



CANCER STEM CELLS AND THERAPEUTIC RESISTANCE: BIOLOGICAL MECHANISMS AND EMERGING TREATMENT STRATEGIES

Arjun R. Patel^{1*}, William C. Zhang²

^{1*}*Department of Cancer Biology, Tata Memorial Centre, Mumbai, India. patel346@hotmail.com*

²*Department of Medical Sciences, University of Hong Kong, Hong Kong*

***Corresponding Author:** Arjun R. Patel, Arjun.patel346@hotmail.com

Received: **17/03/2026**, Revised: **05/07/2026**, Accepted: **10/08/2026**, Published: **25/08/2026**

ABSTRACT

Cancer stem cells (CSCs) are a unique subpopulation of tumour cells that possess self-renewal, differentiation, tumour initiating and adaptive properties that play a major role in the progression, therapeutic resistance and disease relapse. They survive to anticancer treatment due to various biological mechanisms, such as increased drug efflux, highly efficient DNA repair, resistance to apoptosis, cellular quiescence, metabolic reprogramming, epigenetic control, and adaptation to oxidative stress. In addition, major signalling pathways including Wnt/beta-catenin, Notch, Hedgehog, PI3K/AKT/mTOR, JAK/STAT and NF- κ B play a role in regulating CSC behaviour. Moreover, the tumour microenvironment supplies protection signals via hypoxia, stromal cells, immune cells, extracellular matrix, epithelial–mesenchymal transition and the exchange of extracellular vesicles. These mechanisms enable CSCs to be involved in resistance to chemotherapy, radiotherapy, targeted therapy, immunotherapy, and endocrine therapy. New therapeutic strategies thus focus on the eradication of CSCs through targeting of cell surface markers, the disruption of signalling pathways involved in stemness, modification of cellular metabolism, induction of differentiation, immune-mediated elimination, and application of drug delivery strategies using nanotechnology and combination therapies. Yet these successes have been complicated by CSC heterogeneity, phenotypic plasticity, and the variability and similarities of markers with normal stem cells. A better understanding of CSC biology and resistance mechanisms is crucial to designing more accurate and persistent therapeutic options to further lower recurrence and enhance long-term cancer control.

Keyword: Cancer stem cells; Therapeutic resistance; Tumour microenvironment; Signalling pathways; Targeted therapy

Introduction

Cancer is still one of the leading causes of morbidity and mortality worldwide, which is mainly due to its biological complexity, heterogeneity, metastatic capability and treatment resistance. While significant advances have been made in chemotherapy, radiotherapy, targeted therapy, immunotherapy and combination treatment strategies, many cancers have relapsed following an initial therapeutic response. A biological reason for failure of treatment is the existence of a special group of tumour cells called cancer stem cells (CSCs). These cells have stem cell characteristics, such as self-renewal, differentiation, long-term survival and the ability to initiate and sustain tumour growth. CSCs may also create various types of tumour cells and play a significant role in the intratumoural heterogeneity of the tumour, leading to the difficulty in complete tumour elimination with conventional therapeutic methods (Atashzar et al., 2020).

Cancer stem cells have become known as key initiators in determining tumour progression, metastasis, recurrence and initiation. They can retain their stemness as they generate differentiated cancer cells, so that the tumour continues to develop even if a significant fraction of the tumour mass has been killed. Molecular programs can also be activated or changed during cancer and disease progression that allow malignant cells to adapt to the environment and therapeutic stress. These characteristics create close links between stemness, tumour evolution, and the resistance against anticancer treatment (Huang et al., 2020). Therefore, therapies that shrink tumour mass but do not impact on CSC populations could only be clinically beneficial in the short term.

The mechanisms behind therapeutic resistance of CSCs are interwoven. CSCs may possess mechanisms such as increased drug efflux, efficient DNA damage repair, decreased apoptotic response, increased antioxidant defence, metabolic adaptability and cellular quiescence when compared to more differentiated cancer cells. These features can enable them to survive chemotherapy and radiotherapy that often has a greater effect on rapidly dividing tumour cells. Surviving CSCs can subsequently re-enter the cell cycle and re-generate the tumour, which may result in disease recurrence and the development of more resistant subpopulations. Thus, their role in tumour recurrence and drug resistance is a key obstacle to lasting control of cancer (Aramini et al., 2022).

CSCs also have molecular signalling networks and interactions with the tumour microenvironment that regulate their behaviour. These self-renewal, survival, cellular plasticity and treatment tolerance are driven by pathways including Wnt/ β -catenin, Notch, Hedgehog, PI3K/AKT/mTOR, and JAK/STAT. Additional factors in the CSC niche include hypoxia, stromal cells, immune cells, extracellular matrix components, and extracellular signalling factors that can further protect these cells from the damage caused by therapy. The enzymes responsible for these biological interactions have led to the development of strategies aimed at selectively disrupting CSC survival and stemness, while minimizing effects on normal stem cells (Haddadin & Sun, 2025; Zhang et al., 2023).

In the wake of increasing understanding of CSC biology, therapeutic research has thus moved towards targeting both bulk tumour cells and treatment-resistant stem-like cells. These strategies are potentially: targeting CSC-specific markers; interfering with stemness associated signalling pathways; modifying cellular metabolism; interfering with protective tumour niches; promoting differentiation; and combining CSC-directed treatments with conventional or immune-based therapies. These methods can lower the risk of tumour recurrence and enhance the long-term therapeutic outcomes. However, CSC heterogeneity, phenotypic plasticity, the absence of universally specific biomarkers, and the similarity of CSCs with normal stem cells continue to hinder the process of therapeutic development. Thus, a better understanding of the biology behind the resistance mediated by CSC is needed to bring novel strategies to better cancer therapy.

Objectives:

- To describe the major biological characteristics, molecular mechanisms, signalling pathways, and tumour microenvironmental factors associated with cancer stem cell-mediated therapeutic resistance.
- To examine the role of cancer stem cells in resistance to conventional and modern cancer treatments, including chemotherapy, radiotherapy, targeted therapy, immunotherapy, and endocrine therapy.
- To review emerging therapeutic strategies for targeting cancer stem cells and highlight current challenges and future directions for overcoming treatment resistance and cancer recurrence.

2. Biological Characteristics of Cancer Stem Cells

2.1 Self-Renewal and Differentiation Capacity

Characteristics of cancer stem cells include their capacity to self-renew and to produce a diverse range of tumour cells by differentiation. This property is important for a relatively small population of CSCs to sustain long-term tumour growth and to re-populate the tumour after therapeutic intervention. CSCs can maintain stem-like properties of cells, but also generate daughter cells with diverse phenotypic and functional properties, unlike differentiated cancer cells. These properties have been strongly correlated with tumour recurrence, persistence and resistance to treatment in ovarian cancer, highlighting the role of CSCs in disease progression (Alizadeh et al., 2025).

2.2 Tumour-Initiating Potential

One of the hallmarks of CSCs is their increased tumour initiation potential. These cells are able to withstand poor environments, create new tumours and sustain malignant growth for long periods of time. Their capacity to form tumour is correlated with their capacity to withstand therapeutic damage, and to remain viable when most tumour cells are removed. CSCs have been linked to resistance to treatment, maintenance of the malignant cell population and recurrence of the disease in colorectal carcinoma, highlighting their central role in the maintenance of malignant cell populations (Das et al., 2020).

2.3 Cellular Plasticity and Heterogeneity

Cancer stem cells are not necessarily a cellular population that is static. The genetic, epigenetic, environmental and therapeutic pressures can cause the tumour cells to acquire or lose stem-like properties. The plasticity is thought to help drive intratumoural heterogeneity and the ability of cancer cells to quickly adapt to disease evolution and therapeutic response. Targeted therapies can in themselves induce changes in cellular state to make non-stem tumour cells stem-like and help them to survive under selective pressure. This plasticity induced by the therapy is an important mechanism for the maintenance of resistant populations and adaptation to change in the tumour environment (Shi et al., 2023).

2.4 Cancer Stem Cell Biomarkers

A typical approach to identifying CSCs is based on molecular and/or cell-surface markers. Common markers studied are CD44, CD133, ALDH, EpCAM and other tumour specific proteins. However, there are differences in expression of markers between different types of cancer and during the evolution of the disease and/or treatment. Several CSC associated markers have been associated with stemness, tumour progression, therapeutic resistance and activation of signalling pathways in lung cancer. These markers can serve as possible targets for diagnosis and therapy, but because of the markers' variable expression, none of these can be regarded as a universal CSC identifier (Zheng et al., 2022).

2.5 Cancer Stem Cell Niches

Special microenvironmental areas, called stem cell niches, greatly affect the biological behaviour of CSCs. These niches provide signals that keep stemness, restrict the cells to environmental stresses and help cells survive during therapy. Stromal cells, extracellular matrix, cytokines, growth factors, hypoxia and immune cells could influence the maintenance and adaptation of CSCs. Leukemic stem cells, in haematological malignancies, such as AML, may reside in protected bone marrow niches, which may promote their survival and limit their response to therapy. Such crosstalk between cancer stem cells and their microenvironment has a significant role in the persistence of the disease and relapse (Stelmach & Trumpp, 2023). In general, the biology of CSCs is a solid groundwork to understand their involvement in therapeutic resistance. They can survive under therapeutic pressure because they have the ability to self-renew, initiate tumours, are plastic, exhibit marker variability, and can survive in a niche-dependent manner. Therefore, these attributes also account for the need to develop effective therapeutic strategies that directly address both the CSC population and the biological systems that sustain them. The major biological characteristics of cancer stem cells and their relevance to tumour progression are summarized in Table 1. The major biological characteristics and functional roles of cancer stem cells are illustrated in Figure 1.

Table 1. Major Biological Characteristics of Cancer Stem Cells and Their Relevance to Cancer Progression

Biological characteristic	Main biological function	Relevance to tumour behaviour	Contribution to therapeutic resistance	Reference
Self-renewal	Maintains the CSC population through repeated cell division	Supports long-term tumour maintenance and regeneration	Allows residual CSCs to repopulate tumours after treatment	Alizadeh et al. (2025)
Tumour-initiating capacity	Enables a small population of cells to generate new tumours	Promotes tumour establishment and recurrence	Surviving CSCs can regenerate malignant cell populations	Das et al. (2020)
Cellular plasticity	Allows transitions between stem-like and differentiated states	Increases intratumoural heterogeneity and adaptability	Enables tumour cells to acquire resistant phenotypes under treatment pressure	Shi et al. (2023)
CSC marker expression	Identifies populations with stem-like characteristics	Associated with tumour progression and aggressive behaviour	Certain marker-positive populations show reduced treatment sensitivity	Zheng et al. (2022)
Niche-dependent survival	CSCs interact with stromal and extracellular components	Supports maintenance and persistence of stem-like populations	Protective niches reduce treatment-induced damage	Stelmach and Trumpp (2023)

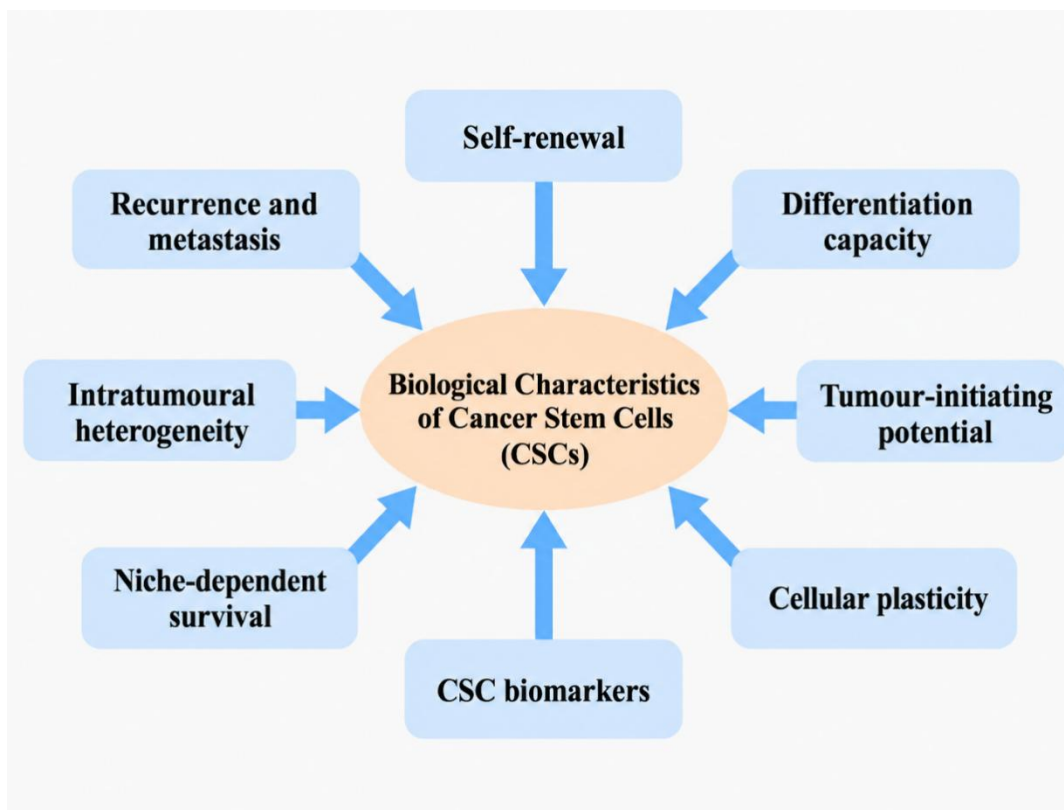


Figure 1. Biological Features and Functional Roles of Cancer Stem Cells

3. Molecular Mechanisms of Therapeutic Resistance

3.1 Drug Efflux and Reduced Intracellular Drug Accumulation

A keyway for cancer stem cells to evade anti-cancer drugs is the reduction of the therapeutic drugs inside the cell. The accumulation of toxic compounds by CSCs is frequently a result of elevated levels of ATP-binding cassette transporters that actively pump out molecules that may otherwise achieve effective levels inside the cell. In this way, this mechanism helps to reduce damage caused by the drug and enables resistant cell populations to survive the chemotherapy. Besides, changes in the transport of drugs across membranes, in the sequestration and in the detoxification pathways inside the cell can also decrease treatment sensitivity. These properties lead to the efflux of drugs and the resulting persistent disease and recurrence after therapy (Li et al., 2021).

3.2 Enhanced DNA Damage Repair

Cancer stem cells may exhibit very efficient DNA damage response and repair, allowing them to 'repair' the damage induced by chemotherapy and radiotherapy. Increased activation of DNA repair mechanisms will help to reduce the accumulation of lethal mutations and help to survive after exposure to stress produced from treatment. CSCs may also have more robust cell-cycle checkpoints that allow them more time to repair damaged DNA, before they resume the cell cycle. Such adaptive circuits are now known to

be relevant to therapeutic resistance and can be involved in the persistence of surviving tumour cells following a successful therapy (Tan et al., 2025).

3.3 Resistance to Apoptosis

Another important property of resistant CSCs is that they do not die programmed as much. These cells can survive a significant amount of therapeutic damage due to alterations in the balance between the pro-apoptotic and anti-apoptotic proteins. Apoptosis can be further inhibited by activation of survival signalling, inhibition of caspase mediated pathways and changes in mitochondrial function. These resistant phenotypes can also be achieved by non-genetic adaptations, where the cancer cells are able to survive the treatment without permanent DNA sequence changes. These reversible cellular states may thus enable the further evolution of the tumour when treated (Marine et al., 2020).

3.4 Quiescence, Dormancy, and Slow-Cycling Phenotypes

Multitude of anticancer drugs works better on rapidly dividing tumour cells, but CSCs can go into quiescent or dormant states where the division of cells is significantly slowed. As a result of this slow-cycling phenotype, they can evade treatments that rely on active DNA replication or mitosis. Dormant CSCs can also persist for a long time clinically undetectable to re-enter the cell cycle at a later stage and cause relapse and metastatic recurrence. Dormancy, stemness and treatment resistance are closely linked to one another and are important cellular states to understand in the context of long-term persistence of cancer (Francescangeli et al., 2023).

3.5 Epigenetic Regulation of Resistance

The epigenetic mechanisms are greatly involved in the identity of CSCs and adaptive responses to therapies. Without changing the DNA sequence, these genes can be modified with DNA methylation, chromatin remodelling and histone modifications, which can regulate their expression in stemness, apoptosis, DNA repair and drug sensitivity. These changes could help CSCs to quickly adapt to therapeutic stress and transition between sensitive and resistant states. Epigenetic regulation has therefore become a potential therapeutic target to overcome SCM and restore treatment responsiveness (Keyvani-Ghamsari et al., 2021). Histone modifications are especially relevant since they modify the accessibility of chromatin and the transcriptional activity of drug-resistant cancer cells. Changes in the way the genes are packaged (histone acetylation and methylation) can allow cells to resemble stem cells, evade the immune system and express genes which increase their survival. These modifications can result in the formation of resistant CSC phenotypes and help maintain the disease despite intensive treatment (Jin & Jeong, 2023). Thus, the modulation of epigenetic regulators is becoming a strategy for overcoming resistant states of cells and to enhance the efficacy of current cancer drugs (Song et al., 2025).

3.6 Metabolic Reprogramming and Oxidative Stress Adaptation

Cancer stem cells can also shift their metabolism to accommodate different energy requirements and thrive in an unfriendly tumour environment. CSCs can be glycolysis-dependent, oxidative-phosphorylation-dependent, fatty-acid-metabolism-dependent, or have a flexible metabolism, depending on the type of tumour and microenvironment. This metabolic adaptability helps them to withstand the deprivation of nutrients and therapeutic stress. It is also possible that CSCs can have potent antioxidant mechanisms that decrease the harmful effect of ROS that are produced during radiotherapy or because of certain chemotherapeutic drugs. Metabolic plasticity and oxidative stress are tightly linked and contribute to the maintenance of resistant stem-like tumour cells and enable further therapeutic intervention. The principal molecular mechanisms responsible for cancer stem cell-mediated therapeutic resistance are presented in Table 2. The molecular mechanisms contributing to therapeutic resistance in cancer stem cells are illustrated in Figure 2.

Table 2. Major Molecular Mechanisms Underlying Cancer Stem Cell-Mediated Therapeutic Resistance

Resistance mechanism	Biological basis	Effect on cancer stem cells	Therapeutic consequence	Reference
Drug efflux	Increased activity of membrane transport proteins	Reduces intracellular accumulation of anticancer agents	Decreased chemotherapy sensitivity	Li et al. (2021)
Enhanced DNA repair	Increased activation of DNA damage-response pathways	Allows recovery from treatment-induced DNA injury	Resistance to chemotherapy and radiotherapy	Tan et al. (2025)
Cellular dormancy	Entry into quiescent or slow-cycling states	Protects CSCs from therapies targeting rapidly dividing cells	Residual disease and later recurrence	Francescangeli et al. (2023)
Epigenetic regulation	DNA methylation and chromatin modifications alter gene expression	Promotes stemness and adaptive resistance	Reversible transition toward resistant cellular states	Keyvani-Ghamsari et al. (2021)
Histone modification	Changes in histone methylation and	Supports survival, stemness, and	Persistence of drug-resistant	Jin and Jeong (2023)

	acetylation	immune evasion	populations	
Non-genetic adaptation	Reversible transcriptional and phenotypic changes	Enables rapid adaptation without permanent mutations	Treatment escape and tumour evolution	Marine et al. (2020)
Epigenetic therapeutic escape	Altered activity of epigenetic regulators	Maintains resistant gene-expression patterns	Reduced response to anticancer treatment	Song et al. (2025)

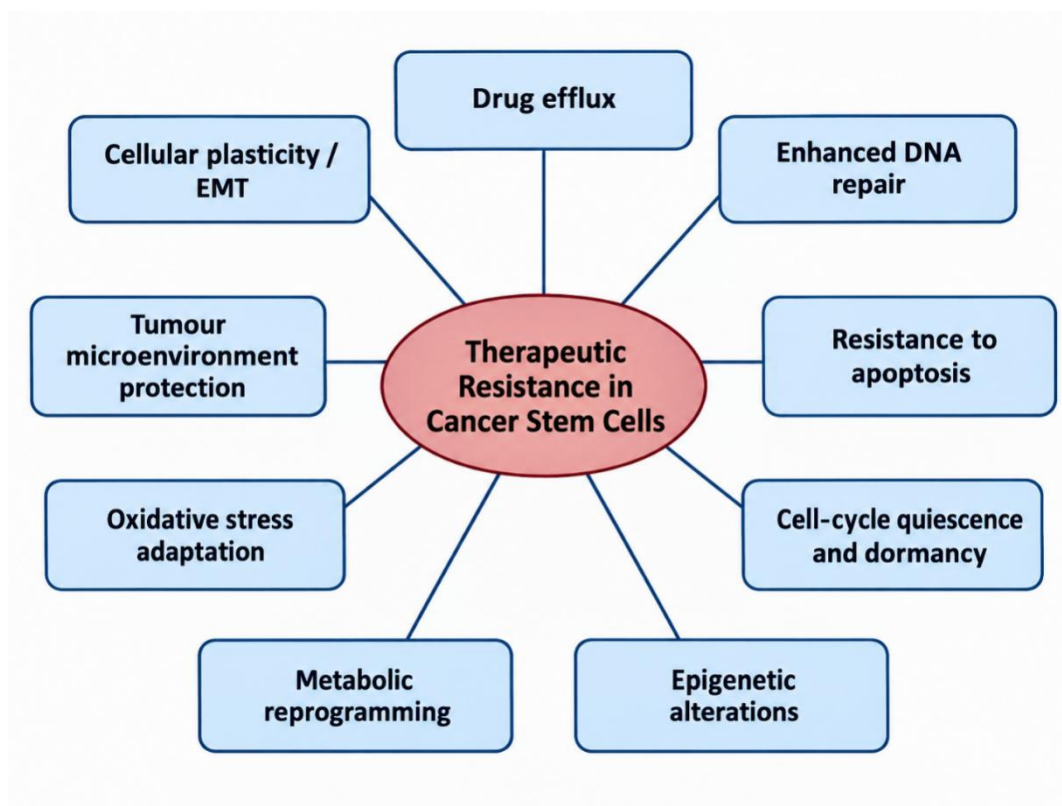


Figure 2. Molecular Mechanisms of Cancer Stem Cell-Mediated Therapeutic Resistance

4. Signalling Pathways Regulating Cancer Stemness and Resistance

4.1 Wnt/ β -Catenin Signalling

Wnt/ β -catenin is one of the key signalling pathways that maintains the properties of cancer stem cells. This pathway can be aberrantly activated leading to self-renewal, proliferation, tumour initiation, EMT and resistance to anticancer treatment. CSC populations can survive therapeutic pressures, due to the accumulation of β -catenin in the nuclei which activates genes linked to stemness and survival. The Wnt/ β -

catenin pathway is a key pathway that maintains stem-like phenotypes and for this reason, it has become a therapeutic target for the development of CSC-directed drugs (Manni & Min, 2022).

4.2 Notch Signalling

Notch signalling plays a role in cell-fate decision, cell differentiation, cell proliferation and cell survival in both normal and cancerous cells. In cancer stem cells, the abnormal activation of Notch can help cells not differentiate and make them more resistant to chemotherapy and radiotherapy. Notch mediated signalling can also converge with other oncogenic pathways, adding to the survival potential of resistant tumour cells. Thus, inhibition of the Notch pathway has been explored as a therapeutic approach to decrease the number of CSCs and increase the sensitivity to conventional treatment. But selective pathway targeting is an important challenge as Notch signaling also has important physiological functions in normal tissues (Yang et al., 2020).

4.3 Hedgehog Signalling

Another important pathway that regulates cancer stemness and tumour development is the Hedgehog pathway. Hedgehog signalling can promote self-renewal, survival, invasion and maintenance of undifferentiated cancer cell populations upon persistent activation. It can also play a role in therapeutic resistance as it helps cells become adapted to the treatment and helps CSCs to cope with the stress caused by treatment. Blocking the Hedgehog pathway components has been found to be effective in decreasing the number of stem-like tumour cells, especially in conjunction with conventional anti-cancer therapies. The pathway thus holds significant promise as a molecular target to overcome treatment resistance in CSCs (Zhou et al., 2021).

4.4 PI3K/AKT/mTOR Signalling

The PI3K/AKT/mTOR pathway is involved in various cellular functions such as protein synthesis, proliferation, growth, survival and metabolism. The abnormal activation of this pathway in cancer stem cells may increase their resistance to apoptotic pathways and allow their survival in hostile environment, such as starvation, hypoxia and therapy exposure. It can also activate stemness related transcription programs and metabolic adaptation and hence the CSCs can survive the treatment. Thus, molecular targeting of this pathway has become a focus to weaken the survival mechanisms of CSCs and enhance responses to other anticancer therapies (Chu et al., 2020).

4.5 JAK/STAT and NF- κ B Signalling

JAK/STAT and NF- κ B signalling pathways are tightly linked to inflammatory response, cell survival and proliferation and tumour progression. They can be persistently activated, leading to more genes encoding anti-apoptotic responses, stemness, invasion and resistance being expressed, which in turn can positively impact CSC maintenance. But also, cytokines and growth factors in the tumour microenvironment shape these pathways and provide a network of protection for resistant cancer cell populations. In highly

resistant tumours like triple-negative breast cancer (TNBC), the activation of several pathways related to resistance has been observed, which has prompted the development of pathway-targeted therapies (Ferrari et al., 2022).

4.6 Crosstalk Between Signalling Networks

Cancer stem cell behaviour is generally not regulated by a single signalling pathway. Rather, Wnt/ β -catenin, Notch, Hedgehog, PI3K/AKT/mTOR, JAK/STAT and NF- κ B often somehow interact with each other and with information from the tumour microenvironment. This crosstalk may result in redundant survival mechanisms and inhibition of one pathway may be complemented by activation of another. This pathway flexibility may be one factor in the temporary response to single-target therapies. Thus, understanding the interaction of these signalling networks is crucial to develop more effective combination therapies that will more efficiently target stemness and limit the chances of therapeutic escape. The major signalling pathways involved in cancer stemness and therapeutic resistance are summarized in Table 3. The major cellular and molecular factors associated with therapeutic resistance in cancer stem cells are illustrated in Figure 3.

Table 3. Signalling Pathways Associated with Cancer Stemness and Therapeutic Resistance

Signalling pathway	Major role in CSC biology	Contribution to resistance	Potential therapeutic approach	Reference
Wnt/ β -catenin	Promotes self-renewal, proliferation, and stemness	Maintains resistant stem-like populations	Wnt or β -catenin pathway inhibition	Manni and Min (2022)
Notch	Regulates cell fate and maintenance of undifferentiated states	Enhances survival and treatment tolerance	Notch receptor or ligand inhibition	Yang et al. (2020)
Hedgehog	Supports CSC maintenance and tumour initiation	Promotes survival during therapeutic stress	Hedgehog pathway inhibitors	Zhou et al. (2021)
PI3K/AKT/mTOR	Regulates metabolism, growth, and cell survival	Suppresses apoptosis and supports metabolic adaptation	PI3K, AKT, or mTOR inhibition	Chu et al. (2020)

JAK/STAT and related survival signalling	Controls inflammatory, proliferative, and survival responses	Supports resistant phenotypes and persistent tumour growth	Targeted inhibition of survival signalling	Ferrari et al. (2022)
--	--	--	--	-----------------------

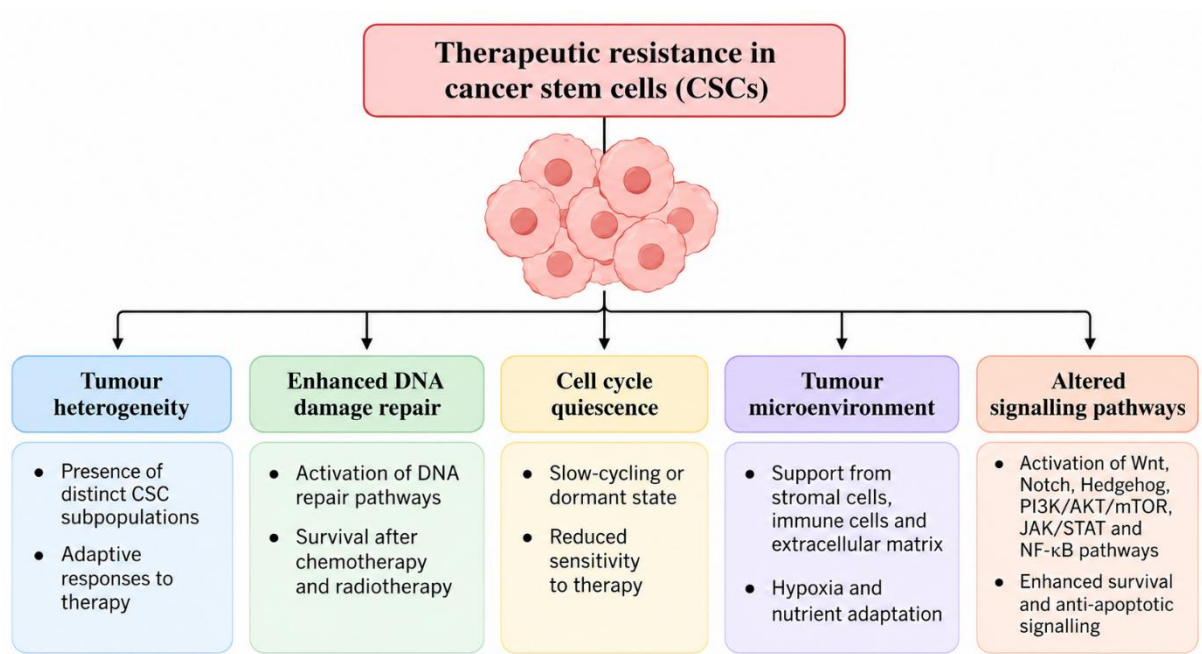


Figure 3. Signalling Networks Regulating Cancer Stemness and Resistance

5. Tumour Microenvironment and Cancer Stem Cell-Mediated Resistance

5.1 Hypoxia and the Cancer Stem Cell Niche

TME is a key contributor to the survival of cancer stem cells (CSCs) and development of therapeutic resistance. Hypoxic tumour zones trigger stress response pathways that promote metabolic switch, tumour stemness, vascularization and cell death resistance. Low oxygen levels can also impair the effectiveness of radiotherapy and affect the reaction of tumour cells to several anti-cancer drugs. This means that cells left behind in the 'safe haven' of protective niches are more likely to survive treatment than the rest of the tumour cells and may be responsible for tumour re-growth following therapy. The crosstalk of CSCs and the TME are now considered as a crucial aspect of drug resistance and persistence (Gao et al., 2023).

5.2 Cancer-Associated Fibroblasts and Stromal Support

CAFs are one of the most prominent cellular components of the tumour microenvironment and can affect CSCs maintenance by secreting cytokines, growth factors, extracellular matrix proteins, and other

signalling molecules. All these factors can facilitate self-renewal, survival, invasion and stress resistance to therapy. Stromal support can also change the physical and biochemical nature of the tumour environment, which can provide protection of CSCs from drug exposure. The interaction between cancer stem cells and stromal cells is bidirectional, promoting the progression of the tumour and its metastatic potential while also maintaining resistance to treatments (Li et al., 2023).

5.3 Epithelial–Mesenchymal Transition and Cellular Plasticity

EMT is tightly linked with the development of stem-like traits and resistance to therapy. In the process, some of the cell-cell adhesion properties are lost and the epithelial tumour cells become more motile and invasive. They may be accompanied by increased self-renewal, survival and resistance to apoptosis. EMT programs have been extensively associated with CSC phenotypes and decreased therapeutic sensitivity, suggesting that cell plasticity may promote the generation and establishment of drug-resistant tumour subpopulations in breast cancer (Gooding & Schiemann, 2020).

5.4 Immune Interactions and Immune Evasion

Cancer stem cells can alter interaction with immune cells, in a manner that renders them immune to destruction by immune cells. They can decrease the presentation of antigens, change the function of immune checkpoints, secrete immunosuppressive factors, or change their phenotypic characteristics to make them less detectable by immune cells. Additionally, some CSC populations can adopt non-malignant cellular states, which leads to decreased immune surveillance and resistance to immunotherapeutic methods. These mechanisms play a role in the chronic nature of cancer and can impact the efficacy of immune-based cancer therapies (Saw et al., 2024).

5.5 Extracellular Matrix and Metastatic Support

The extracellular matrix not only supports tumour cells but can also play an active role in regulating the behaviour of cancer stem cells. Alterations in matrix components, matrix stiffness and cell-matrix communication can affect the survival, migration, invasion and resistance to treatment of CSCs. Such interactions can facilitate metastatic spread and form protective niches at primary and metastatic tumour locations. The role of CSCs and the microenvironment they exist in is therefore crucial in the context of treatment resistance and metastatic spread (Kilmister et al., 2022).

5.6 Extracellular Vesicles and Intercellular Communication

EVs may also play a role in therapeutic resistance by allowing the transfer of proteins, lipids, mRNAs and microRNAs between the tumour cells and the surrounding stromal cells. This information can increase cancer stemness, activate survival pathways and propagate resistant phenotypes in the tumour microenvironment (Yang et al., 2022). Exosomes derived from Mesenchymal stem cells (MSC) could also participate in drug resistance, apoptosis, angiogenesis and immune regulation (Lin et al., 2022). Their biological functions have also sparked the interest of their use as a therapeutic target and delivery system

in cancer therapy (Shan et al., 2024). The key tumour microenvironmental factors that support cancer stem cell survival and treatment resistance are presented in Table 4.

Table 4. Tumour Microenvironmental Factors Promoting Cancer Stem Cell-Mediated Resistance

Microenvironmen tal factor	Effect on CSC biology	Mechanism promoting resistance	Clinical relevance	Reference
Hypoxic niche	Maintains CSC survival and stemness	Activates stress-response and adaptive pathways	Reduced sensitivity to chemotherapy and radiotherapy	Gao et al. (2023)
Epithelial–mesenchymal transition	Promotes plasticity, migration, and stem-like properties	Generates treatment-resistant phenotypes	Associated with recurrence and metastasis	Gooding and Schiemann (2020)
Stromal and niche interactions	Provide growth and survival signals	Protect CSCs from therapeutic stress	Supports tumour persistence	Li et al. (2023)
Extracellular matrix	Regulates adhesion, migration, and signalling	Provides physical and biochemical protection	Contributes to metastasis and treatment resistance	Kilmister et al. (2022)
Immune evasion	Reduces recognition of CSCs by immune cells	Suppresses immune-mediated tumour elimination	Limits immunotherapy effectiveness	Saw et al. (2024)
Extracellular vesicles	Transfer proteins and regulatory nucleic acids	Spreads resistant phenotypes between cells	Potential target and biomarker of resistance	Yang et al. (2022)
Mesenchymal stem cell-derived exosomes	Modify tumour-cell signalling	Regulate apoptosis, drug sensitivity, and survival	Potential therapeutic delivery system	Lin et al. (2022)

Mesenchymal stem cell-derived extracellular vesicles	Facilitate intercellular communication	Alter tumour responses to treatment	Potential translational therapeutic platform	Shan et al. (2024)
--	--	-------------------------------------	--	--------------------

6. Cancer Stem Cells in Resistance to Cancer Therapies

6.1 Chemotherapy Resistance

Cancer stem cells are responsible for significant chemotherapy resistance, including increased drug efflux, efficient DNA repair, resistance to apoptosis, metabolic adaptation and slow cycling. The ability of these cells to survive the cytotoxic treatment when most of the rapidly proliferating tumour cells are killed. The stem-like cells can then continue to grow and help the tumour to regrow. Recent findings suggest that chemoresistance is driven by a multitude of intertwined molecular mechanisms, highlighting the importance of therapies that not only address resistant cell subsets but also the pathways involved in their survival (Gu et al., 2025).

6.2 Radiotherapy Resistance

The main effect of radiotherapy is damage to the cells by injury to the DNA and production of reactive oxygen species. CSCs might be more resistant to these effects due to their ability to repair DNA damage, efficient antioxidant defence and activation of survival signals. Radiation may also be less effective against quiescent CSC. In glioblastoma, the presence of stem-like tumour cells that are involved in treatment resistance and disease recurrence has been appreciated, and these cells may be resistant to the complete eradication of these cells with conventional treatment alone (Alves et al., 2021).

6.3 Targeted Therapy Resistance

Targeted therapies are those which are developed to block a particular change or signal pathway that is necessary for the growth of the tumour cells. But CSCs can overcome such therapies by means of cellular plasticity, pathway redundancy, activation of alternative signaling pathway and phenotypic adaptation. These mechanisms may render resistant stem-like populations, despite early responses to therapy. In breast cancer stem-like cells, for instance, they can use more than one molecular pathway to keep alive and prevent their cells from being targeted by drugs, meaning that it may be necessary to target more than one pathway to achieve long-term control of the tumour (Saha & Lukong, 2022).

6.4 Immunotherapy Resistance

The impact of cancer stem cells on the outcome of immunotherapy could be mediated by changes in the presentation of antigens to the immune system, enhanced immunosuppressive signalling, and/or interactions with protective elements of the niche. Microenvironments associated with CSC can limit immune-cell functions and help in immune escape. These mechanisms are especially relevant to

treatments which rely on adequate recognition and elimination of the malignant cells mediated by the immune system. This close relationship with their niches has, therefore, become an important way in which CSCs evade contemporary immunotherapeutic approaches (Pan et al., 2025).

6.5 Endocrine and Other Therapeutic Resistance

CSC resistance may not only be to chemotherapy, radiotherapy, targeted and immunotherapy. In hormone-dependent cancers, stem-like tumour populations could lose their dependence on the normal hormonal signalling and start using other survival pathways, making them less responsive to endocrine therapy. At a more general level, the shift from traditional cancer therapies to more targeted, immune-based and combination therapies have helped to expand therapeutic options but have not eliminated the issue of adaptive resistance. However, the existence of treatment-resistant cellular subpopulations is still a major issue in various types of cancer therapies (Kaur et al., 2023). Altogether, CSC-mediated resistance impacts on almost all major types of cancer therapy. The ability to withstand therapeutic stress, switch cell states, utilize alternative signaling pathways, and re-grow tumour populations is a serious impediment for long-term therapeutic responses. To reduce the chances of recurrence, thus, therapeutic approaches should be able to eradicate both differentiated tumour cell populations and those of resistant CSC.

7. Emerging Treatment Strategies and Future Perspectives

7.1 Emerging Treatment Strategies

New therapeutic approaches are now being developed to target both cancer stem cells and the main population of tumour cells. The main strategies are targeting CSC associated surface markers, targeting stemness associated signalling pathways, disrupting metabolic adaptation, and targeting CSCs along with traditional therapies. These approaches could help to limit tumour regrowth by weakening the survival mechanisms that enable resistant stem-like cells to survive after treatment (Garg et al., 2024). Differentiation therapy, immune therapy and targeting the protective tumour niche are all other interesting strategies. The differentiation therapy is to promote the maturation of CSCs and increase their sensitivity to therapy, and the immune-based therapy is to enhance the recognition and elimination of resistant stem-like cells. Combined therapeutic approaches may be therefore a more effective means of preventing relapse by eradication of CSC populations (Mai et al., 2023). Similarly, in ovarian cancer, CSC-targeted strategies are based on marker targeting, signaling blocking and targeting the tumour microenvironment, reinforcing the need for multi-target strategies (Terraneo et al., 2020). Selective targeting could be further improved by nanotechnology-based drug delivery through improved drug stability, tumour accumulation, and delivery of combination drugs. But more in the clinic, will be required specificity, safety and reproducibility. The emerging therapeutic strategies for overcoming cancer stem cell-mediated resistance are summarized in Table 5.

Table 5. Emerging Strategies for Overcoming Cancer Stem Cell-Mediated Therapeutic Resistance

Therapeutic strategy	Main target or mechanism	Expected benefit	Major challenge	Reference
CSC surface-marker targeting	CD44, CD133, ALDH and related markers	Selective elimination of stem-like tumour cells	Marker of heterogeneity and expression in normal cells	Garg et al. (2024)
Stemness-pathway inhibition	Wnt, Notch, Hedgehog and related pathways	Reduces CSC self-renewal and survival	Compensatory activation of alternative pathways	Mai et al. (2023)
CSC-directed combination therapy	CSC pathways combined with conventional treatment	Targets both CSCs and differentiated tumour cells	Increased complexity and potential toxicity	Terraneo et al. (2020)
Precision CSC-targeted therapy	Molecular and single-cell characterization	Enables tumour-specific therapeutic selection	Intratumoural heterogeneity and dynamic cell states	Lee et al. (2025)
Adaptive treatment of acquired resistance	Longitudinal molecular monitoring and targeted combinations	Addresses evolving resistant populations	Requirement for reliable predictive biomarkers	Soragni et al. (2025)

7.2 Future Perspectives

Future research should aim at further increasing the specificity of CSC biomarkers, understanding tumour heterogeneity and the dynamic changes that happen during treatment. Single-cell sequencing, spatial profiling, multi-omics, and advanced tumour models can assist in identifying tumour-specific vulnerabilities to aid in more personalized therapies targeting CSCs (Lee et al., 2025). The early detection of acquired resistance and cellular adaptation to the treatment is another priority. Longitudinal molecular monitoring and biomarker guided therapy may be useful to tailor therapy as the tumour evolves. Combination therapies that address multiple resistance mechanisms may have the potential to result in more durable responses and less recurrence in the future (Soragni et al., 2025).

8. Conclusion

Cancer stem cells (CSCs) are a key biological mechanism contributing to tumour persistence, therapeutic resistance, metastasis and disease relapse. They have the capacity to self-renew, differentiate, remain quiescent, adapt metabolically, repair DNA damage, survive without apoptosis and interact with protective tumour niches, which enable them to outlast treatments that effectively eradicate a large percentage of the tumour. These properties render CSCs especially resistant to eradication and one reason why some cancers recur even after a good response to treatment. Maintenance of stemness and resistance is achieved through multiple signalling pathways such as Wnt/ β -catenin, Notch, Hedgehog, PI3K/AKT/mTOR, JAK/STAT and NF- κ B. In parallel, hypoxia, stromal cells, immune interactions, extracellular matrix components, cellular epithelial–mesenchymal transition, and extracellular vesicles-mediated communication further enhance CSC survival. These are resistant to chemotherapy, radiotherapy, targeted therapy, immunotherapy and endocrine therapy, making the need to develop therapy strategies that target CSCs and the tumour microenvironment. New approaches to address CSC-based resistance include marker-based targeting, signalling inhibition, differentiation therapy, metabolism targeting, immune system targeting, targeting with nanoparticles, and rational combination therapy. But heterogeneity, plasticity, biomarker variability and similarity of CSCs and normal stem cells are challenges. Advances in the future will rely on better molecular characterization, progress in experimental models and strategies for personalized targeting that can target dynamic resistant cell populations without compromising the function of normal tissues.

References

1. Alizadeh, H., Akbarabadi, P., Dadfar, A., Tareh, M. R., & Soltani, B. (2025). A comprehensive overview of ovarian cancer stem cells: correlation with high recurrence rate, underlying mechanisms, and therapeutic opportunities. *Molecular Cancer*, 24(1), 135.
2. Alves, A. L. V., Gomes, I. N., Carloni, A. C., Rosa, M. N., Da Silva, L. S., Evangelista, A. F., ... & Silva, V. A. O. (2021). Role of glioblastoma stem cells in cancer therapeutic resistance: a perspective on antineoplastic agents from natural sources and chemical derivatives. *Stem cell research & therapy*, 12(1), 206.
3. Aramini, B., Masciale, V., Grisendi, G., Bertolini, F., Maur, M., Guaitoli, G., ... & Haider, K. H. (2022). Dissecting tumor growth: the role of cancer stem cells in drug resistance and recurrence. *Cancers*, 14(4), 976.
4. Atashzar, M. R., Baharlou, R., Karami, J., Abdollahi, H., Rezaei, R., Pourramezan, F., & Zoljalali Moghaddam, S. H. (2020). Cancer stem cells: A review from origin to therapeutic implications. *Journal of cellular physiology*, 235(2), 790-803.
5. Chu, D. T., Nguyen, T. T., Tien, N. L. B., Tran, D. K., Jeong, J. H., Anh, P. G., ... & Dinh, T. C. (2020). Recent progress of stem cell therapy in cancer treatment: molecular mechanisms and potential applications. *Cells*, 9(3), 563.
6. Das, P. K., Islam, F., & Lam, A. K. (2020). The roles of cancer stem cells and therapy resistance in colorectal carcinoma. *Cells*, 9(6), 1392.
7. Ferrari, P., Scatena, C., Ghilli, M., Bargagna, I., Lorenzini, G., & Nicolini, A. (2022). Molecular mechanisms, biomarkers and emerging therapies for chemotherapy resistant TNBC. *International journal of molecular sciences*, 23(3), 1665.
8. Francescangeli, F., De Angelis, M. L., Rossi, R., Cuccu, A., Giuliani, A., De Maria, R., & Zeuner, A. (2023). Dormancy, stemness, and therapy resistance: interconnected players in cancer evolution.

- Cancer and Metastasis Reviews, 42(1), 197-215.
9. Gao, Q., Zhan, Y., Sun, L., & Zhu, W. (2023). Cancer stem cells and the tumor microenvironment in tumor drug resistance. *Stem Cell Reviews and Reports*, 19(7), 2141-2154.
 10. Garg, P., Malhotra, J., Kulkarni, P., Horne, D., Salgia, R., & Singhal, S. S. (2024). Emerging therapeutic strategies to overcome drug resistance in cancer cells. *Cancers*, 16(13), 2478.
 11. Gooding, A. J., & Schiemann, W. P. (2020). Epithelial–mesenchymal transition programs and cancer stem cell phenotypes: mediators of breast cancer therapy resistance. *Molecular Cancer Research*, 18(9), 1257-1270.
 12. Gu, Y., Yang, R., Zhang, Y., Guo, M., Takehiro, K., Zhan, M., ... & Wang, H. (2025). Molecular mechanisms and therapeutic strategies in overcoming chemotherapy resistance in cancer. *Molecular Biomedicine*, 6(1), 2.
 13. Haddadin, L., & Sun, X. (2025). Stem cells in cancer: from mechanisms to therapeutic strategies. *Cells*, 14(7), 538.
 14. Huang, T., Song, X., Xu, D., Tiek, D., Goenka, A., Wu, B., ... & Cheng, S. Y. (2020). Stem cell programs in cancer initiation, progression, and therapy resistance. *Theranostics*, 10(19), 8721.
 15. Jin, M. L., & Jeong, K. W. (2023). Histone modifications in drug-resistant cancers: From a cancer stem cell and immune evasion perspective. *Experimental & Molecular Medicine*, 55(7), 1333-1347.
 16. Kaur, R., Bhardwaj, A., & Gupta, S. (2023). Cancer treatment therapies: traditional to modern approaches to combat cancers. *Molecular biology reports*, 50(11), 9663-9676.
 17. Keyvani-Ghamsari, S., Khorsandi, K., Rasul, A., & Zaman, M. K. (2021). Current understanding of epigenetics mechanism as a novel target in reducing cancer stem cells resistance. *Clinical Epigenetics*, 13(1), 120.
 18. Kilmister, E. J., Koh, S. P., Weth, F. R., Gray, C., & Tan, S. T. (2022). Cancer metastasis and treatment resistance: mechanistic insights and therapeutic targeting of cancer stem cells and the tumor microenvironment. *Biomedicines*, 10(11), 2988.
 19. Lee, H., Kim, B., Park, J., Park, S., Yoo, G., Yum, S., ... & Youn, B. (2025). Cancer stem cells: landscape, challenges and emerging therapeutic innovations. *Signal transduction and targeted therapy*, 10(1), 248.
 20. Li, Y. R., Fang, Y., Lyu, Z., Zhu, Y., & Yang, L. (2023). Exploring the dynamic interplay between cancer stem cells and the tumor microenvironment: implications for novel therapeutic strategies. *Journal of translational medicine*, 21(1), 686.
 21. Li, Y., Wang, Z., Ajani, J. A., & Song, S. (2021). Drug resistance and Cancer stem cells. *Cell Communication and Signaling*, 19(1), 19.
 22. Lin, Z., Wu, Y., Xu, Y., Li, G., Li, Z., & Liu, T. (2022). Mesenchymal stem cell-derived exosomes in cancer therapy resistance: recent advances and therapeutic potential. *Molecular cancer*, 21(1), 179.
 23. Mai, Y., Su, J., Yang, C., Xia, C., & Fu, L. (2023). The strategies to cure cancer patients by eradicating cancer stem-like cells. *Molecular cancer*, 22(1), 171.
 24. Manni, W., & Min, W. (2022). Signaling pathways in the regulation of cancer stem cells and associated targeted therapy. *MedComm*, 3(4), e176.
 25. Marine, J. C., Dawson, S. J., & Dawson, M. A. (2020). Non-genetic mechanisms of therapeutic resistance in cancer. *Nature Reviews Cancer*, 20(12), 743-756.
 26. Pan, Y., Yuan, C., Zeng, C., Sun, C., Xia, L., Wang, G., ... & Ding, Z. Y. (2025). Cancer stem cells and niches: challenges in immunotherapy resistance. *Molecular cancer*, 24(1), 52.
 27. Saha, T., & Lukong, K. E. (2022). Breast cancer stem-like cells in drug resistance: a review of mechanisms and novel therapeutic strategies to overcome drug resistance. *Frontiers in oncology*, 12, 856974.
 28. Saw, P. E., Liu, Q., Wong, P. P., & Song, E. (2024). Cancer stem cell mimicry for immune evasion and therapeutic resistance. *Cell Stem Cell*, 31(8), 1101-1112.
 29. Shan, C., Liang, Y., Wang, K., & Li, P. (2024). Mesenchymal stem cell-derived extracellular vesicles in cancer therapy resistance: from biology to clinical opportunity. *International Journal of Biological Sciences*, 20(1), 347.
 30. Shi, Z. D., Pang, K., Wu, Z. X., Dong, Y., Hao, L., Qin, J. X., ... & Han, C. H. (2023). Tumor cell plasticity in targeted therapy-induced resistance: mechanisms and new strategies. *Signal Transduction and Targeted Therapy*, 8(1), 113.
 31. Song, J., Yang, P., Chen, C., Ding, W., Tillement, O., Bai, H., & Zhang, S. (2025). Targeting

- epigenetic regulators as a promising avenue to overcome cancer therapy resistance. *Signal transduction and targeted therapy*, 10(1), 219.
32. Soragni, A., Knudsen, E. S., O'Connor, T. N., Tognon, C. E., Tyner, J. W., Gini, B., ... & National Cancer Institute (NCI) Acquired Resistance to Therapy Network (ARTNet). (2025). Acquired resistance in cancer: towards targeted therapeutic strategies. *Nature Reviews Cancer*, 25(8), 613-633.
 33. Stelmach, P., & Trumpp, A. (2023). Leukemic stem cells and therapy resistance in acute myeloid leukemia. *Haematologica*, 108(2), 353.
 34. Tan, Y., Qin, S., Zhang, Z., Liu, Y., Zhou, L., Li, B., ... & Jing, J. (2025). Unraveling the underlying mechanisms of cancer stem cells in therapeutic resistance for optimizing treatment strategies. *MedComm-Oncology*, 4(1), e70009.
 35. Terraneo, N., Jacob, F., Dubrovskaya, A., & Grünberg, J. (2020). Novel therapeutic strategies for ovarian cancer stem cells. *Frontiers in oncology*, 10, 501598.
 36. Yang, L., Shi, P., Zhao, G., Xu, J., Peng, W., Zhang, J., ... & Cui, H. (2020). Targeting cancer stem cell pathways for cancer therapy. *Signal transduction and targeted therapy*, 5(1), 8.
 37. Yang, Q., Xu, J., Gu, J., Shi, H., Zhang, J., Zhang, J., ... & Zhang, X. (2022). Extracellular vesicles in cancer drug resistance: roles, mechanisms, and implications. *Advanced Science*, 9(34), 2201609.
 38. Zhang, S., Yang, R., Ouyang, Y., Shen, Y., Hu, L., & Xu, C. (2023). Cancer stem cells: a target for overcoming therapeutic resistance and relapse. *Cancer biology & medicine*, 20(12), 985-1020.
 39. Zheng, Y., Wang, L., Yin, L., Yao, Z., Tong, R., Xue, J., & Lu, Y. (2022). Lung cancer stem cell markers as therapeutic targets: an update on signaling pathways and therapies. *Frontiers in oncology*, 12, 873994.
 40. Zhou, H. M., Zhang, J. G., Zhang, X., & Li, Q. (2021). Targeting cancer stem cells for reversing therapy resistance: mechanism, signaling, and prospective agents. *Signal transduction and targeted therapy*, 6(1), 62.

This article is licensed under a [Creative Commons Attribution 4.0 International \(CC BY NC ND\)](https://creativecommons.org/licenses/by-nc-nd/4.0/) License; copyright remains with the author(s).