Review Article

# Cancer Stem Cells: Targets for treatment of malignancies and overcoming drug resistance

Maryam Bikhof Torbati[1,2*] , Mahzad Motallebi[2] , Mehrdad Hashemi[3,4]

[1] Department of Biology, Yadegar-e-Imam Khomeini(RAH) Shahr-e-Rey Branch, Islamic Azad University, Tehran, Iran.

[2] Young Researchers and Elite Club, , Yadegar-e-Imam Khomeini(RAH) Shahr-e-Rey Branch, Islamic Azad University, Tehran, Iran.

[3]Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

[4]Medical Convergence Science Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

**Article Information**
Received:2020-10-06
Revised: 2021-03-02
Accepted: 2021-06-07

**Correspondence**
Maryam Bikhof Torbati
Email:maryam.bikhof@gmail.com

**Cite this article as**:
Bikhof Torbati M, Motallebi M, Hashemi M. Cancer Stem Cells: Targets for treatment of malignancies and overcoming drug resistance.Archives of Advances in Biosciences 2021:12(2)

## Abstract

**Context:** In spite of all advancements in anticancer drugs, most tumors have been found to relapse and metastasize to other organs, causing resistance to therapy. It is believed that cancer stem cells (CSCs), due to their special properties like self-renewal and differentiation into heterogeneous cancer cells, could be involved in cancer recurrence and anticancer treatment resistance.

**Evidence Acquisition:** Studies indicate that different molecular mechanisms like signaling pathways, cell surface markers, tumor microenvironment and miRNAs are responsible for drug resistance property of cancer stem cells. Hence, detailed knowledge of these mechanisms could be of help in finding an effective therapeutic strategy to target this group of cells in order to overcome the issue of tumor relapse and drug resistance

**Results**: Taken together, cancer stem cells use various mechanisms to escape from immune system and other defensive obstacles like apoptosis to survive and induce drug resistance. This fact emphasizes the need for combination therapies in addition to targeting each aspect of these cells.

**Conclusions**: It seems reasonable to conclude that finding effective ways to eliminate chemotherapy resistance needs more research and clinical trials in different cancers using various strategies targeting cancer stem cells' properties.

**Keywords:** Cancer Stem Cells , Marker, Cell Signaling, Drug Resistance, Cancer Treatment

## 1. Context

About 20 % of mortality rate in developed countries is due to cancer [1]. Some cancer cells as cancer stem cells (CSCs), which make up less than 1 % of the tumor, often remain after chemotherapy and cause tumor recurrence and metastasis [2,3]. In 1997, for the first time, Cancer stem cells identified in patients with acute myeloid leukemia [4]. These are heterogeneous cells and this heterogeneity is caused by internal factors such as genetic and epigenetic

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

mutations and external factors including the microenvironment around the tumor (Niche) [5,6]. To date, two main stochastic and hierarchical patterns have been proposed to explain this heterogeneity . In stochastic model, it is stated that the occurrence of successive mutations causes heterogeneity in tumor cells and cancer progression and that all cancer cells have the self-renewal property. In hierarchical model, however, it is claimed that only a few cancer cells are able to advance cancer due to their self-renewal profile [7]. One serious problem in cancer treatment is chemotherapy induced drug resistance, in which the CSCs play an important role through various mechanisms. Accurate identification of markers and signaling pathways related to metastasis and drug resistance could be effective in choosing appropriate therapy method for removal of these cells [8]. In the following sections, the importance of different markers and signaling pathways and their targeting methods in treatment will be discussed.

## 2. Evidence Acquisition

### 2.1. Markers of cancer stem cells

These markers are divided into two categories: extracellular and intracellular markers. Extracellular markers which are expressed at the cell surface are often shown as CD s (Cluster of Differentiation) [9] (Table 1). Some of the most important extracellular markers are:

- CD133 (Promimin-1) : A membrane glycoprotein which is also a marker of hematopoietic stem cells [10].
- CD44 : A cell surface glycoprotein that is important in cell migration, cell-matrix interactions and is also a hyaluronic acid receptor [10,11].
- CD24 : A heavy glycosylated protein that is considered a cell adhesion molecule in the lipid bilayer through glycosyl phosphatidyl inositol (GPI ) anchor and its expression is raised in metastasis and apoptosis inhibition in tumor cells [9].
- CD13 : A Type 2 zinc dependent exopeptidase , which is attached to the cell membrane in many mammalian tissues, such as the intestine and liver . The expression of this marker is seen in many tumors and it is involved in cell growth, angiogenesis and metastasis [10].
- CD326 : A transmembrane glycoprotein which is is involved in cell-cell adhesion is referred to as EpCAM (Epithelial Cell Adhesion Molecule) .CD326 is expressed in epithelial tumors, tumor cells in the bloodstream and also in cancer stem cells [9].
- CD47 : A ligand for signal regulatory protein- α (SIRPα) in phagocytic macrophages and it inhibits phagocytosis [12].
- CD90 ( THY1) : A N-glycosylated Surface protein with three sites for N-glycosylation [13].
- CD49f: A marker related to fibroblasts and its expression is increased in fibroblasts in the tumor [14].
- CD166 (ALCAM) : A member of immunoglobulin super family ( IgSF) and cell adhesion molecules [15].
- CD87 : A highly specific marker for cancer fibroblasts [14].
- CD31 : A protein which is expressed on almost all intravascular cells, including on the surface of most leukocytes, such as granulocytes, monocytes and platelets, as well as vascular endothelial cells and it is also known as PeCAM-1 ( Platelet / endothelial Cell Adhesion Molecule). CD31 is involved in cell migration, endothelial metastasis and cell connections [16].
- CD34 : A transmembrane phosphoglycoprotein and an important marker for diagnosis and isolation of hematopoietic stem cells [17].

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

- CD117 : A tyrosine kinase receptor type 3 which is involved in tumorgenesis, metastasis, relapse and resistance to treatment [18,19].
- CD105 : A transmembrane glycoprotein, also known as Endoglin and it is involved in tumor formation and metastasis progression [20].
- Integrin α6: exists in the form of hetero-dimer α6ß1 and α6ß4, expressed by epithelial cells and it is involved in binding to laminin [21].
- Integrin α2ß1 : The most important integrin binds to collagen and it contributes to lymphocyte-T mediated immunity [22].
- CXCR4 : A G-Protein-binding receptor which is expressed during human embryonic development and adulthood, especially in the hematopoietic system [23].
- Sca-1 (Stem Cell Antigen-1) : A surface marker for the formation of trophoblast cells and its gene symbol is Ly6A [24,25].
- LGR5 (Leucine-rich repeat-containing G-protein coupled receptor 5) : An important target for Wnt signaling and it is also a kind of G-protein-binding receptor [26].

Intracellular markers of CSCs are often in the form of intracellular transcription factors. Some of these markers are listed below:

- EZH2 (Enhancer of zeste homolog 2 ): It has the self-renewal ability and involves in tumor recurrence and drug resistance [19].
- TG2 (Tissue transglutaminases) : A type of tissue transglutaminase enzyme that is involved in protein binding [19].
- SOX2 (SRY-Box Transcription Factor 2) : A very important transcription factor in self-renewal and pluripotency of embryonic and neuronal stem cells [27].
- ALDH (Aldehyde dehydrogenase ) : A detoxifying enzyme which converts the retinol to retinoic acid and it contributes to cell proliferation, differentiation and self-renewal [10,28].
- SALL4 (Sal-like protein 4) : A member of zinc finger transcription factors whose cooperation with the Wnt signaling pathway is the main reason for its role in lymph node metastasis [10,29].
- OCT4 (Octamer-binding transcription factor 4): It belongs to POU transcription factor family and it is coded by POU5F1 genes. OCT4 plays a major role in stem cell pluripotency and differentiation inhibition. The fate of embryonic stem cells is determined by its levels [30].
- KlF4 (Kruppel-lik e factor 4) : A member of pseudo-Kruppel factors family which has zinc finger domain . It plays an important role in regulation of physiological and cellular processes such as the dedifferentiation of somatic cells into stem cells, as well as in the pathogenesis of vascular diseases and cancer.
- K19 (keratin 1 9) : A biochemical marker in skin stem cells, hair follicles, thyroid gland and also in fetal epidermal differentiation. Keratin is an intermediate filament responsible for the structural integrity of epithelial cells [8].

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

## 2. 2. Mechanisms of cancer stem cells' drug resistance

Resistance of cancer stem cells to various chemotherapy drugs which is called Multi Drug Resistance ( MDR), is one of their popular features [5] .This phenomenon is caused by several factors , some of which are discussed below and also schematically shown in Figure 1.

### 2.2.1. Epithelial to Mesenchymal Transition (EMT)

In this process, the epithelial features disappear because of reduced cadherin-E and increased mesenchymal markers such as fibronectin and cadherin– N expression. Cancer cells migrate and colonize in other tissues through EMT, becoming more invasive and resistant to apoptosis [36]. EMT is influenced by extracellular matrix components and some signaling pathways such as Transforming Growth Factor ß (TGF-ß), Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), Hepatocyte Growth Factor (HGF), Wnt and Notch pathways in addition to Hypoxia [8]. Some transcription factors like ZEB1 / 2, TWIST And SNAIL1 / 2 regulate the EMT and induce the expression of genes involved in cell migration and metastasis. ZEB1 is the key transcription factor in the EMT early stages whose expression is induced by TGF-ß and results in resistance to chemotherapy and epithelial phenotype destruction by inhibiting the epithelial miRNAs such as the miRNA-200 family. Nevertheless, the exact mechanism of CSCs' MDR induced by EMT is still unknown in many cases . The EMT-induced drug resistance in CSCs could be due to its role in apoptosis inhibition through reducing the Bcl-2 and BIM protein families expression. TWIST-1 leads to reduced expression of BIM and inhibition of apoptosis [37].

### 2.2.2. Detoxifying membrane proteins

Drug-carrying membrane proteins ABC (ATP binding cassette ) such as MDR1, ABCG2, and ABCB 1 act as drug delivery pumps in the cell membrane. They reduce the intracellular concentration of anti-tumor drugs by pumping them out of the cell, leading to drug resistance in cancer stem cells [1,7]. ABC B5 is crucial for natural stem cells' survival and drug resistance development in some cancers [38]. ABCG2 is also one of the few membrane carriers in human cells that removes various chemicals from the cell [32].

### 2.2.3. Cancer stem cell dormancy

During chemotherapy, some tumor cells enter quiescence state due to activation of EMT and their proliferation will stop [5]. While drugs including inhibitors of mitosis spindle like Paclitaxel and Vincristine plus anti-metabolic drugs such as 5-flourouracil , 6-mercaptopurine and methotrexate have anti-cancer effects during the tumor cells' proliferation , the occurrence of CSC dormancy causes drug resistance [39].

### 2.2.4. Tumor Microenvironment and Niche

Tumor microenvironment has a crucial role in regulating neoplastic processes and contains various elements of extracellular matrix (ECM) , immune cells, stromal cells consisting of fibroblasts, endothelial and mesenchymal cells, miRNAs, Hypoxic areas, extracellular acidic pH (6.2-6.8) and a network of cytokines and growth factors [8,40,41]. The effects of tumor microenvironment on drug resistance are as follows:

**2.2.4.1. stromal cells :** These are a collection of fibroblasts, mesenchymal and endothelial cells plus factors secreted by the cells like ECM [4,40].

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

- Cancer-Associated Fibroblasts (CAFs)

Fibroblasts are abundant in tumor stroma. They are called CAFs within the tumors [4]. The production rate of ECM compounds is higher in CAFs and they are involved in the cancer cell stemness through secretion of specific cytokines like CXCL12, Platelet-Derived Growth Factor (PDGF), HGF , FGF and proteins such as collagen, fibronectin and other extracellular matrix proteins [3,4,42]. TGF-ß is the most important factor inducing chemo resistance through secretion of TGF-ß1 [4,42].

- Mesenchymal Stem Cells (MSCs)

MSCs are mature stem cells which could differentiate into a variety of skeletal tissue cells. In stroma, MSCs activate the NF-κB pathway due to cytokines and chemokines secretion such as CXCL12, CXCL7 and IL6 / IL8 and induce chemo resistance especially in breast cancer.
In epithelial ovarian cancer, MSCs' interactions also result in resistance to Carboplatin and Paclitaxel [4]. Pericytes are also mesenchymal cells which are found a lot in tumor microenvironment particularly in colon cancer, their presence being associated with drug resistance and mortality [42].

- Endothelial cells

Endothelial cells of blood vessels, through secretion of growth factors such as EGF and TNF-α and activation of signaling pathways like Notch, cause resistance to drugs including Doxorubicin and Cyclophosphamide in various cancers . These cells also reduce the drug potency to reach CSCs by creating irregularly shaped blood vessels in the tumor [4].

### 2.2.4.2. Extra Cellular Matrix (ECM)

ECM consists of secreted molecules, especially from fibroblasts which provide a physical barrier to separate drugs from cells and protect CSCs against chemotherapy, after becoming stiffed during the formation of solid tumors [4]. Presence of various glycoproteins, proteoglycans especially laminin and hyaluronan in ECM in addition to its association with growth factors provide support for cancer stem cells and chemo resistance. For example, in head and neck cancer, high levels of hyaluronan in ECM induce MDR through interaction with Oct4-Sox2-Nanog [8].

### 2.2.4.3. Immune cells

Immune cells constitute a large part of the tumor microenvironment and have a variety of contents such as lactic acid, and innate immune cells, namely macrophages, neutrophils and mast cells, adaptive immune cells including lymphocytes B , T and macrophages [40]. Macrophages are important immune cells called Tumor-Associated Macrophages ( TAM or M2 ) in the tumor microenvironment [4]. TAMs induce drug resistance in CSCs through direct interaction with the malignant cells and reduced activity of caspase-dependent apoptotic signaling [1].

### 2.2.4.4 Hypoxia and ROS (Reactive Oxygen Species)

Hypoxia plays an essential role in maintaining the self-renewal nature of cancer stem cells. Cancer stem cells within the tumor are often located near hypoxic areas. Hypoxia induces EMT and metastasis in cancer cells either directly or by increasing the rate of ROS in the cell. Increase of ROS, as a carcinogen in healthy tissues, causes proliferation and differentiation of stem cells, genomic instability, increased expression of oncogenes such as RAS ، Bcr-Abl and c-Myc, decreased expression of tumor inhibitors such as P53, mitochondrial dysfunction and antioxidant production, aging and apoptosis in a dose-dependent manner Therefore, in order to maintain the

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

ability of stem cells to induce tissue homeostasis and repair damaged tissues throughout the life of an organism, reduction in ROS production in these cells is fully regulated [43]. The most important regulator of cellular responses to hypoxia is HIF1α (Hypoxia-Inducible Factor1-alpha) which increases cell survival and drug resistance in cancer stem cells through decreasing the ROS production [4]. High expression of CD44 in CSCs also causes the absorption of cysteine for the synthesis of glutathione as an antioxidant leading to a decrease in ROS . Lower level of production of ROS in CSCs not only is important for their survival, but also can lead to resistance to treatment [43]. TiO2 nanoparticle is one of the factors that have anti-cancer effects against UV light through producing ROS, increasing the sensitivity of tumor cells to radiation [44].
COX-2 (Cyclooxygenase-2), a membrane-bound enzyme responsible for prostaglandin-2 production, also induces resistance to chemotherapy in hypoxia by inhibiting apoptosis through delaying the G1 phase, inducing Bcl-2 expression, and reducing caspase-3 expression [45].

### 2.2.5. Epigenetic alterations

Epigenetic alterations such as DNA methylation, acetylation and phosphorylation of lysine, arginine and serine residues in histone proteins play crucial roles in the developmental processes of mammalian evolution and any disruption causes malignancy in the cells. The structure of DNA chromatin and histones are important in regulating the living cells' gene expression. Following chromatin structural changes in CSCs and chromosome instability due to high telomerase activity plus mitochondrial telomerase support of nuclear DNA by decreasing levels of ROS, cancer stem cells develop drug resistance [5].

### 2.2.6. miRNAs

miRNAs could be oncogenic or tumor suppressor, their expression being associated with various diseases such as cancer. Oncogenic miRs cause drug resistance in CSCs such as miR- 196-5P involved in drug resistance in colorectal cancer [8]. In gastric cancer cells, miR-574-5P and exosomes of ovarian cancer epithelial cells containing miR-141-3P have been pointed out to be responsible for angiogenesis [46,47].

### 2.2.7. Autophagy

Autophagy is involved in tumor survival by providing recycled metabolites for growing, altering mitochondrial activity through mitophagy, and affecting cell invasion [48]. Continuous autophagy also causes metabolic adaptation to hypoxia and acidosis of tumor microenvironment plus drug resistance in cancer cells [49]. Many anti-cancer therapies also induce autophagy and increase the growth and survival of cancer cells [50].

### 2.2.8. Protein glycosylation

A subset of resistance-inducing cancer cell lines has modified glycosylation models, especially at the N-glycosylation level. Some findings relate the upregulation of ABC transporters ( MRP1 and MRP4) and CD14 , demonstrating altered N-glycosylation pattern, with multi drug resistance. Besides, the use of a bio-inhibitor of N-glycosylation like Tunicamycin causes sensitization in chemotherapy-resistant cancer cells [51].

### 2.2.9. BMI 1 Oncogene

BMI1 is a transcription suppressor, belonging to Polycomb gene group, highly expressed in various cancers and is involved

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

in drug resistance [52]. In BMI1 + CSCs , the activity of AP-1 (Activator Protein-1) enhances and these cells are considerably resistant to Cisplatin .The tumor susceptibility to chemotherapy with Cisplatin could be augmented due to AP-1 inhibition [53].

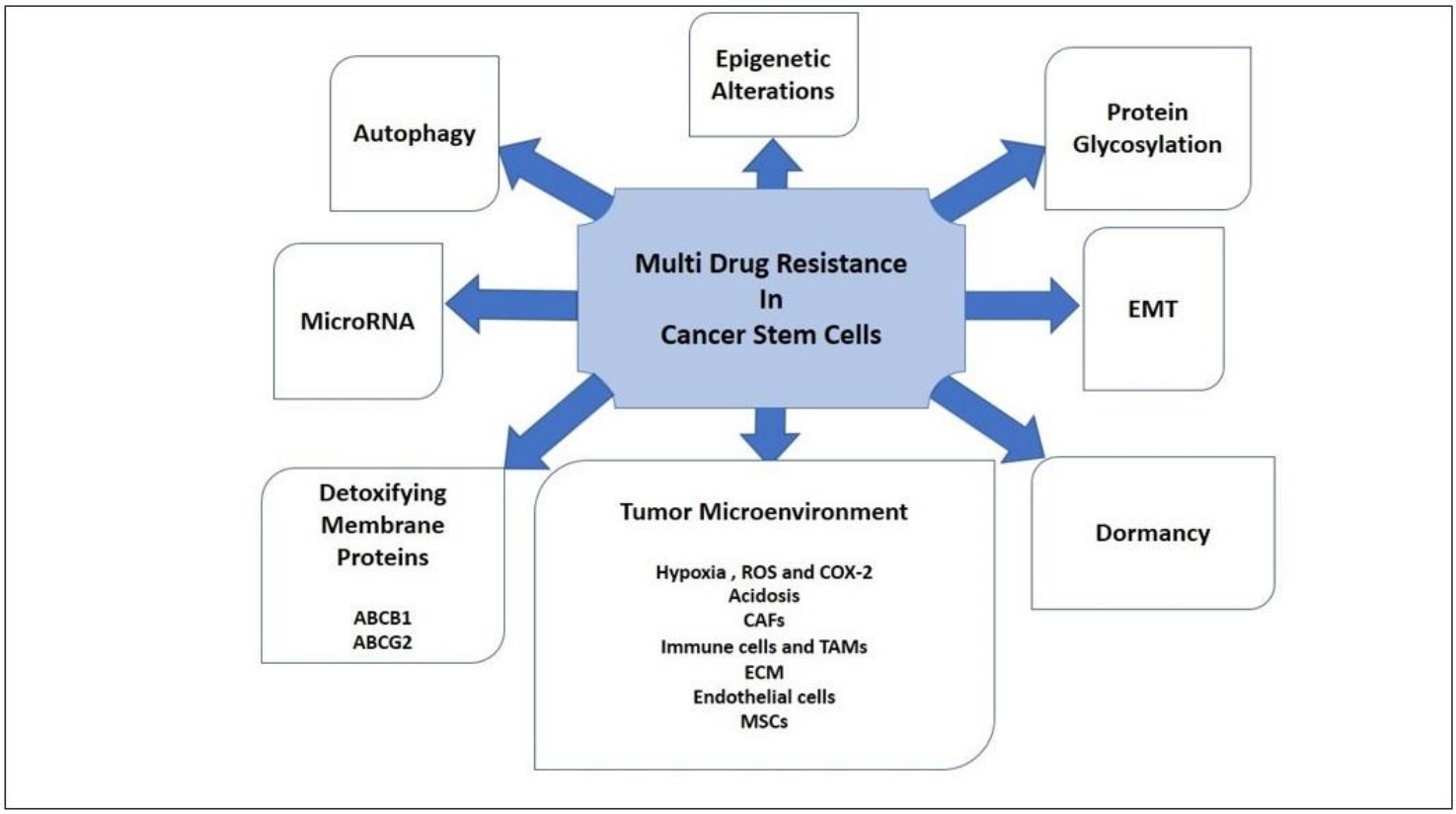


**Figure1**. Schematic illustration of mechanisms involved in cancer stem cell drug resistance

### 2.3. Signaling pathways in cancer stem cells and targeting them in cancer therapy

Today, cancer stem cell targeting based on cell surface markers is applied through immunotherapy, small molecular inhibitors against signaling pathways, and tumor microenvironment targeting [54] (Figure 2).

#### 2.3.1. Notch signaling Pathway

In cell junctions, Jagged or Delta ligands activate membrane proteolytic enzyme, gamma secretase (GSIs) and cut a soluble piece of ligand - receptor complex called NICD by connecting to the membrane receptor Notch [7]. NICD activates the transcription of genes responsible for proliferation, differentiation and cell communication (3) and causes metastasis by altering EMT and angiogenesis [55] . Some gamma secretase inhibitors which inhibit Notch pathway are MK0752 with Docetaxel in metastatic breast cancer and DAPT plus MRK-003 which increase the effectiveness of Paclitaxel and Doxorubicin in lung cancer [31,35].

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

### 2.3.2. Hedgehog signaling pathway

Hedgehog (Hh) Protein, secreted from CSC adjacent cells , activates the SMO membrane protein by sticking to PTCH membrane receptor and releasing a factor which activates the transcription of a growth-promoting gene called Gli1 / 2 that has been inactively attached to the SMO complex [7,8,56]. In basal cell carcinoma, Vismodegib reduces the number of CSCs by restraining the Hh pathway [4]. A study on mouse model breast cancer showed that applying Smoothened (SMOi) inhibitors reduces the cancer stem cell marker expression and the tumors becomes sensitized to Docetaxel [57].

### 2.3.3. Wnt /ß Catenin signaling pathway

In this pathway, Wnt protein sticks to the Frizzled and LRP5/6 receptors in cell membrane and Dishevelled (DVL) protein gets activated. DVL inhibits the destructive complex of APC ،Axin1 ،GSK3ß and CK1 proteins and, therefore, by catenin-ß entrance into the nucleus the transcription of genes involved in self-renewal and proliferation of CSCs is induced. In gastric and lung cancers, Enodiamnine and Trifluoroperazine target the Wnt pathway in cancer stem cells, respectively [7] . Because cancer stem cells are located inside the tumor, in a study, Actinomycin-D (AD) plus an angiotensin receptor antagonist like Telmisartan were used to increase the penetration of the drug into the lung tumor. The results demonstrated that simultaneous combination of AD + TS reduces the catenin- ß levels in tumors more effectively [58]. Salinomycin is also an important drug to control the Wnt pathway [54].

### 2.3.4. LIF/ JAK / STAT signaling pathway

JAK kinase proteins get phosphorylated and activated since LIF ligand binds to the membrane receptor in the cytoplasm and the RAS signaling pathway is activated by GRB2 and SOS proteins binding to the membrane complex. JAK regulates the expression of genes involved in CSC self-renewal property through phosphorylation of STAT3 as an active transcription factor [59]. In ovarian cancer, combination therapy of Paclitaxel and a specialized inhibitor of JAK2 like CYT38, inhibits the activity of JAK2 / STAT3 and as a result, the expression of cancer stem cell markers attenuates [60]. Endostar (ES), a vascular endothelium inhibitor, hinders metastasis and angiogenesis in ovarian cancer cells by inhibiting the STAT3 and PD-L1 activity . PD-L1 activity causes metastasis through lowering immunity in the tumor microenvironment [61].

### 2.3.5. Estrogen Receptor pathway (ER)

This pathway could be targeted, especially in hormone-dependent breast cancer. Endocrine therapy with an anti-estrogen drug like tamoxifen is a promising treatment of advanced and metastatic breast cancers through inhibiting estrogen function [62].

### 2.3.6. NANOG signaling pathway

NANOG and STAT3 transcription factors work together to express the genes involved in cell pluripotency. Some popular NANOG inhibitors are 3-O- methylfunicone in breast cancer and BBI50 3 plus BBI608 (STAT3 Inhibitor) in hepatocellular carcinoma [31,35].

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

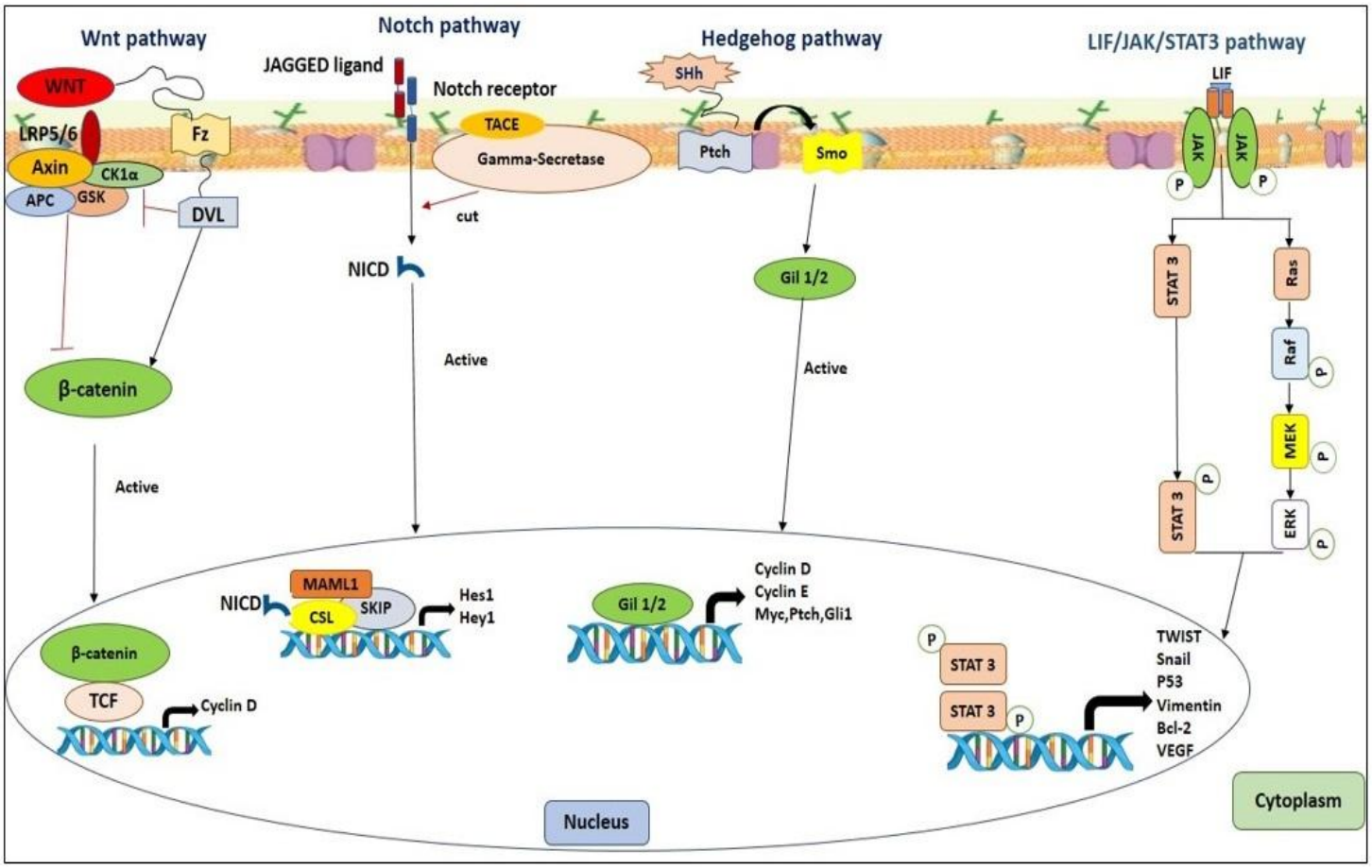


**Figure 2.** Schematic illustration of main signaling pathways in cancer stem cells

### 2.3.7. Apoptotic pathways

Apoptosis is activated through extracellular pathway in which binding death ligands like TNFα, FAS and TRAIL to death receptor stimulates apoptosis and also through intracellular pathway, where mitochondrial membrane permeability is regulated by pro-apoptotic proteins like Bax, Bak and Puma plus anti-apoptotic family Bcl-2, FLIP and Inhibitors of Apoptosis-IAPs [8,63,64]. Due to inactivity of many apoptotic pathways in CSCs, they could avoid the cytotoxic effects of anticancer drugs and survive [8]. Research has shown that many anticancer compounds such as some common synthetic drugs, natural compounds, and nano medicines could inhibit the cancer cells growth by inducing apoptosis . For example, Sulforaphane in pancreatic cancer cells and natural compounds such as exopolysaccharides from probiotic bacteria L.Paracasei and L.brevis in colon cancer cells HT-29 induces apoptosis [35,65] . Another study showed that the magnetic chitosan hydroxyurea nanoparticle induces apoptosis in Hela cervical cancer cells [62,66] .

### 2.3.8. Inhibition of DNA repair

DNA Damage Repair (DDR) is essential for normal cell function and these damages are identified and repaired at cell cycle checkpoints. After chemotherapy and radiotherapy ,DDR is stimulated by DNA damage; thus, the activity of checkpoints

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

such as CHK1 and CHK2 is increased and these lead to tumor progression and CSC chemo resistance [2,67]. Nevertheless, inhibition of these factors like CHK1 in pancreatic adenocarcinoma, enhances the sensitivity of these CSCs to medications like Gemcitabine [68]. Application of local heat of about 43℃ on tumors also interferes with DNA repair pathways, increases the DNA fraction and accumulation of DNA damaged cells which result in apoptosis and decrease in CSC population [69].

### 2.3.9. Targeting EMT pathways

EMT which is induced by factors such as TGF-ß and tyrosine kinase receptor ligands is associated with complex changes in gene expression [68]. Three major groups of factors are identified for targeting EMT, including:

- Extracellular regulators of EMT like: TGF-ß ،EGF ،Axl/Gas6 , Hypoxia and ECM ingredients .
- Transcription factors which regulate EMT like: Twist1 ،Snail1 ،Zeb1/2 ،T-box/ Brachyury and downstream effectors including Cadherin- E / N , Vimentin and HoxA9.
- Epigenetic regulators [1].

## 2.4. Other strategies for cancer stem cell targeting in cancer therapy

### 2.4.1. Targeting cell surface markers and immunotherapy

Immunotherapy is a specific therapy for targeting CSCs using monoclonal antibodies . For instance, HAb18IgG ( Anti-antibody against CD147) enhances the pancreatic cancer stem cells' vulnerability to medications [70] . Here are some of the most important currently approved antibodies : bevacizumab (anti-VEGF-A) ,cetuzimab (anti-EGFR) ,ipilimumab (anti-CTLA-4), pembrolizumab (anti - PD-1) ,rituximab (anti-CD20) and trastuzumab (anti-HER2) [71]. Natural Killer cells (NKCs) and active T-lymphocytes tied to specific anti-HER2/CD3 antibodies are also involved in targeting stem cells in glioma , oral squamous cell carcinoma and HER-2 breast cancer cells, respectively [72,73]. In general, stem cell-related antigens like ALDH ،CD44 ،CD133 and HER2 are the main targets for immunotherapy [72].

### 2.4.2. Targeting cancer stem cells through miRNA

miRNAs are important regulators of gene expression and cancer stem behavior. So far several miRNAs have been reported to be effective in cancer therapy. For example ,increased expression of miR-185 through inhibiting the proliferation of prostate cancer stem cells and targeting the feedback loop miR-130b / TNF-α / NF-κB / VEGF-A could be effective in treating prostate cancer [74,75]. miR-451 and miR-328 also reduce drug resistance in colorectal cancer [8].

### 2.4.3. Targeting cancer stem cell microenvironment

Various components of tumor microenvironment like CAFs and TAMs which secrete factors for EMT induction could be targeted in order to eliminate metastasis and drug resistance. For instance, in breast cancer stem cells, Vismodegib could eliminate drug resistance by restraining the Hh pathway and CAFs reduction. The number of CSCs in colon cancer has also been reduced after using Celecobix (COX-2 inhibitor) [4] . Despite the good results of targeting tumor microenvironment, due to the dynamic and heterogeneous nature of cancer stem cells, targeting only one part of the microenvironment is not sufficient and effective treatment requires the use of a

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

combination of conventional and specific microenvironment targeting elements [76].

### 2.4.4. Effects of pH and temperature on targeting cancer therapy

Acidic pH and increased local temperature are the characteristics of the tumor microenvironment. This property can be used to transport drugs by highly sensitive carriers. Different liposomes, micelles, polymers has been designed for nanodrug delivery and controlled release based on acidic pH of tumor niche [7,62].

### 2.4.5. Targeting the angiogenesis in tumor

Since the VEGFs are involved in blood vessel formation and tumor growth, targeting VEGF / VEGFR by antibodies and inhibitors such as bevacizumab, pazopanib , sorafenib and sunitinib leads to destruction of cancer stem cell niche [7]. In colorectal cancer , decreased expression of PROX1 (transcription factor prospero homeobox 1) and inhibition of VEGF- A and ANGPT-2 (Angiopoietin-2) by CD40 agonist antibodies could destroy tumor fibrosis, inhibit angiogenesis and eventually kill cancer cells by T-lymphocytes [55]. Peptide ALM201 in ovarian cancer disrupts angiogenesis and reduces the CSC population in areas where blood vessels are abundant and the IL-6 level is Low [77]. In lung cancer, Bevacizumab (anti- VEGF-A antibody) and Apa ( VEGFR-2 inhibitor ) were reported to reduce glucose metabolism in tumor tissue and kill non-small lung tumor cells by inhibiting angiogenesis [78].

### 2.4.6. Inhibition of autophagy

These strategies are mainly focused on reducing activity of mTOR (Mammalian Target Of Rapamycin) [50]. In ER+ breast cancer , inhibition of autophagy in resistant tumors enhances the sensitivity to tamoxifen or in prostate cancer, inhibition of autophagy leads to overcoming the Enzalutamide resistance [59]. Salinomycin (SAL) also could be a suitable drug to eliminate therapeutic resistance by inhibiting autophagy in the case of acute acidosis of the tumor environment [49].

### 2.4.7. Application of nano-drugs in chemotherapy

The use of nanoparticles smaller than 100 nm in dimension and having variable size, shape and dispersion to target cancer stem cells has made it possible for nanotechnology to overcome the limitations of common cancer treatments such as drug low solubility and side effects [62,79]. One example in this field is TiO2 (Titanium dioxide) nanotubes coated with hydroxyapatite and silver which can eliminate breast cancer cells MCF-7 through inducing apoptosis [44,80].

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

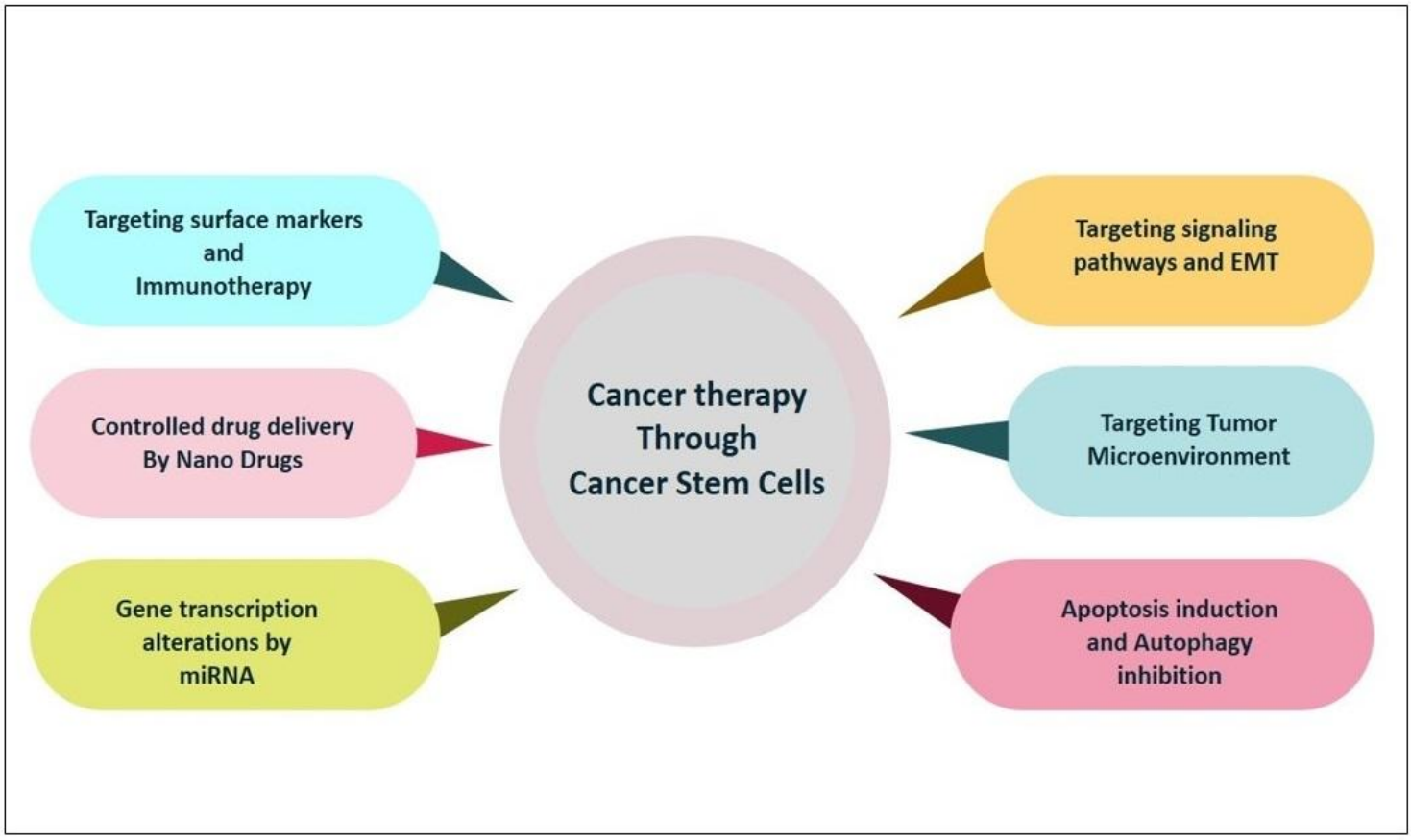


**Figure 3**. Different strategies to target and remove cancer stem cells

## 3.Results

For decades, cancer stem cells have been identified as the main cause of tumor recurrence, metastasis and resistance to conventional cancer therapies, through a variety of mechanisms including surface marker expression, epigenetic alterations and EMT .Today, the main goal of cancer research is to find the right way to target these cells without damaging healthy tissues and to minimize the side effects of chemotherapy and radiotherapy . Using nanoparticles and the combination of several methods, the research conducted so far has attempted to target cell surface markers, tumor microenvironment, important signaling pathways and miRNAs. Undoubtedly, immunotherapy and nanodrugs, which use specific antibodies and drug-carrying nanoparticles respectively, are new effective strategies in cancer therapy .A good number of researchers have emphasized the need for combination therapies; for example, Ragusa et al demonstrated that after targeting the CD40 signaling pathway and tumor blood vessels in colon cancer, activation of CD40 showed limited anti-tumor effects alone, but only if combined with inhibition of angiogenic factors VEGF-A, it could well stimulate the anti-tumor response in the immune system . Reviewing such studies highlights the significance of targeting various aspects of cancer stem cells and helps us stay hopeful of finding an effective way of cancer treatment.

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

## 4.Conclusion

Despite tremendous efforts made to prevent and treat cancer, the disease is still deadly around the world . This indicates the need for more clinical trials and research to find the best strategy for cancer therapy, particularly through cancer stem cell targeting.

## Acknowledgments

The authors express their appreciation and gratitude to all those who have helped to improve the quality of this article through valuable suggestions.

## Conflict of interest

The authors have no conflict of interest.

## References

1. Phi LTH, Sari IN, Yang Y-G, Lee S-H, Jun N, Kim KS, et al. Cancer stem cells (CSCs) in drug resistance and their therapeutic implications in cancer treatment. Stem cells international. 2018; 2018:5416923

2.Ayob AZ , Ramasamy TS.Cancer stem cells as key drivers of tumour progression.Journal of Biomedical science. 2018; 25(20).

3. Papaccio F, Paino F , Regad T, Papaccio G, Desiderio V , Tirino V.Concise Review: Cancer Cells, Cancer Stem Cells,and Mesenchymal Stem Cells: Influence in Cancer Development.Stem Cells Translational Medicine. 2017; 6:2115–2125.

4. Prieto-Vila M, Takahashi R-U, Usuba W, Kohama I , Ochiya T.Drug Resistance Driven by Cancer Stem Cells and Their Niche. International Journal of Molecular Sciences. 2017;18(2574).

5. Kuşoğlu A, Biray Avcı Ç. Cancer stem cells: A brief review of the current status.Gene . 2019; 681:80-85.

6. Iseghohi SO,.Cancer stem cells may contribute to the difficulty in treating cancer.Genes & Diseases. 2016; 3: 7-10.

7. Yadav A , Desai N. Cancer Stem Cells: Acquisition, Characteristics, Therapeutic Implications, Targeting Strategies and Future Prospects.Stem Cell Reviews and Reports. 2019; 15(3):331-355.

8. Prasad S, Ramachandran S, Gupta N, Kaushik I , Srivastava S.K.Cancer cells stemness: A doorstep to targeted therapy.BBA-Molecular Basis of Disease. 2020 ;1866(4):165424.

9.Tarhriz V, Bandehpour M, Dastmalchi S, Ouladsahebmadarek E, Zarredar H, Eyvazi S. Overview of CD24 as a new molecular marker in ovarian cancer.Journal of Cellular Physiology. 2018;1-9.

10. Sun JH, Luo Q, Liu LL , Song GB.Liver cancer stem cell markers: Progression and therapeutic implications.World Journal of Gastroenterology. 2016; 22(13):3547-3557.

11.Zakaria N, Abdul Satar N, Abu Halim NH, Ngalim SH, Yusoff NM, Lin J et al.Targeting Lung Cancer Stem Cells:Research and Clinical Impacts.Frontiers in Oncology. 2017; 7(80): 1-10.

12. Caras I. Two cancer stem cell-targeted therapies in clinical trials as viewed from the standpoint of the cancer stem cell model.Stem Cells Translational Medicine. 2020; 1-6.

13.Kumar A , Bhanja A , Bhattacharyya J , Jaganathan BG.Multiple roles of CD90 in cancer.Tumor Biol. 2016; 37(9):11611-11622.

14.J. Agorku D, Langhammer A , Heider U , Wild S, Bosio A , Hardt O.CD49b, CD87, and CD95 Are Markers for Activated Cancer-Associated Fibroblasts Whereas CD39 Marks Quiescent Normal Fibroblasts in Murine Tumor Models.Frontiers in Oncology. 2019; 9(716): 1-13.

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

15.von Lersner A, Lenny Droesen L, Zijlstra A. Modulation of cell adhesion and migration through regulation of the immunoglobulin superfamily member ALCAM/CD166.Clin Exp Metastasis. 2019;36(2):87-95.

16.Lertkiatmongkola P, Liaoa D, Meib H, Hub Y, J. Newmana P.Endothelial functions of PECAM-1 (CD31).Curr. Opin .Hematol. 2016; 23(3):253-259.

17.Patel J, Donovan P, Khosrotehrania K.Concise Review: Functional Definition of Endothelial Progenitor Cells: A Molecular Perspective.StemCells Translational Medicine. 2016;5:1302-1306.

18.M. Foster B , Zaidi D , R. Young T , E. Mobley M , A. Kerr B.CD117/c-kit in Cancer Stem Cell-Mediated Progression and Therapeutic Resistance.Biomedicines. 2018; 6(1):31

19. Harris KS , A. Kerr B.Prostate Cancer Stem Cell Markers Drive Progression,Therapeutic Resistance, and Bone Metastasis.Stem Cells International. 2017; 2017:8629234..

20.Corro C , Moch H. Biomarker discovery for renal cancer stem cells. The Journal of Pathology: Clinical Research. 2018;4:3-18.

21.Singh N, Xu H, Thiemann R, A. DeSantis K, Larsen M, E. LaFlamme S.Alpha 6 integrins promote cytokinesis by regulating the expression of RSK2 and MKLP1.bioRxiv. 2019.

22.Abderrazak A, El Azreq MA, Naci D, R. Fortin P , Aoudjit F. Alpha2beta1 Integrin (VLA-2) Protects Activated Human Effector T Cells From Methotrexate-Induced Apoptosis.Frontiers in Immunology. 2018; 9(2269): 1-12.

23.Kircher M, Herhaus P, Schottelius M , K. Buck A , A. Werner R, Wester HJ et al.CXCR4-directed theranostics in oncology and inflammation.Annals of Nuclear Medicine. 2018; 32: 503-511.

24. Basati G, Khaksarian M, Abbaszadeh S, Esmaeil Lashgarian H, Marzban A.Cancer stem cells and nanotechnological approaches for eradication.Stem Cell Investigation. 2019; 6 (38).

25. Natale B, Schweitzer C, Hughes M, A. Globisch M, Kotadia R, Tremblay E et al.Sca-1 identifies a trophoblast population with multipotent potential in the mid-gestation mouse placenta.scientific Reports. 2017;7(5575).

26.Komal Qureshi-Baig K, Ullmann P, Haan S , Letellier E.Tumor-Initiating Cells: a critical review of isolation approaches and new challenges in targeting strategies. Molecular Cancer. 2017; 16(40).

27.L. Wuebben E, Rizzino A.The dark side of SOX2: cancer - a comprehensive overview. Oncotarget. 2017; 8(27): 44917-44943.

28.Sin WC, Lim CL.Breast cancer stem cells—from origins to targeted therapy.Stem Cell Investigation. 2017; 4(96).

29.Hao L, Zhao Y, Wang Z, Yin H, Zhang X, He T et al. Expression and clinical significance of SALL4 and b-catenin in colorectal cancer.J Mol Hist. 2016.

30.Shi G, Jin Y. Role of Oct4 in maintaining and regaining stem cell pluripotency.Stem Cell Research & Therapy. 2010; 1(39).

31. Desai A , Yan Y, L. Gerson S.Concise Reviews: Cancer Stem Cell Targeted Therapies: Toward Clinical Success. Stem Cells Translational Medicine. 2019; 8:75-81.

32.Kapoor P, J. Horsey A, H. Cox M , D. Kerr I. ABCG2: does resolving its structure elucidate the mechanism?. Biochemical Society Tranactions. 2018; 46:1485-1494.

33- Muinao T, Deka Boruah HP, Pal M.Diagnostic and Prognostic Biomarkers in ovarian cancer and the potential roles of cancer stem cells.Experimental Cell Research. 2018; 362:1-10.

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

34.Zhang B. CD73 promotes tumor growth and metastasis . OncoImmunology. 2012; 1(1): 67-70.

35. Ahmed M, Chaudhari K, Babaei-Jadidi R, V. Dekker L , Nateri A.S.Concise Review: Emerging Drugs Targeting Epithelial Cancer Stem-Like Cells.Stem Cells . 2017; 35:839–850.

36.Ashrafizadeh M, Hushmandi K, Hashemi M, Akbari M.E, Kubatka P, Raei M et al. Role of microRNA/Epithelial-to-Mesenchymal Transition Axis in the metastasis of Bladder Cancer. Biomolecules. 2020;10(1159):1-26.

37.Song K.A, Faber A.C. Epithelial-to-mesenchymal transition and drug resistance:transitioning away from death. Journal of Thoracic Disease. 2019; 11(6): E82-E85.

38.Guo Q, Grimmig T, Gonzalez G, Giobbie-Hurder A, Berg G, Carr N et al. ATP-binding cassette member B5 (ABCB5) promotes tumor cell invasiveness in human colorectal cancer.J. Biol. Chem. 2018; 293(28):11166–11178.

39.J. Yoshida G, Saya H.Therapeutic strategies targeting cancer stem cells.Cancer Science. 2016; 107:5-11.

40.Roscigno G, Cirella A, Affinito A, Quintavalle C, Scognamiglio I, Palma F et al.miR-216a Acts as a Negative Regulator of Breast Cancer by Modulating Stemness Properties and Tumor Microenvironment. International Journal of Molecular Sciences. 2020; 21(2313).

41.Vander Linden C, Corbet C.Therapeutic Targeting of Cancer Stem Cells: Integrating and Exploiting the Acidic Niche. Frontiers in Oncology. 2019; 9(159): 1-12.

42.Garza Treviño EN , Delgado González P, I C, Salgado V, Martinez Garza A.Effects of pericytes and colon cancer stem cells in the tumor microenvironment. Cancer Cell International. 2019; 19(173).

43.Zhou D, Shao L, R. Spitz D. Reactive Oxygen Species in Normal and Tumor Stem Cells. Adv Cancer Research. 2014;122: 1-67.

44.Ghahremani Farasfaji R, Bikhof Torbati M, Tafvizi F, Shaabanzadeh M. Cytotoxic Effect of Titanium Dioxide-Hydroxyurea Nanocamposit on Hela Cancer Cell Line. Journal of Babol University of Medical Sciences. 2019; 21: 116-121. [Full text In Persian].

45.Hashemi Goradel N, Najafi M, Salehi E, Farhood B, Mortezaee K.Cyclooxygenase-2 in cancer: A review. Journal of Cellular Physiology. 2018; 1-17.

46.Zhang S, Zhang R, Xu R, Shang J, He H, Yang Q. MicroRNA-574-5p in gastric cancer cells promotes angiogenesis by targeting protein tyrosine phosphatase non-receptor type 3 (PTPN3).Gene. 2020; 733: 1-9.

47.Masoumi-Dehghi S, Babashah S, Sadeghizadeh M. microRNA-141-3p-containing small extracellular vesicles derived from epithelial ovarian cancer cells promote endothelial cell angiogenesis through activating the JAK/STAT3 and NF-κB signaling pathways. Journal of Cell Communication and Signaling. 2020;14:233–44.

48.E. Drake L, Z. Springer M, P. Poole L, J. Kim C , F. Macleod K.Expanding perspectives on the significance of mitophagy in cancer.Sem. Cancer Biology. 2017; 47 :110-124.

49.Pellegrini P, Dyczynski M, Sbrana FV, Karlgren M, Buoncervello M, Hägg-Olofsson M et al. Tumor acidosis enhances cytotoxic effects and autophagy inhibition by salinomycin on cancer cell lines and cancer stem cells. Oncotarget. 2016; 7(24): 35703-35723.

50.Smith AG , Macleod KF.Autophagy, cancer stem cells and drug resistance. Journal of Pathology. 2019; 247:708-718.

51.Ferreira JA, Peixoto A, Neves M, Gaiteiro C, A. Reis C, G. Assaraf Y et al. Mechanisms of Cisplatin resistance and targeting of cancer stem cells: Adding glycosylation to the equation.Drug Resist Updat. 2016;24: 34-54.

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

52.Wang MC, Li CL, Cui J, Jiao M, Wu T, Jing L et al.BMI-1, a promising therapeutic target for human cancer. Oncology Letters. 2015; 10: 583-588.

53.Chen D, Wu M, Li Y, Chang I, Yuan Q, Ekimyan-Salvo M et al.Targeting BMI1+ Cancer Stem Cells Overcomes Chemoresistance and Inhibits Metastases in Squamous Cell Carcinoma.Cell Stem Cell. 2017; 20: 1-14.

54. Zhang GF, Li CX, Liu ZQ, Ma S, Chen HB. Cancer stem cell targets - a review. European Review for Medical and Pharmacological Sciences. 2016; 16:2045-2051.

55.Ragusa S, Prat-Luri B, Gonzalez-Loyola A, Nassiri S, Squadrito ML, Guichard A et al.Antiangiogenic immunotherapy suppresses desmoplastic and chemoresistant intestinal tumors in mice. The Journal of Clinical Investigation. 2020; 130(3): 1199-1216.

56.Yang L, Shi P, Zhao G, Xu J, Peng W, Zhang J et al.Targeting cancer stem cell pathways for cancer therapy. Signal Transduction and Targeted Therapy. 2020; 5(8).
57. Cazet, A.S., Hui, M.N., Elsworth, B.L., Wu S, Roden D, Chan CL et al. Targeting stromal remodeling and cancer stem cell plasticity overcomes chemoresistance in triple negative breast cancer. Nature Communications. 2018; 9(2897): 1-18.

58.Green R, Howell M, Khalil R, Nair R, Yan J, Foran E et al. Actinomycin D and Telmisartan Combination Targets Lung Cancer Stem Cells Through the Wnt/Beta Catenin Pathway. Scientific Reports. 2019; 9(18177): 1-13.

59.Nguyen HG, Yang JC, Kung HJ, Shi XB, Tilki D, Jr PNL et al.Targeting autophagy overcomes Enzalutamide resistance in castration-resistant prostate cancer cells and improves therapeutic response in a xenograft model. Oncogene. 2014; 33: 4521-4530.

60.Chang JC. Cancer stem cells: role in tumor growth, recurrence, metastasis, and treatment resistance. Medicine.2016; 95(S1): S20–25.

61.Pardoll D. The blockade of immune checkpoints in cancer immunotherapy. Cancer. 2012; 12:252-264.

62.Nankali E, Shaabanzadeh M , Bikhof Torbat M. Fluorescent tamoxifen-encapsulated nanocapsules functionalized with folic acid for enhanced drug delivery toward breast cancer cell line MCF-7 and cancer cell imaging. Naunyn-Schmiedeberg's Archives of Pharmacology. 2020; 393(7):1211-1219

63.Papaliagkas V, Anogianaki A, Anogianakis G, Ilonidis G. The proteins and the mechanisms of apoptosis:A mini-review of the fundamentals. HIPPOKRATIA. 2007; 11(3): 108-113.

64.Busca A, Saxena M, Kryworuchko M, Kumar A. Anti-Apoptotic Genes in the Survival of Monocytic Cells During Infection. Current Genomics. 2009;10(5): 306-317.

65.Mojibi P, Tafvizi F, Bikhof Torbati M. Cell-bound Exopolysaccharide Extract from Indigenous Probiotic Bacteria Induce Apoptosis in HT–29 cell-line. Iranian Journal of Pathology. 2019; 14(1): 41-51.

66.Khakrizi E, Bikhof Torbati M, Shaabanzadeh M. The Study of Anticancer Effect of Magnetic Chitosan-Hydroxyurea Nanodrug on HeLa Cell line: A Laboratory Study. Journal of Rafsanjan University of Medical Sciences. 2018; 17(8): 715-30. [Full text in Persian].

67.Sun H.R, Wang S, Yan S.C, Zhang Y, Nelson P.J, Jia H.L, Qin L.X, Dong Q.Z. Therapeutic Strategies Targeting Cancer Stem Cells and Their Microenvironment. Frontiers in Oncology. 2019; 9(1104): 1-14.

68.Chen W, Dong J, Haiech J, Kilhoffer MC, Zeniou M. Cancer Stem Cell Quiescence and Plasticity as Major Challenges in Cancer Therapy. Stem Cells International.2016; 18:1-16.

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

69.Oei A.L, Vriend L.E.M, Krawczyk P.M, Horsman M.R, Franken N.A.P , Crezee J. Targeting therapy-resistant cancer stem cells by hyperthermia. International Journal of Hyperthermia. 2017; 33(4):419-427.

70.Fan X, He D, Sheng CB, Wang B, Wang LJ, Wu XQ et al. Therapeutic anti-CD147 antibody sensitizes cells to chemoradiotherapy via targeting pancreatic cancer stem cells. Am. J .Transl. Res. 2019; 11(6):3543-3554.

71.Kwiatkowska-Borowczyk E, Gąbka-Buszek A, Jankowski J, Mackiewicz A.Immunotargeting of cancer stem cells. Contemporary Oncology. 2015; 19(1A):A52-A59.

72.Pan Q, Li Q, Liu S, Ning N, Zhang X, Xu Y et al. Concise Review: Targeting Cancer Stem Cells Using Immunologic Approaches. STEM CELLS. 2015; 33:2085-2092.

73.Carnero A , Garcia-Mayea Y , Mir C , Lorente J , Rubio IT , Lleonart ME. Anti-Tumor Treatment, The cancer stem-cell signaling network and resistance to therapy. Cancer Treatment Reviews. 2016; 49: 25-36.

74.Li Y, Zhong W, Zhu M, Li M, Yang Z.miR-185 inhibits prostate cancer angiogenesis induced by the nodal/ALK4 pathway. BMC Urology. 2020; 20(49).

75.Mu HQ, He YH, Wang SB, Yang S, Wang YJ, Nan CJ et al.MiR-130b/TNF-α/NF-κB/VEGFA loop inhibits prostate cancer angiogenesis. Clinical and Translational Oncology. 2019; 1: 111-121.

76.Pützer B , Solanki M, Herchenröder O.Advances in cancer stem cell targeting: How to strike the evil at its root. Advanced Drug Delivery Reviews. 2017; 120:89-107.

77. Annett S, Moore G, Short A, Marsha A, McCrudden C, Yakkundi A et al. FKBPL-based peptide, ALM201, targets angiogenesis and cancer stem cells in ovarian cancer. British Journal of Cancer. 2020; 126: 361.

78. Wang M, Zeng Q, Li Y, Imani S, Xie D, Li Y et al. Bevacizumab combined with apatinib enhances antitumor and anti-angiogenesis effects in a lung cancer model in vitro and in vivo. Journal of Drug Targeting. 2020; 28(9): 961-969.

79.Sohrabi M, Amirnasr M, Meghdadi S, Lutz M, Bikhof Torbati M, Farrokhpour H. A highly selective fluorescence turn-on chemosensor for Zn 2+, and its application in live cell imaging and as a colorimetric sensor for Co2+: Experimental and TD-DFT calculations. New.J.Chem. 2018; 42: 12595-12606.

80. Rahimnejad S, Bikhof Torbati M. Synthesis of Hydroxyapatite/Ag/TiO2 Nanotubes and Evaluation of Their Anticancer Activity on Breast Cancer Cell Line MCF-7.Journal of Chemical Health Risks. 2016; 6(3): 1-10.

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,

# Table:

| Tumor Type | Markers of cancer stem cells | References |
|---|---|---|
| Pancreatic Cancer | CD44,CD24,CD133,ALDH,ESA,ABCG2,EpCAM | [1,8] |
| Hepatic Cancer | CD44,CD133,EpCAM,CD13,CD90,K19,SALL4,ICAM-1,CD49f,ALDH,ESA,CD24,ABCG2 | [10,8, 13, 29,14,1] |
| Lung Cancer | CD44,CD166,ALDH,CD133,ABCG2,CD87,CD90,Sca1CD45,PeCAMACD34 | [31, 15,25,8,32, 16,1,14,24,17] |
| Prostate Cancer | CD117,CD133,CD44,α6-Int,ALCAM,CD166,α2β1-Int,CXCR4,E-cad,ABCG2,Cyt.keratin-5,ALDH1,TG2,EZH2 | [23,19,21,22] |
| Ovarian Cancer | CD117,CD24,CD44,CD133,ALDH1,MyD88,CXCR4,SOX2,HSP,ABCG2,BCRP1,EpCAM | [8,33, 27] |
| Kidney Cancer | CD105,CD133,CD24,CD73,CXCR4,CD44,ALDH1 | [20, 34] |
| Breast Cancer | CD24,CD44,CD133,ALDH1,ESA,EpCAM,CD49,OCT4 | [24,1,5,35] |
| Brain Cancer | CD49,CD36,L1CAM,CD15,CD133,CD90,CD163,CD44,CX43 | [31,5,24] |
| Leukemia | CD123,CD34,CD44,CD19,CD47,TIM3,CD96,IL1RAP,CLL-1 | [31,24,1] |
| Colon Cancer | ESA,ALDH,EpCAM,CD166,CD24,CD44,CD133,CD29 | [1,5] |
| Gastric Cancer | CD24,CD44,CD133,CD90,CD71 | [1,24] |

**Table 1.** Markers of cancer stem cells

Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,