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Therapeutics strategies against cancer stem cell in breast cancer

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ABSTRACT

Breast cancer is known as a most prevalent cancer and second deadly cancer, among women worldwide. Due to the high incidence rate of breast cancer and limitations of conventional therapy it seemed essential to look for new targets in cancer cells and directly target them such as target therapy on breast cancer stem cells. In this review we indicate some of therapeutic uses of cancer stem cells in breast cancer. Some strategies are targeting surface specific markers and activated signaling pathways in their microenvironment such as Notch, Hedgehog, Wnt/b-catenin, PI3K/Akt, NF-kB, BMP and TGF-β and their maintenance and drug resistance, using various miRNAs, enhancement of CSCs apoptosis, differentiation therapy, blocking epithelial to mesenchymal transition and using different natural compounds. Recent studies have shown that cancer stem cells play major roles in target therapy on breast cancer. The new manipulation approaches of cancer stem cells can be used as target therapy of breast cancer that were highlighted for immunotherapy of cancer.

1. Breast cancer

Breast cancer (BC) is known as a most prevalent cancer with an estimated incidence of 266,120 new cases and 40,920 estimated deaths in 2018 in the United States and second deadly one after lung cancer, among women worldwide (Ginsburg et al., 2017; ShahidSales et al., 2018). The advances in oncology, including BC study, was remarkable in last years and scientists reached new and interesting findings in prediction, diagnose and the treatment. Finding novel treatments that lead to the complete eradication of tumor cells, is one of the interesting parts in cancer study (Fernández et al., 2010). Breast cancer is considered heterogeneous disease with the alteration of both genetic and epigenetic factors and with different, subtypes and stages (Toss and Cristofanilli, 2015). The treatments for BC, like other types of cancer were, first, surgery and radiotherapy that even today are inseparable part of treatment and mostly are used for local disease (Maughan et al., 2010; Wu et al., 2006). Being unable in controlling metastatic cancer, that reaches even distant organs, and its role as a responsible for more than 90% of cancer- related death, led to the advent of chemotherapy, hormonal therapy and target therapy (Li and Kang, 2016; EBCTC, 2005). The FDA has approved more than 25 drugs in treatment of BC, high majority belong to cytotoxic chemotherapies, hormonal therapies are in the second position and the third position belongs to Only 4 drugs that target tumor and microenvironment specifically(Fernández et al., 2010; Wang et al., 2016). Despite cytotoxic drug's efficacy in eradicating primary tumors, they have some limitations including major side effects in different organs, because they target all proliferative and growing cells including both normal and tumoric cells(Diaby et al., 2015). Endocrine therapy like chemotherapy is used systemically and even its efficacy comes down in targeting metastatic breast cancer. Long time endocrine therapy finally leads to drug resistance. (Massarweh and Schiff, 2006). Due to the high incidence rate of breast cancer and limitations of conventional therapy it seemed essential to look for new targets in cancer cells and directly target them, especially metastatic one(Padma, 2015), so attempts in finding new and responsive targets in the area of target therapy (In these treatments scientists look for targets that are specifically belong to cancer cells) (Marofi et al., 2017; Toss et al., 2017), led to the discovery of cancer stem cells. In this review we indicate some of therapeutic uses of therapeutics strategies against cancer stem cells (CSCs) in BC.

2. Cancer stem cell

As mentioned before, one of the most challenging area of cancer therapy, is tumor relapse and the metastasis of tumor. So even with common treatments (like chemo therapy and radio therapy), the

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satisfactory results did not obtain. Different efforts have been made to overcome these challenges (Forouzanfar et al., 2018). One of these efforts, led to the identification of first Human CSCs in AML by Bonnet and Dick in 1997 (Reya et al., 2001). CSCs (like all stem cells in normal tissues) are defined as a subpopulation of tumor cells, known with four characteristics including self-renewal, differentiation, tumorgenicity and specific surface markers (Rao and Mohammed, 2015; Esmaeilzadeh and Farshbaf, 2015). Possessing some specific features, make them responsible for cancer initiation, progression, metastasis, recurrence and drug resistance and is known as an important factor in conventional therapy failure and tumor relapse (Hu et al., 2017; Dorado et al., 2011). They are identified in various malignancies, like leukemia and solid cancers including breast, pancreas, prostate, head and neck, colon, liver, bladder and lung cancer (O'Connor et al., 2014). CSCs formation is consisted of two hypotheses: 1-genetic and epigenetic instability leads to various gene mutations in normal stem cells or progenitor cells and transform them into CSCs. 2-Oncogene-induced plasticity turn tumor cells to stem cell (Pattabiraman and Weinberg, 2014). Scientists use different methods for detecting CSCs in tumor cells, in vitro. It should be mentioned that each method has special benefits and limitations: 1-Use of cancer stem cells capacity to form sphere in serum-free medium or soft agar: in this method we harvest CSCs, that are derived from tumor specimen cells and seed them at low density in medium that is serum-free and in a mixture of epidermal growth factor (EGF) and fibroblast growth factor (bFGF), so CSCs capacity can be detected, in forming colony (Cortes-Dericks et al., 2014), 2- another way of detecting CSCs is dye exclusion or the capacity of CSCs to overexpress drug-efflux pumps like (ATP binding cassette or multidrug resistance transporters) (Bellamakondi et al., 2014),3- enzymatic activity of aldehyde dehydrogenase 1 can also be as a guide in CSCs detection (Kesharwani et al., 2015), 4- special biomarkers on the surface of these cells including: CD133, CD24, hyaluronicacid (HA) receptor CD44, cytoprotective enzymes (like aldehyde dehydrogenase, ALDH), transcription factors (e.g., OCT-4,SOX-2), drug-efflux pumps (e.g., ATP-binding cassette (ABC), and drug transporters and multi drug resistance transporter1 (MDR1), that are helpful in detection and CSCs can be identified, isolated, purified and characterized using flow cytometry analysis, fluorescence-activated cell sorting (FACS) analysis, polymerase chain reaction (PCR) analysis and immunofluorescentstaining analysis (Han et al., 2013). It should be proved in vivo, using some assays like the ability to proliferate after serial transplantation (Chen et al., 2012). CSCs discovery opened a new window in a field of cancer therapy in the following part we will focus on its role and its potential uses in breast cancer.

3. CSCs and breast cancer

In order to eliminate all cancer cells, beside targeting primary cancer cells, it's essential to target small population of tumor cells, responsible for tumor initiation, progression, metastasis, recurrence and drug resistance in BC (Hesari et al., 2018), are called BCSCs (Breast Cancer Stem cells) (Forouzanfar et al., 2018; Velasco-Velázquez et al., 2012). With better understanding of CSCs phenotype, in different tumor type's scientists are able to target them with different methods: Targeting surface specific markers and activated signaling pathways in their microenvironment and their maintenance and drug resistance, using various miRNAs, enhancement of CSCs apoptosis, differentiation therapy, blocking epithelial to mesenchymal transition and using different natural compounds. Detection can be done using surface markers, for example BCSC have been identified as CD44+, CD24−/low, and ESA+ (epithelial specific antigen) and non-cell-surface markers such as elevated aldehyde dehydrogenase (ALDH) activity and combination of these markers with the help of functional assays, lead to the correct detection when compared with individual markers (Smalley et al., 2013). Here some efforts in targeting these stem cells in breast cancer are listed.

3.1. Targeting surface markers

Targeting surface markers is the commonly used technique, like targeting (CD133, CD44, CD24, ESA CD34+CD38-, CD47). For example surface marker CD44 was used as a target in AML therapy or ESA + CD44+CD24–, ALDH-1 are surface markers in breast cancer and CD133+, CD44+, CD166+, EpCAM+, CD24+ can be detected in colon cancer and so on (Pattabiraman and Weinberg, 2014; Hoseini et al., 2017). But it should be noticed that they are not specialized and one marker may be common in many cancers, e.g. CD133 antigen can be isolated in brain, prostate, pancreatic and other types of cancer (Prieto-Vila et al., 2017; Liu et al., 2014). CD44 as a transmembrane protein, is important in tumor cell growth and proliferation, migration, differentiation, apoptosis, self-renewal, microenvironment, epithelial-mesenchymal transition and drug resistance. In aggressive breast cancer combining anti-human CD44 monoclonal antibody with doxorubicin and cyclophosphamide prevent tumor recurrence (Sell, 2006). CD133 as a marker is detected in various cancer types like breast cancer and results in poor survival results and blocking this marker may increase the clinical prognosis. (Mannello, 2013) B6H12.2 is monoclonal antibody against CD47, prevents growth of tumors, such as breast cancer (Korkaya et al., 2011).

3.2. Targeting CSCs signaling pathways

Many studies show that CSCs do not choose the same signaling pathways as normal stem cells. Abnormalities and Dysregulation in signaling pathways may lead to malignant transformation, (Notch, Hedgehog, Wnt/b-catenin, PI3K/Akt, NF-kB, BMP (bone morphogenetic proteins) and TGF-β (transforming growth factor β) are some of important pathways (Takebe et al., 2015) that take part in cancer stem cell formation, their transition and warranty tumor viability (Chen et al., 2013). Targeting signal cascades with specific components is popular strategy for eradication of CSCs. Aberrant activation of Notch signaling pathway has been reported in the breast CSC population. It has four receptors (Notch 1, Notch 2, Notch 3 and Notch 4) and five ligands. Notch4 and Notch1 are activated in breast CSCs and blocking these receptors, especially Notch4, declined the activity of breast CSCs in vitro and reduced tumor development in vivo. MK-0752(Merck), RO4929097 (Roche) and DAPT are Notch inhibitors. One significant example in blocking this pathway is DAPT, that is a y-secretase inhibitor and can reduce CSC activity (Lawson et al., 2015). EGFR belongs to the cell signaling pathways, active in breast cancer stem cells. Its upregulation also, has reported in breast cancer stem cells for mammosphere formation. Reduction of both EGFR and Notch1 expression was detected in cancer stem cells treatment with an EGFR inhibitor called Gefitinib (Ibrahim et al., 2017). Wnt signaling pathway consists of canonical and non-canonical pathways and each member of this pathway may have defect in different cancers. Aberrations in the Wnt/B catenin is likely to induce hematopoietic stem cell transformation into leukemia stem cells, so plays important role in origination of AML (Polakis, 2012). The canonical pathway has shown to take part in self-renewal and maintenance of CSCs in mammary gland. Blocking Wnt/β-catenin signaling, reduced the growth of CSCs and induced their differentiation (Takahashi-Yanaga and Kahn, 2010). Wnt signaling is found to influence the cell fate of CSCs in the breast. Salinomycin, being a Wnt antagonist inhibits Wnt signalling and that can remove breast surface markers such as CD44, ALDH and drug resistance markers ABCG2 (Zhan et al., 2017). Overexpression of the Hedgehog pathway has been shown to play role in the maintenance of self-renewal in CSCs of different cancers including breast cancer, GDC-0049 is a Hedgehog inhibitor (Takebe et al., 2011). Cyclopamine, a SMO signaling element inhibitor, inhibits the hedgehog signaling pathway, and has been shown to hinder of the proliferation, invasion and metastasis of breast cancer (Kim et al., 2016). STAT3 is another pathway involves in maintenance, growth and viability of stem-like cells of BCSC (Badve and Nakshatri,

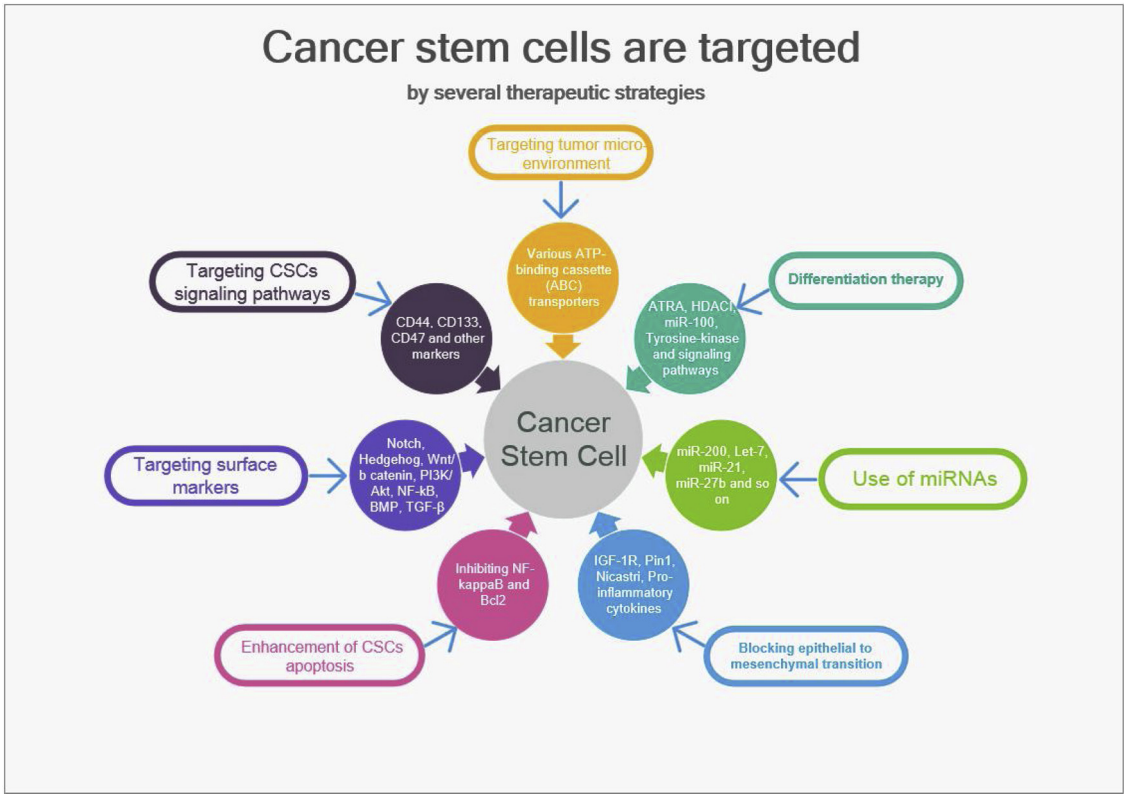

Fig. 1. Models for cancer stem cells by several therapeutic strategies. There are targeting CSCs signaling pathways, targeting tumor micro environment, differentiation therapy, use of miRNA, enhancement of CSCs apoptosis and blocking epithelial to mesenchymal transition.

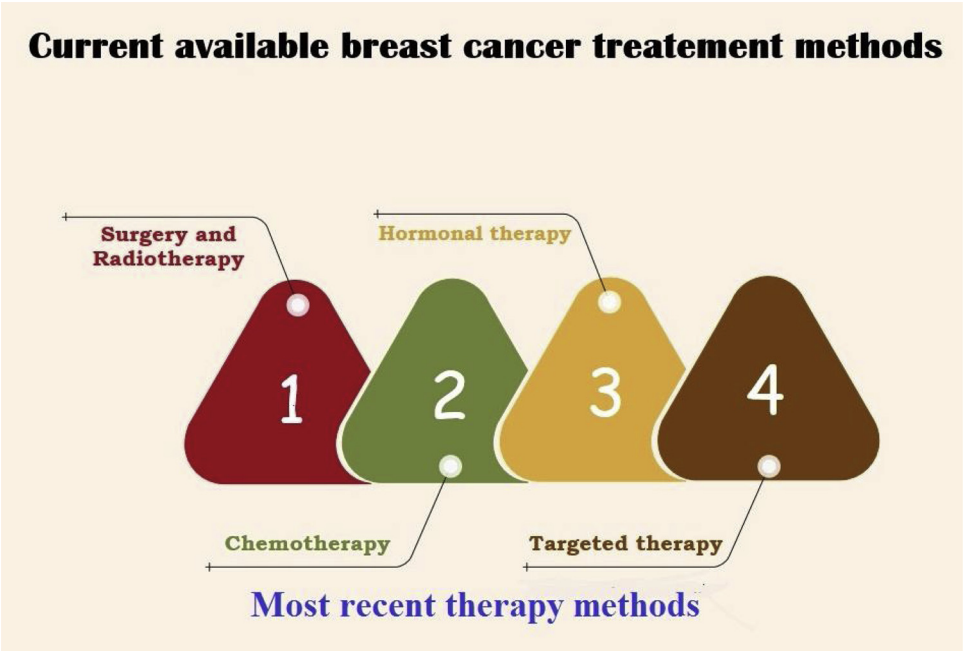

Fig. 2. Current available breast cancer treatment methods.

2012). TAZ is a Hippo pathway transducer induces metastatic and EMT ability and chemo resistance of BCSCs (Bartucci et al., 2015) (Figs. 1 and 2).

3.3. Enhancement of CSCs apoptosis

Optimizing cell cycle control and increased free-radical scavengers for DNA repair through Poly (adenosine disphosphate-ribose) polymerase (PARP), that inhibits pathways involved in apoptotic resistance, has shown to be efficacious in triple negative and metastatic breast cancer (Ablett et al., 2012). Another strategy is sensitization of CSCs to treatment by inhibiting pathways such as NF-kappaB and Bcl2 (BCL-2 family is deregulated in breast cancer and enhances drug resistance) (Delbridge et al., 2016), involved in apoptotic resistance. Induction of

CSCs apoptosis attracts scientists to invest in this promising type of cancer therapy (Dufour et al., 2017). Combination of TRAIL with cisplatin and other anticancer agents was effective in Wnt signaling inhibition and inducing apoptosis in cancer stem cells. Thus efficacious results gained in reducing triple negative breast cancer stem cells (Yang et al., 2017). In breast cancer, NF-kB activity is essential for maintaining the survival of cancer stem cells. Small molecules like parthenolide, pyrrolidinedithiocarbamate and its analog diethyldithiocarbamate, inhibit this pathway so can target breast cancer stem cells (Shostak and Chariot, 2011). One of the helpful drugs that is administered for other diseases but it can also be used in CSCs eradication is Metformin that induces cell apoptosis in a level of glucose dependent manner, thus reduces the development of breast cancer (Bao et al., 2014; Esmaeilzadeh et al., 2014).

3.4. Blocking epithelial to mesenchymal transition

BCSC have great tendency to undergo epithelial to mesenchymal transition called EMT. EMT is important process in initiating metastases, because it helps tumors to disseminate to distant sites of the body. EMT induces transcriptional factors, SNAIL and Twist, in the following, induce CSC phenotype in breast cancer epithelial tissue (Scheel and Weinberg, 2012). In this process some signaling pathways are active, The TGF-β pathway is the best-studied signaling cascade induces the EMT process in various cancers (Yu et al., 2012). TGF-β is a well-known EMT inducer, through regulators such as Snail and Twist. In claudin/low cancer cell lines, TGF-β increases CSC numbers but in certain basal-like and luminal cell lines it decreases the population (Carey et al., 2006). IGF-1R, Pin1, Nicastrin and Pro-inflammatory cytokines are some of targets that scientists use to inhibit this process (Kotiyal and Bhattacharya, 2014).

3.5. Role of miRNAs

Various non-coding RNAs, especially some microRNAs, such as (miR-21, miR-34, miR-124, and miR-137) are aberrantly expressed and act as key regulators of CSC signaling. Set of 37 miRNAs were found to be altered in BCSCs (Guo, 2014). MiR200 is down regulated in BCSCs so induces the accumulation of EMT transcription factors (Mutlu et al., 2016). The inhibition of miR-200 increases the number of CSCs in breast, miR-200 targets genes associated with many stem cells and interfere with some key stem cell signaling pathway such as notch (Iqbal et al., 2013). In breast cancer inhibition of tumor proliferation, growth and migration may be facilitated thorough miR-21 (Han et al., 2012). Loss of microRNA-27b increase docetaxel resistance in Luminal A breast-type cancer by elevating the expression of ABCG2 (Prieto-Vila et al., 2017). Let-7 is regulator and suppressor of self-renewal in BCSC (Liu et al., 2012; Yu et al., 2007). MiR-205-5p is detected to be highly expressed in BCSCs and subsequently represses ERBB2 and EGFR leading to therapy resistance (De Cola et al., 2015).

3.6. Differentiation therapy

CSCs have the tendency to differentiate into different types of cells, such as non-tumorigenic-differentiated cancer cells, when exposed to specific differentiation signals (Ronen, 2016; Nadri et al., 2017). Induction of CSCs differentiation may be another promising target, many studies are currently in progress trying to use, differentiation agents like ATRA (retinoic acid and its analogs), HDACI, miR-100, tyrosine-kinase and signaling pathways inhibitors (Sell, 2006). ATRA (all-trans retinoic acid) is a carboxylic acid form of vitamin A has been used in different cancer cells including breast cancer stem-like cells (Sun et al., 2015), results were: induction of differentiation, reduction in tumor invasion and migration, and increase sensitivity to anticancer treatment (Li et al., 2011). MiR-100 assists breast CSCs differentiation by changing a basal like phenotype into luminal. It boosts basal like phenotype of breast cancer response to hormonal therapy by expressing estrogen receptor (Petrelli et al., 2015). HDACI has potential use in numerous hematologic malignancies as differentiation therapy and target therapy, this type of therapy was suggested for breast CSCs differentiation and treatment (Pathania et al., 2016; Witt et al., 2017). Bone morphogenetic protein (BMP) is a regulator of Wnt pathway, belongs to the (TGF-β) superfamily. BMP activation leads to the translocation of phosphorylated Smads to the nucleus and as a result, regulation of downstream genes that regulate terminal differentiation occurs. BMP antagonists express in high levels in breast cancer (Davis et al., 2016; Ren and ten Dijke, 2017).

3.7. Targeting microenvironment of tumor

Normal tissue stem cells and cancer stem cells are located in a space in order to guaranty their stemness and composed of different cell types including growth factors, ECM and cytokines, known as *niche* of these cells (Yoshida and Saya, 2016; Plaks et al., 2015). Tumor microenvironment is chemo resistant and radiation resistant via inflammatory cytokines like CXCL12 that binds its receptor CXCR4 to induce tumor proliferation and metastasis. One of the CXCR4 antagonists is CTCE-9908 that shown to have satisfactory results in declining tumor proliferation and metastasis in mouse models. Angiogenesis, hypoxia and acidic pH are also factors that used to target microenvironmen t (Guo, 2014). Hypoxia regulation is done by two inducible transcription factors which are called HIF-1 and HIF-2. In a study growth of primary breast cancer stem cell, inhibited by blocking HIF activity using RNA (Schulenburg et al., 2015). There are studies show the relevance between angiogenesis and CSCs, due to the same biomarkers and using the same signaling pathways, e.g. Notch. Targeting ovarian cancer by anti-angiogenic agent called bevacizumab had successful results (Markowska et al., 2017). Metabolic activity of cancer cells results in acidic extracellular pH and following drug resistance, besides as what revealed in a study of A B Hjelmeland and his team low pH induced cancer stem cells survival and elevated the grade of tumor malignancy (Hjelmeland et al., 2011).

3.8. Targeting drug resistance

Drug resistance has turned to be a major problem in cancer therapy and CSCs are shown to be culprit for this phenomenon with a special focus on Chemotherapy and radiotherapy (Cojoc et al., 2015). CSCs manifest a high number of proteins on their cell surface called ATP-binding cassette (ABC) transporters, ABCB1 (P-gp, MDR1), ABCG2 (BCRP1), ABCC11 (MRP8) and ABCB are strongly expressed in the CSC's chemo resistance (Dean, 2009). Targeting ABC cassette may be done using Verapamil, cyclosporine A, MS-209 (Colak and Medema, 2014). Transporters like ABCG2 and ABCG5 (Ejendal and Hrycyna, 2002) have been identified to contribute to drug resistance in different types of cancers. For example ABCG2 is upregulated in breast cancer stem cells and targeting ABCG2 or MDR1 with Cyclopamine, through inhibition of Hedgehog signaling, has shown to regulate the expression of ABCG2 and ABCG5, and decrease their expression (Smalley et al., 2013; Mao and Unadkat, 2015).

Beside these emerging efforts, compounds such as Curcumin are considered multifaceted in cancer therapy with numerous abilities (Shanmugam et al., 2015) and that can be either used in targeting CSCs. In one study curcumin and piperine inhibit breast stem cell self-renewal and indicated their potential in CSCs eradication (Kakarala et al., 2010; Zhang et al., 2017; Esmaeilzadeh et al., 2016).

4. Conclusion

Cancer stem cells detection with different abilities was a remarkable hint in cancer treatments. With knowing emerging ways of targeting CSCs as mentioned above, they have been sensitized to common cancer

therapies like chemotherapy and this can be impressing progress in hindering tumor relapse. Targeting breast cancer stem cells can be done using one or combination of mentioned therapies. Beside these approaches, one of the best methods of the modern therapies is administration of nano-carriers to directly take drugs to CSCs niche and block active pathways. Detecting specific targets that intrude with CSCs maintenance is of essential factor needs to be mentioned in further studies.

Conflict of interest

The authors have no conflict of interest to disclose.

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