzyme. Nicastrin overexpression in breast cancer (BC) confers reduced survival in invasive, ERα negative patients [22]. Overexpression of nicastrin is also linked to induction of EMT regulators [23]. Using the γ-secretase inhibition, Notch1/4 siRNA, and Akt inhibition, it has been shown that nicastrin regulates breast cancer stem cells partly through Notch1 and the Akt pathway [21]. Knockdown of nicastrin in HCC1806 breast cancer cells reduced cell invasiveness and conferred a morphological change to a rounded cell phenotype and down-regulation of vimentin, Snail, Twist, MMP2, and MMP9 [21]. A threefold and twofold reduction in pool of $CD44^+/CD24^-$ and ALDH1 high breast cancer stem cells, respectively, was also seen in stable nicastrin knockdowns in HCC1806 breast cancer cells [21].
- SHIP2: The percentage of SH2-containing-5′-inositol phosphatase-2 ($SHIP2^+$) cells is positively correlated with that of $CD24^-$ $CD44^+$ cells in breast cancer specimens and with distant metastasis [24]. Estrogen receptor negative$(ER)^-$ samples from 20 patients showed higher SHIP2 expression in $CD24^-$ $CD44^+$ subpopulation than the remaining subpopulation [24]. Patient-derived mouse xenograft studies showed that SHIP2 protein and its tyrosine 1135 phosphorylation are significantly higher in BCSCs, than in non-BCSCs [24]. SHIP2 silencing or inhibitor of SHIP2 phosphatase reduced not only mammosphere-forming efficiency, but also $ALDH^+$(Aldehyde dehydrogenase) subpopulation *in vitro* and tumorigenicity of BCSCs *in vivo*. Overexpression of SHIP2 enhances the expression of epithelial–mesenchymal transition markers including vimentin (VIM), in ER-negative breast cancer cells with higher level in mammospheres than in monolayer cultures [24]. Removal of c-Jun N-terminal kinase 1, JNK2 or VIM reduces the increased $ALDH^+$ population and tumorigenicity induced by SHIP2 overexpression [24]. BCSCs display greater expression of phospho-JNK than non-BCSCs and silencing of JNK suppresses SHIP2-mediated upregulation of VIM [24]. SHIP2 overexpression enhances Akt activation, but Akt inhibition does not effect SHIP2-induced phospho-JNK/VIM upregulation. SHIP2 plays a key role in BCSCs of ER-negative breast cancers through activation of Akt and JNK with VIM upregulation, and can be exploited as a target against BCSCs.
- Pro-inflammatory cytokines: Inactivation of tumor suppressors, p53 and phosphatase and tensin homolog (PTEN) is strongly associated with triple negative breast cancer [25,26]. These tumor suppressors also have important roles in regulating self-renewal in normal and malignant stem cells. Knockdown of p53 and PTEN synergized activation of pro-inflammatory Interleukin-6 (IL6)/Stat3/NFκB signaling in human mammary cells and in non-transformed MCF10A cells resulting in generation of EMT and cancer stem cells leading to metastatic tumors whose gene expression profile mimicked to that found in basal/claudin-low molecular subtype within the triple negative breast tumors [27]. Activation of IL6 inflammatory loop in transformed cells was dependent on proteolytic degradation of suppressor of cytokine signaling 3 (SOCS3) resulting in low levels of this protein in basal/claudin-low cell lines and primary tumors [27]. In transformed cells, enforced expression of SOCS3 or interfering with IL6 pathway via IL6R blockade inhibited tumor growth and metastasis in mouse xenograft models [27]. Blocking pro-inflammatory cytokines might be an effective strategy to target triple negative breast tumors, which currently lack molecularly targeted therapies [27].
- *Syndecan 1:* Heparan sulfate proteoglycan Syndecan-1 (also a molecular marker associated with EMT) modulates many signal transduction pathways in breast cancer stem cells including the Wnt and IL-6/JAK2/STAT3 pathway involved in tumor progression [28–30]. It is a co-receptor for growth factors, angiogenic factors, morphogens and chemokines. Both syndecan 1 and Wnt modulate the growth and differentiation of the mammary progenitor population [31]. Knockdown of syndecan 1 significantly reduced the $CD44^+$ $CD24^-$ cell population and increased the $CD44^+/CD24^+$ phenotype in the human triple negative MDA-MB-231 cells along with a reduced ALDH1-positive cell pool [32]. IL-6, its receptor sIL-6R, and the chemokine CCL20, involved in regulating stemness-associated pathways, were down-regulated in syndecan1 silenced cells [33] with reduced activation of STAT-3 and NF-κB transcription factors and expression of LRP-6 (co-receptor for Wnt signalling) were observed [33]. Syndecan-1 is a promising target for therapeutic approaches as it modulates the cancer stem cell phenotype via regulation of the Wnt and IL-6/STAT3 signaling pathway [33].

5. miRNAs in breast cancer

The biology of tumor cell plasticity is tightly linked to functions of non-coding RNAs (ncRNAs), especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) [34]. miRNAs are commonly deregulated in human malignancies acting as regulatory molecules, oncogenes or tumor suppressors. It has been experimentally shown that increased matrix stiffness modulates microRNA expression to drive tumor progression through integrin activation of β-catenin and MYC [35]. Tables 1 and 2 provide a brief view of some of the miRNAs which are either upregulated or downregu-

Table 1
Upregulated miRNAs in regulation of Breast cancer stem cells.

miRNA	Mechanism of action	Reference
miR-101	Suppresses expression of guanylate kinase inverted 2 and reduces the activity of PTEN	[36]
miR-18a	Decreases levels of homeobox A9 (HOXA9)	[35]
miR-495	Suppresses E-cadherin expression and inhibits REDD1 expression	[37]
miR-181	Targets ATM	[38]
miR-21	Targets PTEN, downregulates PDCD4 gene	[36]

Table 2
Downregulated miRNAs in regulation of Breast cancer stem cells.

miRNA	Mechanism of action	Reference
miR-205	Post-transcriptional inhibition of HER3 expression	[39]
miR-200 family	Targeting ZEB1, ZEB2,SLUG, ZNF217,BMI1 and SUZ12	[40,41]
miR-200c	TrkB and Bmi1	[42]
miR-17/20a	Inhibiting the expression of MHC class I (H2D)	[43]
miR-30	Targets Ubc9, ITGB3 and AVEN	[44]
let-7 family	Targets RAS and HMGA2	[45–48]
miR-34c	Targets Notch4	[49]
miR-128	Targets Bmi-1 and ABCC5	[50,51]
miR-16	Targets Wip1	[52]
miR-34a	Inhibits AXL expression	[53]

lated in BCSCs, and play an integral role in the induction of breast cancer.

Thus, BCSCs can also be targeted at the transcriptional level by targeting the participating miRNA [50]. Researches have made possible not only to identify target biomolecules of the BCSC/EMT pathway but also many clusters of mi-RNAs which are upregulated or downregulated in BCSCs [54]. This approach towards cancer treatment by targeting BCSCs, the very seed of tumors has a lot of potential and is very promising.

References

[1] C.D. Holmes, P. Silverman, Breast cancer: overview & updates, Nurse Pract. 36 (2011) 20–26.
[2] A.P. Morel, M. Lievre, C. Thomas, et al., Generation of breast cancer stem cells through epithelial–mesenchymal transition, PLoS One 3 (2008) e2888, http://dx.doi.org/10.1371/journal.pone.0002888.
[3] S. Chuthapisith, J. Eremin, M. El-Sheemey, O. Eremin, Breast cancer chemoresistance: emerging importance of cancer stem cells, Surg. Oncol. 19 (2010) 27–32.
[4] K. Kai, Y. Arima, T. Kamiya, H. Saya, Breast cancer stem cells, Breast Cancer 17 (2010) 80–85.
[5] C.A. Pinto, E. Widodo, M. Waltham, E.W. Thompson, Breast cancer stem cells and epithelial mesenchymal plasticity – implications for chemoresistance, Cancer Lett. 341 (2013) 56–62.
[6] S. Liu, Y. Cong, D. Wang, et al., Breast cancer stem cells transition between epithelial and mesenchymal states reflective of their normal counterparts, Stem Cell Rep. 2 (2014) 78–91.
[7] M.A. Huber, N. Kraut, H. Beug, Molecular requirements for epithelial–mesenchymal transition during tumor progression, Curr. Opin. Cell Biol. 17 (2005) 548–558.
[8] Y. Wang, B.P. Zhou, Epithelial–mesenchymal transition in breast cancer progression and metastasis, Chin. J. Cancer 30 (2011) 603–611.
[9] J.I. Yook, X.Y. Li, I. Ota, et al., A Wnt–Axin2–GSK3bold beta cascade regulates Snail1 activity in breast cancer cells, Nat. Cell Biol. 8 (2006) 1398–1406.
[10] C. Min, S.F. Eddy, D.H. Sherr, et al., NF-kappa B and epithelial to mesenchymal transition of cancer, J. Cell. Biochem. 104 (2008) 733–744.
[11] Y. Wu, J. Deng, S. Qiu, et al., Stabilization of snail by NF-kappa B is required for inflammation-induced cell migration and invasion, Cancer Cell 15 (2009) 416–428.
[12] K.G. Leong, K. Niessen, I. Kulic, et al., Jagged1-mediated Notch activation induces epithelial-to-mesenchymal transition through Slug-induced repression of E-cadherin, J. Exp. Med 204 (2007) 2935–2948.
[13] G.M. Collu, K. Brennan, Cooperation between Wnt and Notch signalling in human breast cancer, Breast Cancer Res. 9 (2007) 105, http://dx.doi.org/10.1186/bcr1671.
[14] M.P. de Caestecker, E. Piek, A.B. Roberts, Role of transforming growth factor-β Signaling in cancer, J. Natl Cancer Inst. 92 (2000) 1388–1402.
[15] J. Gotzmann, M. Mikula, A. Eger, et al., Molecular aspects of epithelial cell plasticity: implications for local tumor invasion and metastasis, Mutat. Res. 566 (2004) 9–20.
[16] A. Nigam, Breast cancer stem cells, pathways and therapeutic perspectives 2011, Indian J. Surg. 75 (2013) 170–180.
[17] W.W. Chang, R.J. Lin, A.L. Yu, et al., The expression and significance of insulin-like growth factor-1 receptor and its pathway on breast cancer stem/progenitors, Breast Cancer Res. 15 (2013) R39.
[18] A. Rustighi, A. Zannini, G.D. Sal, et al., Prolyl-isomerase Pin1 controls normal and cancer stem cells of the breast, EMBO Mol. Med. 6 (2014) 99–119.
[19] M.L. Luo, C. Gong, C.H. Chen, et al., Prolylisomerase Pin1 acts downstream of miR-200 to promote cancer stem-like cell traits in breast cancer, Cancer Res. 74 (2014) 3603–3616.
[20] J. Wanngren, P. Lara, H. Karlström, et al., Changed membrane integration and catalytic site conformation are two mechanisms behind the increased Aβ42/Aβ40 ratio by presenilin 1 familial Alzheimer-linked mutations, in: FEBS Open Bio. 4 (2014) 393–406.
[21] Y. Lombardo, A. Filipović, R.C. Coombes, et al., Nicastrin regulates breast cancer stem cell properties and tumor growth in vitro and in vivo, Proc. Natl. Acad. Sci. U.S.A. 109 (2012) 16558–16563.
[22] A. Filipović, J.H. Gronau, A.R. Green, et al., Biological and clinical implications of nicastrin expression in invasive breast cancer, Breast Cancer Res. Treat. 125 (2011) 43–53.
[23] Y. Lombardo, M. Faronato, A. Filipovic, et al., Nicastrin and Notch4 drive endocrine therapy resistance and epithelial to mesenchymal transition in MCF7 breast cancer cells, Breast Cancer Res. 26 (2014) R62.
[24] C.H. Fu, R.J. Lin, J. Yu, et al., A novel oncogenic role of inositol phosphatase SHIP2 in ER-Negative breast cancer stem cells: involvement of JNK/Vimentin activation, Stem Cells 32 (2014) 2048–2060.
[25] W.D. Foulkes, I.E. Smith, J.S. Reis-Filho, Triple-negative breast cancer, N. Engl. J. Med. 363 (2010) 1938–1948.
[26] S. Cleator, W. Heller, C. Coombes, Triple-negative breast cancer: therapeutic options, Lancet Oncol. 8 (2007) 235–244.
[27] G. Kim, M. Ouzuonova, A.A. Quraishi, et al., SOCS3-mediated regulation of inflammatory cytokines in PTEN and p53 inactivated triple negative breast cancer model, Oncogene (2014), http://dx.doi.org/10.1038/onc.2014.4.
[28] G.K. Malhotra, X. Zhao, H. Band, et al., Shared signaling pathways in normal and breast cancer stem cells, J. Carcinog. 10 (2011) 38.
[29] L.L. Marotta, V. Almendro, A. Marusyk, et al., The JAK2/STAT3 signaling pathway is required for growth of $CD44^{+}CD24^{-}$ stem cell-like breast cancer cells in human tumors, in: J. Clin. invest. 121 (2011) 2723–2735.
[30] G.W. Yip, M. Smollich, M. Götte, Therapeutic value of glycosaminoglycans in cancer, Mol. Cancer Ther. 5 (2006) 2139–2148.
[31] B.Y. Liu, S.P. McDermott, S.S. Khwaja, et al., The transforming activity of Wnt effectors correlates with their ability to induce the accumulation of mammary progenitor cells, in: Proc. Natl. Acad. Sci. U.S.A. 101 (2004) 4158–4163.
[32] S.A. Ibrahim, H. Hassan, M. Götte, et al., Syndecan-1 (CD138) modulates triple-negative breast cancer stem cell properties via regulation of LRP-6 and IL-6-mediated STAT3 signaling, PLoS One 8 (2013) e85737, http://dx.doi.org/10.1371/journal.pone.0085737.
[33] S.A. Ibrahim, H. Hassan, B. Greve, Syndecan-1 (CD138) modulates breast cancer stem cell properties via regulation of IL-6-mediated STAT3 signaling, in: Exp. Clin. Endocrinol. Diab. 121 (2013) OP3_20, http://dx.doi.org/10.1055/s-0033-1336628.
[34] L. BoDu, S. LiJuan, S. ErWe, Non-coding RNAs regulate tumor cell plasticity, Sci. Chin. Life Sci. 56 (2013) 886–890.
[35] J.K. Mouw, Y. Yui, L. Damiano, et al., Tissue mechanics modulate microRNA-dependent PTEN expression to regulate malignant progression, Nat. Med. 20 (2014) 360–367.
[36] H.L. Martin, L. Smith, D.C. Tomlinson, Multidrug-resistant breast cancer: current perspectives, Breast Cancer 6 (2014) 1–13.
[37] W.W. Hwang-Verslues, P.H. Chang, P.C. Wei, et al., MiR-495 is upregulated by E12/E47 in breast cancer stem cells, and promotes oncogenesis and hypoxia resistance via downregulation of E-cadherin and REDD1, Oncogene 30 (2011) 2463–2474.
[38] Y. Wang, Y. Yu, A. Tsuyada, et al., Transforming growth factor β regulates the sphere-initiating stem cell-like feature in breast cancer through miRNA-181 and ATM, Oncogene 30 (2011) 1470–1480.
[39] Z. Wang, H. Liao, Z. Deng, et al., MiRNA-205 affects infiltration and metastasis of breast cancer, Biochem. Biophys. Res. Commun. 441 (2013) 139–143.
[40] H.F. Zhang, L.Y. Xu, E.M. Li, A family of pleiotropically acting microRNAs in cancer progression, miR-200: potential cancer therapeutic targets, Curr. Pharm. Des. 20 (2014) 1896–1903.
[41] W.D. Bai, X.M. Ye, M.Y. Zhang, MiR-200c suppresses TGF-β signaling and counteracts trastuzumab resistance and metastasis by targeting ZNF217 and ZEB1 in breast cancer, Int. J. Cancer (2014), http://dx.doi.org/10.1002/ijc.28782.
[42] F. Kopp, P.S. Oak, A. Roidl, MiR-200c sensitizes breast cancer cells to doxorubicin treatment by decreasing TrkB and Bmi1 expression, PLoS One 7 (2012) e50469, http://dx.doi.org/10.1371/journal.pone.0050469.
[43] H. Jiang, P. Wang, X. Li, et al., Restoration of MiR-17/20a in solid tumor cells enhances the natural killer cell anti-tumor activity by targeting Mekk2, Cancer Immunol. Res. 2 (2014) 789–799.
[44] F. Yu, H. Deng, H. Yao, et al., MiR-30 reduction maintains self-renewal and inhibits apoptosis in breast tumor-initiating cells, Oncogene 29 (2010) 4194–4204.
[45] F. Yu, H. Yao, P. Zhu, X. Zhang, et al., Let-7 regulates self renewal and tumorigenicity of breast cancer cells, Cell 131 (2007) 1109–1123.
[46] C.D. Johnson, A. Esquela-Kerscher, G. Stefani, et al., The let-7 microRNA represses cell proliferation pathways in human cells, Cancer Res. 67 (2007) 7713–7722.
[47] M.S. Kumar, S.J. Erkeland, R.E. Pester, et al., Suppression of non-small cell lung tumor development by the let-7 microRNA family, Proc. Natl. Acad. Sci. U.S.A. 105 (2008) 3903–3908.
[48] Y. Wang, X. Hu, J. Greshock, et al., Genomic DNA copy-number alterations of the let-7 family in human cancers, PLoS One (2012), http://dx.doi.org/10.1371/journal.pone.0044399.

[49] F. Yu, Y. Jiao, Y. Zhu, et al., MicroRNA 34c gene down-regulation via DNA methylation promotes self-renewal and epithelial-mesenchymal transition in breast tumor-initiating cells, J. Biol. Chem. 287 (2012) 465–473.
[50] D. Schwarzenbacher, M. Balic, M. Pichler, The Role of MicroRNAs in breast cancer stem cells, Int. J. Mol. Sci. 14 (2013) 14712–14723, http://dx.doi.org/10.3390/ijms140714712.
[51] Y. Zhu, F. Yu, Y. Jiao, et al., Reduced miR-128 in breast tumor-initiating cells induces chemotherapeutic resistance via Bmi-1 and ABCC5, Clin. Cancer Res. 17 (2011) 7105–7115.
[52] X. Zhang, G. Wan, S. Mlotshwa, Oncogenic Wip1 phosphatase is inhibited by miR-16 in the DNA damage signaling pathway, Cancer Res. 70 (2010) 7176–7186.
[53] M. Mackiewicz, K. Huppi, J.J. Pitt, et al., Identification of the receptor tyrosine kinase AXL in breast cancer as a target for the human miR-34a microRNA, Breast Cancer Res. Treat. 130 (2011) 663–679.
[54] J.G. Sun, R.X. Liao, S.X. Zhang, Microarray-based analysis of microRNA expression in breast cancer stem cells, J. Exp. Clin. Cancer Res. 29 (2010) 174.