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REVIEW

Pharmacological targets of breast cancer stem cells: a review

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Abstract

Breast cancers contain small population of tumor-initiating cells called breast cancer stem cells (BCSCs), which are spared even after chemotherapy. Recently, BCSCs are implicated to be a cause of metastasis, tumor relapse, and therapy resistance in breast cancer. BCSCs have unique molecular mechanisms, which can be targeted to eliminate them. These include surface biomarkers, proteins involved in self-renewal pathways, drug efflux transporters, apoptotic/antiapoptotic proteins, autophagy, metabolism, and microenvironment regulation. The complex molecular mechanisms behind the survival of BCSCs and pharmacological targets for elimination of BCSCs are described in this review.

Keywords Breast cancer · Breast cancer stem cells · Tumor relapse · Metastasis · Chemoresistance

Abbreviations

ABC	ATP-binding cassette
ATM	Ataxia telangiectasia-mutated serine/threonine kinase
Bcl2	B cell lymphoma 2
BCRP	Breast cancer resistance protein
BCSCs	Breast cancer stem cells
BIK	Bcl2 interacting killer
Bmi-1	B cell-specific Moloney murine leukemia virus integration site 1
BMP2	Bone morphogenetic protein 2
CAIX	Carbonic anhydrase-IX
CAT	Catalase
CSL	*C*BF-1/RBPJ-κ in *Homo sapiens*/*Mus musculus*, respectively, *S*uppressor of hairless in *Drosophila melanogaster*, *L*ag-1 in *Caenorhabditis elegans*
CDK	Cyclin-dependent kinases
ChKs	Checkpoint kinases
c-myc	C-terminus of myc protein
DHh	Desert Hedgehog
DLL4	Delta-like 4 ligand
DOX	Doxorubicin
DRs	Death receptors
EMT	Epithelial-to-mesenchymal transition
EpICD	EpCAM intracellular domain
FAS	Fatty acid synthase
FTC	Fumitremorgin C
Gl	Glioma-associated oncogene
GLUT	Glucose transporter
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPO	Glutathione peroxidase
GSK-3β	Glycogen synthase kinase *3* β
HDR	Homology-directed recombination
Hh	Hedgehog
HK	Hexose kinase
IHh	Indian Hedgehog
IL	Interleukin
JAK	Janus kinase
LRP	Low-density lipoprotein-related receptor
MAML	Mastermind like
m-TOR	Mammalian target of rapamycin
Nanog	Gene named after the Tír na nÓg legend
NHEJ	Nonhomologous end joining
NICD	Notch intracellular domain
non-BCSCs	Non-breast cancer stem cells or bulk tumor cells
Oct-4	Octamer-binding transcription factor
PDZ	Disheveled PDZ domain
PI3-k	Phosphoinositide 3-kinase
PTEN	Phosphatase and tensin homolog

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SCs	Normal stem cells
SHh	Sonic Hedgehog
SMADs	Homologs of Sma and MAD proteins
Smo	Smoothened
SOD	Superoxide dismutase
SOX	Sry-related HMG box
STAT	Signal transducers and activators of transcription
STAT3	Signal transducer and activator of transcription factor 3
TGF-β	Transforming growth factor-β
TR	Thio-redoxin

Introduction

Breast cancer is the most common type of cancer in women and is the second leading cause of cancer-related deaths worldwide. According to the World Health Organization (WHO) report, 17.5 million breast cancer-related deaths can be expected per year, by 2050 (Ferlay et al. 2010). Resistance to conventional therapies, metastasis, and relapse of tumors are emerging as major causes of breast cancer-related deaths (Singh and Settleman 2010). Recently, it was identified that breast cancer stem cells (BCSCs) are one of the major responsible factors for therapy resistance, tumor relapse, and metastasis (Al-Hajj et al. 2003; Chen et al. 2013). It was reported that BCSCs express high levels of drug efflux transporters, which can be determined by treatment with Hoechst 33342 dye. The cells containing high levels of the drug efflux transporters expulse Hoechst and are designated as side population (SP) cells (Patrawala et al. 2005). Accumulating evidence has shown that numerous cell lines and tumors contain SP cells and that this cell population possesses a greater capacity for chemoresistance and tumorigenesis than non-SP cells (Britton et al. 2012). The quiescence of BCSCs (i.e., they spend more time in G_0 cell cycle phase) and their high DNA repair capacity also makes them to resist apoptosis caused by chemotherapeutic agents (Reya et al. 2001). The pool of BCSCs which are spared by conventional therapies will convert into tumor cells in future, thus leading to tumor relapse (Li et al. 2011).

Unlike bulk tumor cells (non-BCSCs), BCSCs grow in a nonattached (suspension) form when moving from their source to other locations in the body. Due to the nonattached growth nature, BCSCs proliferate in blood stream during cancer metastasis and give rise to spread of tumor. BCSCs promote cancer metastasis by a process called epithelial-to-mesenchymal transition (EMT), in which epithelial cells lose their intercellular adhesion, accompanied by gain of invasive and migratory properties, which is a prerequisite for metastasis (Karnoub et al. 2007; Sabe 2011; Liu et al. 2012; Hu et al. 2015). In this review, we discuss potential avenues for the pharmacological targeting of BCSCs based on their molecular features, including surface biomarkers (CD44, CD133, EpCAM, and ALDH1), proteins involved in self-renewal pathways (Wnt/β signaling proteins, Smo, γ-secretase, STAT-3, etc.), drug efflux transporters (ABCG2 and ABCB1), apoptotic/antiapoptotic proteins (Bcl2, survivin etc.), proteins involved in autophagy, metabolism, epigenetic regulation, and microenvironment regulation (Ablett et al. 2012; Britton et al. 2012; Vinogradov and Wei 2012; Chapellier and Maguer-Satta 2016).

Breast epithelial hierarchy and origin of BCSCs

Understanding the cell of origin of breast cancer is of great importance to unravel the cause of tumor heterogeneity. The mammary epithelium is composed of two types of cell lineages, luminal cells and myoepithelial (basal cells), which are organized into a series of branching ducts that terminates into secretary alveoli and aids in lactation. Luminal cells surround the central lumen and basal cells are located in basal position adjacent to basement membrane of mammary epithelium. It was reported that luminal cells and basal cells originate from multipotent mammary stem cells (MaSCs) during the development of mammary epithelium. Breast epithelial hierarchy suggests that BCSCs can be derived from normal MaSCs, transformed by the deregulation of normal self-renewal (Dontu et al. 2003; Wicha et al. 2003). Compelling body of evidence suggest that although MaSCs are required for the long-term maintenance of mammary gland homeostasis, postnatal glands, luminal, and basal unipotent progenitor cells can independently sustain luminal and basal lineages, respectively, for a long period of time (Van Keymeulen et al. 2011; Rios et al. 2014). Multiple mammary cell types, therefore, can have long-term self-renewal abilities and BCSCs may originate from these precursor cells due to mutations. In addition, it was reported that different breast cancer subtypes may originate from different mammary cell lineages (Lim et al. 2009; Visvader 2011; Visvader et al. 2014). For example, basal-like breast cancer is likely to originate from luminal progenitor cells, whereas multipotent MaSCs are likely the precursor of the claudin-low subtype (Lim et al. 2009; Molyneux et al. 2010).

According to "misplacement somatic stem cell" theory, BCSCs may originate from misplacement of somatic stem cells de novo (Wang et al. 2013a). According to this theory, somatic cells of the normal tissue would undergo successive DNA mutations that allow the cell to evolve and acquire the malignant phenotypes of BCSCs. According to this model, long-lived nature of normal stem cells (NSCs) allows them

more time to acquire mutations to become BCSCs. It was also reported that BCSCs can originate from tumor cells via induction of epithelial to mesenchymal transition (EMT) as a part of disease progression or in response to chemotherapeutic agents and environmental stress (Owens and Naylor 2013).

Pharmacological targets of BCSCs

BCSC surface markers

BCSCs express specific biological markers or antigens on their surface that can be used to identify or label them. Fluorescence-activated cell sorting (FACS) uses specific cell surface biomarkers to sort BCSCs (Chen et al. 2013). The expression of these unique surface biomarkers on BCSCs is reported to be associated with chemo/radioresistance in breast cancer (Ablett et al. 2012). A number of therapeutic antibodies, various small molecules, have been proposed for targeting these biomarkers for identifying and elimination of BCSCs. CD44, CD133, EpCAM, and ALDH1 are the important biomarkers of BCSCs. It was reported that triple negative breast cancer (TNBC) cells have higher percentage of these markers compared to other breast cancer subtypes (Croker et al. 2009). It was also reported that BCSC surface markers are enriched in normal tissues adjacent to TNBC cells (Atkinson et al. 2013).

Cluster of differentiation44

Cluster of differentiation44 (CD44) is a surface glycoprotein that is known to participate in a wide variety of cellular functions including regulation of cell adhesion, proliferation, migration, growth, survival, angiogenesis, differentiation, and matrix cell-signaling processes in collaboration with other cellular proteins (Phillips et al. 2006; Honeth et al. 2008; Goodarzi et al. 2014; Yan et al. 2015; Muntimadugu et al. 2016). It was reported that CD44 activates the Rho family of GTPases and initiate recruitment of signaling molecules like T lymphoma invasion and metastasis-inducing protein (Tiam1), p115, Ras-related C3 botulinum toxin substrate-1(Rac1), Rho-associated protein kinase, and proto-oncogene c-Src. These signaling molecules activates the phosphoionositide kinase (PI3K) pathway that is necessary for survival and migration of cancer cells (Bourguignon et al. 2000, 2008, 2009). More recently, it was also reported that CD44 expression is associated with chemoresistance by upregulation of the multidrug resistance receptor through activation of STAT3 (Bourguignon et al. 2008; Louderbough and Schroeder 2011). Clinical studies have shown a positive correlation between expression of CD44-positive BCSCs and tumor aggressiveness in patients with breast cancer (Balic et al. 2006; Yang et al. 2016).

Cluster of differentiation133

Cluster of differentiation133 (CD133) or prominin-1 is another important surface biomarker of BCSCs mainly associated with chemoresistance. It was reported to upregulate antiapoptotic genes like survivin and c-FLIP, promote autophagy, and associate with the Wnt/β-catenin self-renewal signaling pathway and vasculogenic mimicry (VM). The over expression of CD133 has been reported to have negative correlation with breast cancer patient survival (Wu and Wu 2009; Li 2013; Liu et al. 2013; Leon et al. 2016).

Epithelial cellular adhesion molecule

Epithelial cellular adhesion molecule (EpCAM) is a type I transmembrane glycoprotein, belonging to the family of adhesion molecules, which is overexpressed in BCSCs and is associated with poor survival rate in breast cancer (Munz et al. 2009; Königsberg et al. 2011). EpCAM comprise of an extracellular domain (EpEx) and an intracellular domain (EpICD). Cleavage of EpICD (upon EpCAM) activation results in signal transduction and activation of EpICD target genes like Nanog, Oct4, Klf4, and Sox2. These genes are involved in cell cycle regulation and apoptosis (Munz et al. 2009). In addition, it was reported that EpCAM inhibits E-cadherin-mediated adhesion and also activates Wnt/β-catenin pathway to promote survival of BCSCs (Fig. 1).

Aldehyde dehydrogenase1 (ALDH1)

Aldehyde dehydrogenases (ALDHs) are superfamily of enzymes which are involved in the oxidation of intracellular aldehydes to carboxylic acids, retinoic acid, and γ-amino butyric acid (GABA) (Ginestier et al. 2007). These enzymes were reported to be overexpressed and associated with chemo/radioresistance in BCSCs (Resetkova et al. 2010; Croker and Allan 2012). It was reported that $ALDH^{high}$ subtype in BCSCs was a predictor of poor survival in patients (Ginestier et al. 2007). High ALDH activity also reported to prevent apoptosis due to anticancer agents by metabolizing them into inactive metabolites. It was reported that ALDHs influence various pathways like Wnt, notch, transforming growth factor-β (TGF-β), extracellular signal-regulated kinases (ERK) in $ALDH^{high}$ subpopulation of cancer cells that influence proliferation and cell fate, epithelial-to-mesenchymal transition (EMT), retinoic acid synthesis, hypoxia, DNA damage response, and cell migration (Rodriguez-Torres and Allan 2016).

Components of self-renewal pathways

Self-renewal is one of the key features of NSCs, responsible for proliferation and maintenance. The signaling pathways such as Wnt/β-catenin, Notch, Hedgehog (Hh), TGF-β, signal

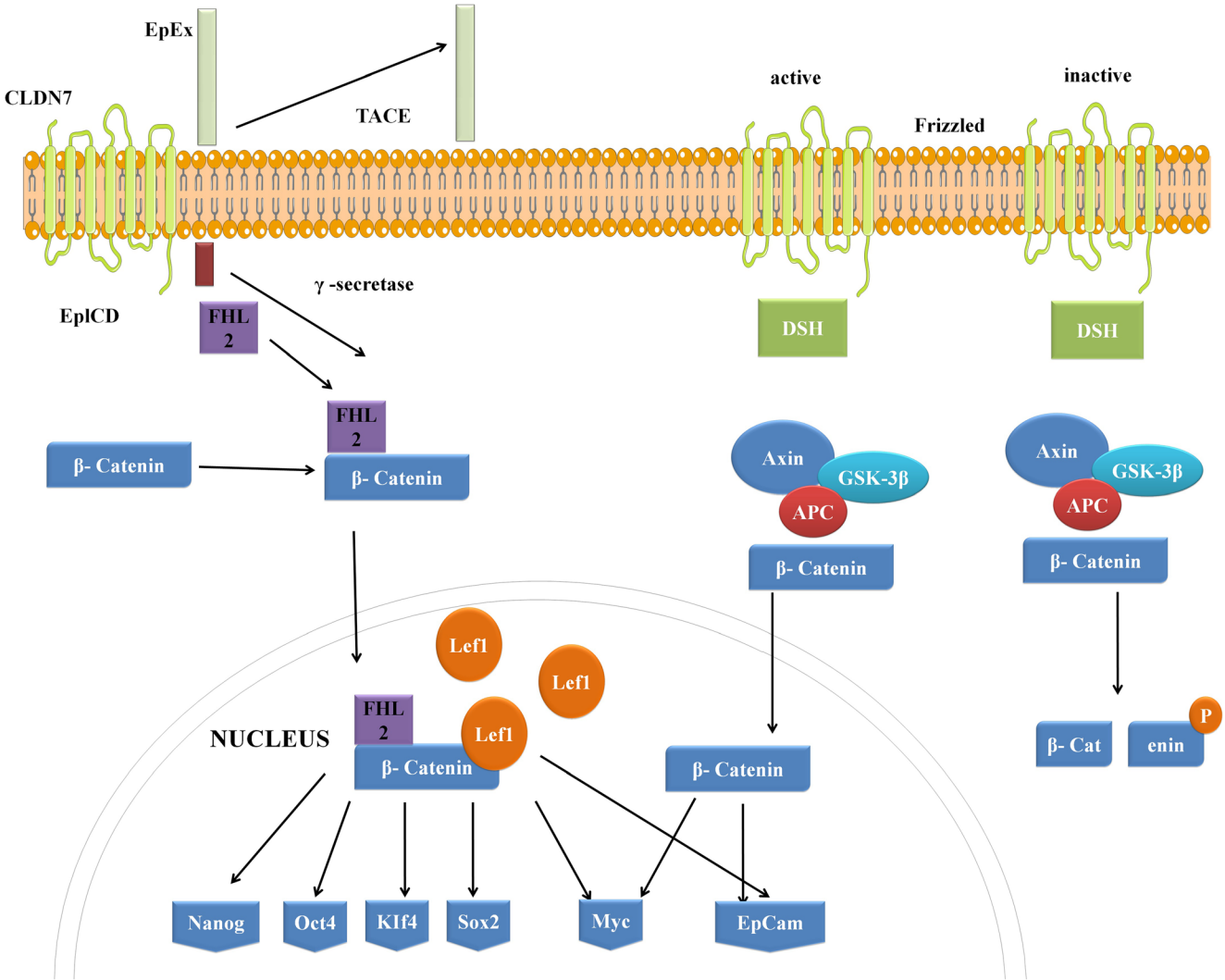

Fig. 1 Cross talk between EpCAM signaling and the *Wnt/β-catenin* pathway. Activation of the frizzled receptor by members of the Wnt family of ligands induces the inhibition of GSK3β and the subsequent stabilization of β-catenin. Upon nuclear translocation, β-catenin controls Lef-1-dependent transcription. EpICD interacts with the very same components to form a nuclear complex comprised of β-catenin, FHL2, and Lef-1. This nuclear complex binds with promoters of genes like Nanog, Oct4, Klf4, and Sox2 which are involved in cell cycle regulation and stemness of BCSCs. (Source Imrich et al. 2012)

transducer and activator of transcription factor 3 (STAT3), and B cell-specific Moloney murine leukemia virus integration site 1 (Bmi-1) implicated in the self-renewal of NSCs (Clarke et al. 2006). In BCSCs, these self-renewal signaling pathways are deregulated and result in extensive cell proliferation and also considered as an early event in the process of carcinogenesis (Fillmore and Kuperwasser 2008). Inhibition of self-renewal pathways, therefore, can be an attractive strategy for elimination of BCSCs (Liu et al. 2006; Kai et al. 2010) (Table 1).

Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway is an evolutionarily well-conserved pathway that regulates growth, regeneration, and self-renewal (Branda and Wands 2006). The activation of Wnt/β-catenin pathway occurs when a Wnt ligand binds to the transmembrane receptor that in turn results in binding of the low-density lipoprotein-related receptor (LRP). This leads to the suppression of glycogen synthase kinase-3β (GSK-3β) protein, thereby improving the stability of β-catenin. Consequently, β-catenin forms a complex with the transcription factor/lymphocyte enhancer factor and activates the expression of Wnt target gene such as c-terminus of myc protein (c-myc) and cyclin D1 (Fleming et al. 2008; Choi et al. 2010). Altered activation of Wnt/β-catenin signaling is a key feature of breast cancer where it is considered to be critical for self-renewal of BCSCs and also reported to enhance tumor metastasis by promoting EMT (Zhao et al. 2007; MacDonald et al. 2009) (Fig. 2).

Table 1 Molecular targets of BCSCs

Molecular targets	Experimental results	Ref.
Surface biomarkers		
CD44	Plays an important role in cell–cell interaction, cell adhesion, and migration	(Klonisch et al. 2008, Wright et al. 2008)
CD133	CD133 inhibition using anti-CD133 antibody results in elimination of BCSCs and prevented tumor relapse	(Swaminathan et al. 2013, Bostad et al. 2015)
ALDH1	Inhibition of ALDH1 resulted in sensitization of BCSCs to chemo and radiation therapy	(Croker et al. 2009, Croker and Allan 2012)
EpCAM	EpCAM downregulation using SiRNA resulted in elimination of BCSCs	(Osta et al. 2004, Gilboa-Geffen et al. 2015)
Self-renewal pathways		
Wnt/β-catenin pathway		
Fz receptor	Blockade of frizzled receptor using monoclonal antibody (OMP-18R5) resulted in silencing of Wnt pathway and eliminated BCSCs	(Gurney et al. 2012)
β-catenin	CWP232228, a β-catenin antagonist resulted in elimination of BCSCs and also non-BCSCs	(Jang et al. 2015)
Disheveled PDZ domain	Disheveled PDZ peptides inhibits PDZ domain and down regulated Wnt/β-catenin mediated signaling	(Zhang et al. 2009)
Axin 2	Inhibitor of Axin2 results in loss of β-catenin function and down regulates Wnt/β-catenin pathway	(Chen et al. 2009, Takebe et al. 2011)
Notch signaling pathway		
γ-Secretase	Inhibition of γ-secretase enzyme using MRK-003 (a γ-secretase inhibitor) resulted in inhibition of notch signaling in BCSCs and prevented mammosphere and colony formation	(Grudzien et al. 2010)
MAML	ANTP/DN MAML, a fusion protein that targets Notch nuclear co-activator MAML1 to inhibit notch signaling	(Epenetos et al. 2009)
Delta-like 4 ligand (DLL4)	Inhibition of DLL4 by monoclonal antibodies or small molecule inhibitor resulted in anticancer activity by inhibiting notch signaling pathway	(Noguera-Troise et al. 2006, Ridgway et al. 006, Scehnet et al. 2007, Hoey et al. 2009)
Hedgehog (Hh) pathway		
Smo	A novel synthetic derivative of Smo antagonist (cyclopamine) inhibits drug resistance in MCF-7/ADR cells and eliminates BCSCs	(Liu et al. 2016c)
Glioma-associated oncogene (Gli)	GANT61, a Gli inhibitor effectively silenced Hh signaling pathway in breast cancer	(Benvenuto et al. 2016)
TGF-β	Inhibition of TGF-β signaling using dominant-negative TGF-β type II receptor (DNRII) resulted in elimination of BCSCs and prevent metastasis	(Liu et al. 2012)
Bmi-1	Bmi-1 silencing using SiRNA inhibits tumor growth and metastasis in breast cancer	(Deng et al. 2016)
IL-6/JAK/STAT3 pathway		
STAT3	Inhibition of STAT3 signaling results in elimination of BCSCs and prevention of metastasis	(Thakur et al. 2015)
Apoptotic/antiapoptotic proteins		
PTEN/PI3/Akt axis	Pharmacological inhibition of AKT with perifosine, an AKT inhibitor resulted in inhibition of BCSCs as indicated by formation of fewer mammospheres and resulted in complete eradication of tumor	(Korkaya et al. 2009)
m-TOR	Inhibition of m-TOR by rapamycin resulted in sensitization of BCSCs to radiation	(Lai et al. 2016)
Bcl2	Down regulation of Bcl2 using SiRNA resulted in chemosensitization	(Lima et al. 2004)
Fatty acid synthase (FAS)	Supression of lipogenesis by modulating FAS expression resulted in apoptosis in BCSCs	(Pandey et al. 2011)
Death receptor (DR-5)	DR-5 inhibition using anti-DR5 antibody resulted in cytotoxicity of BCSCs	(Londoño-Joshi et al. 2012)
Autophagy proteins		
Beclin1	Depletion of Beclin1 resulted in inhibition of autophagy in BCSCs	(Gong et al. 2013)
Metabolic enzymes and transporters		
Hexose kinases (HK)	Inhibition of HK activity by metformin impairs glucose metabolism and resulted in tumor growth inhibition in breast cancer and BCSCs	(Hirsch et al. 2009, Marini et al. 2013)
Glucose transporters (GLUT)	Inhibition of GLUT1 transporter using small molecule inhibitor (WZB117) resulted in radio sensitization effects in breast cancer	(Zhao et al. 2016)
Microenvironment		
Hypoxia inducible factor1α (HIF1α)	HIF1α promotes growth of BCSCs. Inhibitors of HIF1α resulted in chemosensitization of BCSCs	(Samanta et al. 2014, Zhang et al. 2015)
Carbonic anhydrase-IX (CAIX)	CAIX is required for expansion of BCSCs in hypoxic environment. Inhibition of CAIX expression with novel small molecule inhibitor resulted in inhibition of BCSCs and hypoxia	(Lock et al. 2013)
CXCR1	CXCR1 inhibitor effectively eliminated BCSCs in vitro and in vivo	(Ginestier et al. 2010)

Notch signaling pathway

The Notch signaling pathway is essential for differentiation of BCSCs (Yin et al. 2010). It was reported that the aberrant activation of notch signaling in BCSCs is associated with activation of notch target genes which are involved in the maintenance of self-renewal in BCSCs (Artavanis-Tsakonas et al. 1999; Reya et al. 2001; Androutsellis-Theotokis et al.

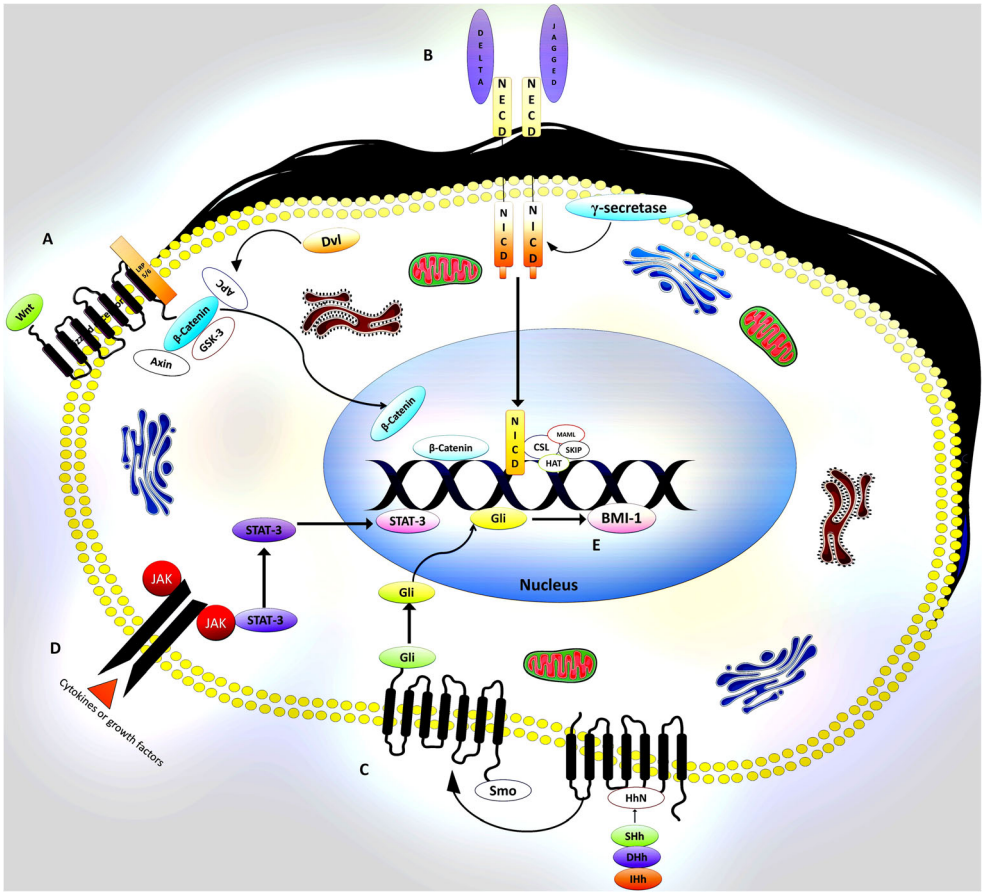

Fig. 2 Wnt/β-catenin (**a**), Notch (**b**), Hedgehog (**c**) and STAT3 (**d**) and Bmi (**e**) mediated signaling for self-renewal of BCSCs. *STAT3* signal transducer and activator of transcription factor 3, *TGF-β* transforming growth factor-β, *Hh* Hedgehog, *Smo* Smoothened, *SHh* Sonic Hedgehog, *IHh* Indian hedgehog, *DHh* desert hedgehog, *NICD* Notch intracellular domain, *NECD* Notch extracellular domain, *GSK-3β* glycogen synthase kinase 3 β, *DHh* desert Hedgehog, *DLL4* delta-like 4 ligand, *Bmi-1* B cell-specific Moloney murine leukemia virus integration site 1, *JAK* Janus kinase, *Gli* glioma-associated oncogene

2006; Hori et al. 2013). This signaling pathway is activated through four Notch receptors (Notch 1–4); among those, Notch 4 and Notch 1 are implicated in self-renewal of BCSCs (Bray 2006; Cerdan and Bhatia 2010; Harrison et al. 2010b; Zhong et al. 2016). Ligand protein binding to Notch receptors leads to their cleavage by γ-secretase to release the Notch intracellular domain (NICD), and following the nuclear translocation, it induces transcriptional activation of Notch target genes to promote survival of BCSCs (Schweisguth 2004). Inhibitors of γ-secretase, therefore, prevent the proteolysis of Notch receptors and suppress the Notch activity in BCSCs. Mastermind-like (MAML) and Delta-like 4 ligand (DLL4) proteins are the other important molecular targets from Notch signaling pathway to inhibit self-renewal of BCSCs (Fig. 2).

Transforming growth factor-β pathway

Transforming growth factor-β (TGF-β)-mediated signaling is essential during the initial phase of development and regeneration of cells (Pryce et al. 2009; Greenow and Clarke 2012). TGF-β ligands binding activates TGF-β type I receptor. The type I receptor triggers the phosphorylation of SMADs (transcription factors) and results in ligand-induced transcription of self-renewal genes in BCSCs (Fig. 2) (Massagué 2000; Liu et al. 2012). TGF-β signaling exerts tumor suppressor effects in normal cells and early carcinomas. However, the mutations in TGF-β results in tumor genesis. As tumors develop and progress, the protective and cytostatic effects of TGF-β will be lost. TGF-β signaling then promotes cancer progression, invasion, and tumor metastasis. TGF-β, therefore, have dual role in both tumor suppression and tumor progression (Moses and Barcellos-Hoff 2011). Higher TGF-β levels in the serum and urine was correlated with poor survival rate and advanced disease state in cancer patients (Tsai et al. 1997). Designing novel therapeutic agents targeting TGF-β is, however, challenging due to its dual role in carcinogenesis. It is necessary to develop drugs that specifically aimed at blocking the prometastatic effects of the TGF-β signaling pathway without affecting its tumor suppressive effects.

Hedgehog signaling pathway

Hedgehog (Hh) signaling pathway is an important pathway that is responsible for the maintenance and self-renewal capacity of the BCSCs. The Sonic Hh (SHh), Desert Hh (DHh), and Indian Hh (IHh) are the three gene homologs of Hh (Ingham and McMahon 2001; Micchelli et al. 2002; Takebe

et al. 2011). In Hh pathway, the activation of Smoothened (Smo), a seven-pass transmembrane receptor, is necessary for signaling process. In the presence of Hh ligand, Smo activates the glioma-associated oncogene (Gli) family of transcription factors (Gli1/2/3) to carry out the further downstream signaling required for self-renewal of BCSCs (Svärd et al. 2006). Smo receptor and Gli family of proteins, therefore, can be druggable molecular targets to inhibit self-renewal of BCSCs (Fig. 2).

B cell-specific Moloney murine leukemia virus integration site-1

The B cell-specific Moloney murine leukemia virus integration site-1 (Bmi-1) is one of the polycombcomplex proteins, reported to be involved in the differentiation and self-renewal mechanisms of BCSCs (Alkema et al. 1993; Jacobs et al. 1999; Gil et al. 2005). Bmi-1 affects morphogenesis during embryonic development and in hematopoiesis with a pervasive expression in almost all tissues (Van der Lugt et al. 1994). It is noted that BCSCs are dependent on Bmi-1 for their maintenance and self-renewal (Fig. 2) (Sawa et al. 2005; Borah et al. 2015). In addition, it was reported that Hh signaling act along with Bmi-1 to regulate the self-renewal of BCSCs (Kubo et al. 2004; Liu et al. 2006).

JAK/STAT3 pathway

Signal transducers and activators of transcription (STATs) are a family of transcription factors required for regulation of growth, survival, and differentiation of cells (Darnell Jr et al. 1994; Ihle 2001). So far, seven STAT proteins have been recognized in mammalian cells. Among all, STAT3 plays a key role in carcinogenesis by regulating the transcription of genes involved in cell proliferation, differentiation, apoptosis, angiogenesis, and metastasis (Akira et al. 1994; Yu and Jove 2004). IL-6/JAK/STAT3 is the canonical STAT3 activation signaling pathway, reported to be deregulated in cancer. Since the receptor of IL-6 does not contain a kinase catalytic domain, it induces STAT3 phosphorylation by activating members of the JAK family (Fig. 2) (Ihle et al. 1994; Heim et al. 1995; Ihle and Kerr 1995; Stahl et al. 1995; Ihle 2001). The IL-6/JAK2/STAT3 pathway was found to be active in CD44+/CD24− BCSCs. It was demonstrated that inhibition of STAT3 pathway suppressed growth of xenograft tumors. In addition, it has been reported that cancer cells can be converted into a cancer stem cells via the IL-6/JAK1/STAT3 signaling pathway (Marotta et al. 2011; Wang et al. 2012; Kim et al. 2013; Xiong et al. 2014; Chung and Vadgama 2015). STAT3 is an important molecular drug target for inhibition of this pathway. Recently, it was identified that niclosamide, an antihelmenthic drug, is an inhibitor of STAT3 phosphorylation (Li et al. 2013; Wang et al. 2013b; Li et al. 2014). In addition, niclosamide is also reported to prevent conversion of non-BCSCs to BCSCs (Kim et al. 2013) and reduced resistance to chemotherapy (Liu et al. 2016a; Liu et al. 2016b) (Table 2). Recently, Wang et al. have shown that leptin-JAK/STAT3 regulate lipid metabolism through fatty acid β-oxidation (FAO) to promote breast cancer stemness and chemoresistance. Blocking FAO and/or depleting leptin sensitized cancer cells to chemotherapy while reducing BCSCs in vivo (Wang et al. 2018).

Apoptotic/antiapoptotic proteins

Deregulation of apoptosis and antiapoptotic (survival) signaling pathways is a characteristic of cancer and a critical determinant of efficacy of chemotherapy (Fig. 3) (Brown and Attardi 2005). In this context, a compelling body of evidence suggests that BCSCs use several mechanisms to deregulate apoptotic/antiapoptotic pathways and promote resistance to treatment (Wicha et al. 2006; Karnoub et al. 2007). The B cell lymphoma2 (Bcl2), FLICE like inhibitory protein (c-FLIP), nuclearfactor-κ-B (NF-κB), phosphatase and tensin homolog (PTEN), mammalian target of rapamycin(m-TOR), and death receptors (DR)-4/5 proteins are the well-characterized regulators of apoptosis and molecular targets for elimination of BCSCs (Martinou and Youle 2011). Bcl2 is an antiapoptotic protein that is reported to be overexpressed in 75% of breast cancer cells (Domen et al. 1998; Honma et al. 2015; Merino et al. 2016). It was reported that breast tumor-targeted gene therapy with pro-apoptotic gene Bcl2 interacting killer (BIK) improved the efficacy of the chemotherapeutic agents against breast cancer (Lang et al. 2011).

Drug efflux transporters

Drug efflux transporters or ATP-binding cassette transporters (or ABC transporters) like P-glycoprotein (P-gp) or ABCB1 and breast cancer resistance protein (BCRP) or ABCG2 are implicated in chemoresistance (Shervington and Lu 2008; Yin et al. 2008). ABCB1 is reported to be expressed and responsible for chemoresistance in breast cancer. Studies have shown that higher expression of CD133 is also accompanied with an elevated ABCB1 efflux activity (Moitra 2015). Hoechst 33342 assay which is used to isolate BCSCs is based on the principle that BCSCs are Hoechst dim due to overexpression of the ABCG2 drug efflux transporter that pumps the dye out of the cells (Kim et al. 2008; Britton et al. 2012). Several inhibitors of ABCG2, like Fumitremorgin C (FTC), Tryprostatin-A, and Tariquidar, have been proposed to kill BCSCs in order to achieve radical cure in breast cancer. However, the clinical application of these compounds is limited due to their low inhibition capacity and off-target effects on the healthy cells (Rabindran et al. 1998; Rabindran et al. 2000; Zhao et al. 2002; Woehlecke et al. 2003; Robey et al. 2004; Peired et al. 2016).

Table 2 Various anti-BCSCs agents and their mechanism of action for elimination of BCSCs

Anti-BCSC agent	Mechanism of action	Ref.
Disulfiram	Modulator of MAPK signaling pathway	(Yip et al. 2011)
Flubendazole	Cell cycle arrest at G2/M phase and induced monopolar spindle formation through inhibition of tubulin polymerization	(Hou et al. 2015)
Metformin	Inhibition of Akt and hexose kinase	(Vazquez-Martin et al. 2011)
Niclosamide	Inhibition of Wnt, STAT-3, Notch, and NF-κB pathways of self-renewal	(Pan et al. 2012)
Salinomycin	Inhibition of self-renewal	(Zhang et al. 2012)
Simavastatin	Inhibition of mevalonate metabolism	(Ginestier et al. 2012)
Thioridazine	Antagonism of dopamine receptor on CSCs	(Ke et al. 2014)
Tranilast	Activation of aryl hydrocarbon receptor	(Prud'homme et al. 2010)
Epigallocatechin gallate analogs	Activation of AMPK	(Chen et al. 2012)
Everolimus	Not established	(Zhu et al. 2012)
Sulforaphine	Downregulation of Wnt/β-catenin signaling	(Li et al. 2010)
Cyclopamine	Smo inhibitor	(You et al. 2015)

DNA repair capacity

Radiation therapy and chemotherapeutic agents cause DNA damage for induction of apoptosis (Cheung-Ong et al. 2013). BCSCs possess DNA repair ability by activation of various checkpoint mechanisms (Al-Assar et al. 2011; Kim et al. 2012; Peitzsch et al. 2013). DNA damage can be repaired by homology-directed recombination (HDR) or through nonhomologous end joining (NHEJ) (Brandsma and van Gent 2012). The HDR involves resegmentation of the two ends of

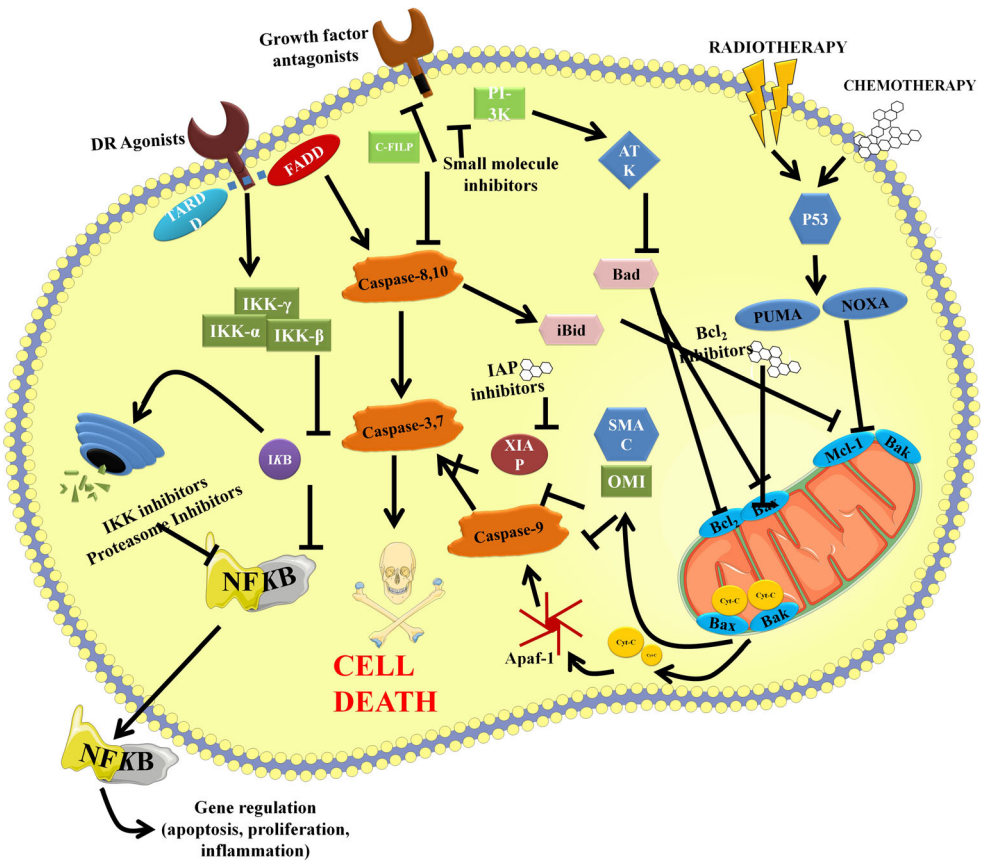

Fig. 3 Apoptotic and antiapoptotic signaling in cancer stem cells. *Bcl2* B cell lymphoma 2, *BIK* Bcl2 interacting killer, *DRs* death receptors, *IL* interleukin, *PTEN* phosphatase and tensin homolog, *PI3-K* phosphoinositide 3-kinase, *NF-κB* nuclear factor-κB, *Bad* Bcl-2-associated death promoter, *PUMA* p53 upregulated modulator of apoptosis, *IAP* inhibitor of apoptosis protein, *XIAP* X-linked inhibitor of apoptosis protein, *IKK* I-kappa kinase, *c-FLIP* FLICE like inhibitory protein (Signore et al. 2013)

DNA from 3′ to 5′, formation of single-strand DNA at the 3′ end, assembly of RAD51 filaments (a protein family contributing in the repair of DNA double-stand breaks), and finally repair by annealing at the end of the double-strand break. The HDR repair occurs during the S and G2 phases of the cell cycle. NHEJ utilizes the Lupus Ku autoantigen protein p70/80 (KU70/80) to join the DNA strands. In addition, nucleases, polymerases, DNA-dependent protein kinases, and ligases participate in the NHEJ repair process (Jackson 2002; Jasin and Rothstein 2013). DNA damage checkpoint proteins, like checkpoint kinases (ChK 1/2) are the important molecular targets for prevention of DNA repair and inhibition of BCSCs (Niida and Nakanishi 2006; Yin and Glass 2011).

Oxidative stress

Many anticancer agents and radiation therapy lead to reactive oxygen species (ROS) production to induce apoptosis in cancer cells by either intrinsic or extrinsic pathways (Cook et al. 2004; Sena and Chandel 2012; Sinha et al. 2013). However, BCSCs maintain low ROS levels in addition to high endogenous antioxidant levels (Trachootham et al. 2009). Upregulation of genes encoding the antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPO) can be found in BCSCs (Diehn et al. 2009). In addition, BCSCs are regularly localized in the hypoxic regions of the tumors to avoid ROS-mediated apoptosis. This makes BCSCs to avoid oxidative DNA damage and maintain their quiescent state for their survival (Phillips et al. 2006; Gilbertson and Rich 2007). Induction of oxidative stress and reduction of antioxidant defense, however, is not considered as an effective strategy for elimination of BCSCs, due to deleterious effects on healthy cells.

BCSCs metabolism

Differentiated bulk cancer cells rely primarily on glycolysis for production of ATP and to manage high rate of proliferation (Ward and Thompson 2012). In contrast, BCSCs can be highly glycolytic or oxidative phosphorylation (OXPHOS) dependent. In both cases, mitochondrial function is important (Sancho et al. 2016). Inhibition of the mitochondrial metabolic function, therefore, became a potential strategy in recent years for elimination of BCSCs and prevention of tumor relapse. It was reported that BCSCs show distinct glucose and mevalonate metabolism (Ginestier et al. 2012; Dong et al. 2013). It has been recently demonstrated that adenine nucleotide translocator-2 (ANT2), which is involved in glycolytic metabolism (Raaijmakers et al. 2005), and Hexokinase 2 (HK2), which catalyzes the first committed step of glucose metabolism, can be targeted for elimination of BCSCs. Using HK2 conditional knockout mice, it was demonstrated that HK2 is required for tumor initiation and maintenance in breast cancer (Patra et al. 2013). Metformin has been reported to eliminate BCSCs by inhibiting HK2 and thereby enhanced the effects of chemotherapy (Salani et al. 2014) (Fig. 4).

BCSCs microenvironment/niche

BCSCs require a specialized microenvironment or niche which is regulated by various factors for their survival. The factor that regulate BCSCs microenvironment include fibroblast stimuli, immune cells, autocrine signals, and extracellular matrix (ECM) components, as well as physical/chemical factors such as oxygen pressure, nutrients levels, and low pH (Bozorgi et al. 2015; He et al. 2016). Growth factors and cytokines released by tumor cells and cancer-associated fibroblasts and immune cells have strong effects on the survival and metastasis of BCSCs (Culig 2011; Korkaya et al. 2012). It was reported that combination therapy with an IL-6 receptor antibody is required to suppress acquired trastuzumab resistance in breast cancer in vivo. In addition, it was reported that the IL-8 receptor, CXCR1, is highly expressed in BCSCs. Interestingly, chemotherapy may increase the CSC pool by stimulating the release of IL-8, whereas a CXCR1 small molecule inhibitor helped to eliminate the residual BCSC population following docetaxel therapy (Ginestier et al. 2010).

Autophagy proteins

Autophagy is a survival promoting physiological process in BCSCs against various environmental stress, radiation, chemotherapeutic drugs, and hypoxia (Choi et al. 2013). Autophagy plays an important role in breast cancer initiation or transformation of mammary epithelial cells, chemoresistance, and metastasis. Excessive self-eating can promote death, and low levels of autophagy activated in response to cellular stress is believed to promote resistance of breast cancer cell to chemotherapy, radiation, and targeted therapy in most settings (Jain et al. 2013). In BCSCs, it was reported that autophagy is also responsible for chemoresistance, tumor relapse, and metastasis (Sui et al. 2013; Ojha et al. 2015). Mechanisms by which autophagy promotes cancer include induction of the p53 and altering metabolic function of mitochondria (White 2015). It was reported that treatment with autophagy inhibitors or silencing of autophagy-associated genes affects stem cell renewal, differentiation, and stress-resistant abilities that results in elimination of BCSC population and enhanced the sensitivity to chemotherapeutic agents (Mai et al. 2012; Singh et al. 2012). Recently, it was reported that autophagy inhibition with chloroquine (CQ) resulted in elimination of BCSCs in triple negative breast cancer (TNBC) and potentiated the cytotoxic effects of carboplatin (Liang et al. 2016).

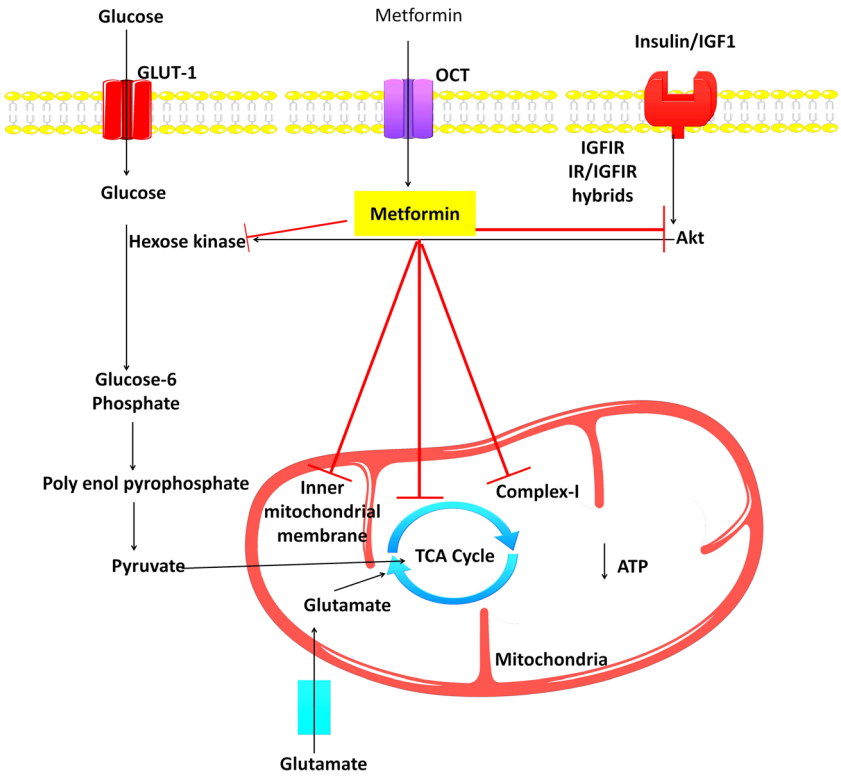

Fig. 4 Mechanism of action of metformin for elimination of BCSCs

Epigenetic regulation of BCSCs

Epigenetic regulation of the genome is one of the primary mechanisms by which genetic code is altered to control cellular developmental hierarchies without change in DNA sequences. Epigenetic mechanisms include histone modifications, DNA methylation, chromatin remodeling, and changes in noncoding RNAs including miRNAs. Emerging evidences suggest that deregulation of various epigenetic mechanisms can contribute to tumor initiation and progression, particularly with respect to maintenance and BCSCs. Histone methylation is a critical factor in epigenetic regulations and is mediated by methyltransferases which catalyze the mono-, di-, or trimethylation of specific lysine residues (Wei et al. 2008). Histone methylation occurs predominantly on lysine (K) and arginine (R) residues (Stallcup 2001). The histone lysine methylation occurs at three different levels: mono-, di-, and trimethylation and commonly associated with gene activation or repression. Histone H3 lysine 4 (H3K4), histone H3 lysine 36 (H3K36), and histone H3 lysine 79 (H3K79) are associated with gene activation and histone H3 lysine 9 (H3K9), histone H3 lysine 27 (H3K27), and histone H4 lysine 20 (H4K20) are associated with gene repression. Aberrations in histone modifications can lead to deregulated gene expression as seen in various human disease and malignancies. It was reported that epigenetic enzymes will be recruited to the E-cadherin promoter by Snail and cause transcriptional silencing of E-cadherin and lead to EMT. Dong et al. have investigated the interaction of Suv39H1 (Snail binding protein) with Snail and identified Suv39H1 is critical for the enrichment of H3K9me3 on the E-cadherin promoter in breast cancer cells and in the induction of EMT (Dong et al. 2012, 2013). It was also reported that the stemness of BCSCs is maintained by the epigenetic marker H3K27me3. In a recent study, Ningning Yan et al. have proposed H3K27me3 as a target for elimination of BCSCs. It was reported that inhibition of H3K27me3 demethylation specifically target BCSCs by inactivation of JMJD3 and UTX, which facilitate target gene activation by catalyzing the conversion of H3K27me3 and H3K27me2 to H3K27me1 and maintain the balance between methylation and demethylation (Yan et al. 2017). Recent studies in epigenomics have, therefore, led to understand the key mechanisms by which epigenetic regulations contribute to tumor progression. Further understanding of the mechanisms involved in epigenetic regulations and testing the epigenetic modulating drugs, offer new avenues for targeting BCSCs.

Future prospects

One major challenge for targeting BCSCs is the molecular cross talk between the self-renewal signaling pathways in BCSCs and NSCs. Multiple developmental signaling pathways implicated in regulating BCSCs, like TGF-β, Wnt, and Notch, have been shown to regulate normal stem and progenitor cells. Selective targeting of BCSCs, therefore, will be

challenging. TGF-β is a potent EMT inducer that is reported to be secreted by multiple cell types in tumors (Padua and Massagué 2009). TGF-β is reported to activate EMT programs in both mammary epithelial cells and also BCSCs. In BCSCs, TGF-β activation leads to expression of surface markers $CD44^{high}CD24^{low}$, and the increase the ability to form mammospheres (Mani et al. 2008; Scheel et al. 2011; Bruna et al. 2012). In normal human mammary cells, efficient activation of EMT requires co-operation of both TGF-β and Wnt signaling pathways. However, such co-operation is reported to be essential only in early developmental stage (Nishita et al. 2000). In adult mammary glands, MaSCs exhibit elevated Wnt signaling (van Amerongen et al. 2012) and the overexpression of Wnt proteins or activation of canonical Wnt by Axin2 mutation or MMP3 overexpression promotes the expansion of MaSCs (Shackleton et al. 2006; Zeng and Nusse 2010; Kessenbrock et al. 2013). In contrast to Wnt, Notch is reported to induce the commitment of MaSCs to luminal-specific progenitors (Bouras et al. 2008). However, basal-like breast cancer is likely to originate from luminal progenitor cells (Molyneux et al. 2010). Notch signaling, therefore, is particularly important for this breast cancer subtype (Harrison et al. 2010a). It was also reported that although TGF-β increases BCSC numbers in claudin-low subtype, it suppresses BCSC in certain basal-like and luminal breast cancer subtypes (Bruna et al. 2012). Similarly, Wnt-overexpressing fibroblasts promoted the growth of one patient-derived xenograft (PDX) model but inhibited another PDX (Green et al. 2013). Future therapeutic strategies can, therefore, be tailored based on the molecular signature of specific tumor subtypes. In addition, understanding the complex differences in the biology of NSCs and BCSCs is necessary for selective targeting of BCSCs. For instance, designing therapeutic strategies to target mutation present only in BCSCs and selective targeting mechanisms of tumor propagation that are distinct from NSC regulation are possible strategies. For example, the cyclopamine (inhibitor of Hh pathway) is inactive in normal cells due to expression of patched (Ptc) gene. Ptc gene products are reported to prevent binding of cyclopamine to its target. However, tumor cells respond well to treatment with cyclopamine due to mutations in Ptc gene. Thus, cyclopamine was expected to selectively kill tumor cells (Goodrich and Scott 1998; Borah et al. 2015). In recent years, researchers have also focused on designing suitable nano-drug delivery systems to specifically target BCSCs. The application of nanocarriers for BCSC-targeting, however, is in its infancy, and many issues need to be well studied in clinical settings (Pindiprolu et al. 2017). Due to complex signaling network and their high dynamic plasticity according to the need of the environment, there are greater chances for development of drug resistance in BCSCs. Multi-targeted anti-BCSC agents need to be designed, therefore, to overcome drug resistance. Various pathways of BCSCs like Hh, notch, and Wnt have multiple points which can be targeted simultaneously. The existence of cross talk among these signaling pathways needs to be understood for designing novel therapeutic agents for targeting BCSCs (Bashyal Insan and Jaitak 2014). Accumulating body of evidences also suggests that although BCSCs are eliminated, non-BCSCs which are left behind will revert back to acquire characteristics of BCSCs. Combination therapy with chemotherapeutic agents and anti-BCSC agent is, therefore, needed to achieve a radical cure.

Conclusion

Compelling body of evidence suggest that the presence of BCSCs is the major cause of tumor relapse, metastasis, and chemoresistance in breast cancer. As discussed in the review, many molecular targets have been identified in BCSCs. They include surface markers, self-renewal pathways, apoptotic pathways, autophagy, metabolism, and microenvironment. The current research is focused on developing anticancer agents against these targets to eliminate BCSCs and to achieve radical cure in breast cancer therapy. The identification of strategies that take advantage of these targets of BCSCs needs to be well studied.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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