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REVIEW

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Unraveling the triad of hypoxia, cancer cell stemness, and drug resistance

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Abstract

In the domain of addressing cancer resistance, challenges such as limited effectiveness and treatment resistance remain persistent. Hypoxia is a key feature of solid tumors and is strongly associated with poor prognosis in cancer patients. Another significant portion of the development of acquired drug resistance is attributed to tumor stemness. Cancer stem cells (CSCs), a small tumor cell subset with self-renewal and proliferative abilities, are crucial for tumor initiation, metastasis, and intra-tumoral heterogeneity. Studies have shown a significant association between hypoxia and CSCs in the context of tumor resistance. Recent studies reveal a strong link between hypoxia and tumor stemness, which together promote tumor survival and progression during treatment. This review elucidates the interplay between hypoxia and CSCs, as well as their correlation with resistance to therapeutic drugs. Targeting pivotal genes associated with hypoxia and stemness holds promise for the development of novel therapeutics to combat tumor resistance.

Keywords Cancer, Hypoxia, Cancer stem cell, Drug resistance

Introduction

Each year, over 20 million people are diagnosed with cancer, resulting in around 10 million deaths, or roughly one-sixth of all global fatalities [1]. The limited effectiveness of current therapies against drug resistance is one of the main reasons for the high mortality rates associated with cancer [2]. Drug resistance can be attributed to the tumor microenvironment (TME) and the considerable intra-tumoral heterogeneity [3, 4].

Studies have shown that various TME components contributing to drug resistance development [5, 6]. Hypoxia, a common TME characteristic of solid tumors, arises because the rapid and unregulated growth of tumors restricts the supply of oxygen [7]. In response to hypoxic conditions, cancer cells adapt and transform into a more aggressive phenotype that is resistant to pharmaceutical interventions [8].

Cancer stem cells (CSCs), characterized by self-renewal, differentiation potential, and resistance to

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chemotherapy and radiotherapy, contribute significantly to tumor progression [9–12]. Furthermore, studies demonstrate that hypoxia further impacts CSC pluripotency, driving tumor progression, metastasis, and resistance to therapies [7]. However, current research has not definitively proven a causal relationship between hypoxia, pluripotency, and drug resistance, and there is a notable absence of clinical strategies addressing both hypoxia and drug resistance concurrently [13, 14].

This review elucidates the relationship between hypoxia and CSCs, underscoring their contribution to the development of resistance to cancer therapies. Furthermore, it explores the underlying mechanisms and identifies prospective therapeutic targets to guide future research initiatives.

The hypoxic TME enhances the stemness of cancer stem cells

Tumors have the ability to attract surrounding endogenous stromal cells [15], which play a role in facilitating extracellular matrix modification, angiogenesis, cellular movement, invasion, and resistance to drugs. Moreover, stromal cells generate a TME that can evade immune surveillance through the production and release of diverse chemokines, cytokines, and growth factors [16]. There are at least six distinct cellular origins for stromal cells associated with tumors, including fibroblasts, pericytes, mesenchymal stem cells (MSCs) from bone marrow, adipocytes, and endothelial and tumor cells post-EMT. Hypoxia, a key feature of the TME, arises from rapid cancer cell growth and heightened metabolic demands, requiring significant energy to sustain proliferation [17]. Tumor expansion can stimulate angiogenesis, but disorganized blood vessel formation creates spatial gaps exceeding the oxygen diffusion capacity, leading to localized hypoxia [18]. During hypoxia, significant changes occur in non-cancerous components, including increased activation and growth of stromal cells such as stellate cells and cancer-associated fibroblasts (CAFs), as well as an accumulation of stromal elements such as fibrin [19]. These modifications contribute to the morphological restructuring of cancer, including the compression of blood vessels, which may lead to impaired circulation and insufficient oxygen supply. This sequence of events can ultimately lead to thrombosis and tissue hypoxia, which plays a critical role in regulating cancer cell populations, particularly CSCs [7].

CSCs were first identified in 1997 and are characterized by two fundamental properties: self-renewal and pluripotency [20]. These characteristics are essential for understanding intra-tumoral heterogeneity within the CSC hypothesis, which is a key concept in the hierarchical model of tumor development [21]. CSCs are typically characterized by their robust proliferative capacity [22]. Cancer cell proliferation is strongly influenced by the activation of key signaling pathways, such as AKT, mTOR, and MAPK/ERK, which upregulate proteins that control the cell cycle [23]. Conversely, interventions aimed at inhibiting stemness tend to diminish the proliferative potential of these cells [24]. CSCs are also responsible for resistance to chemotherapy, radiotherapy, and immunotherapy [14]. The survival of CSCs enables the replenishment of tumor cell populations, ultimately contributing to cancer recurrence [9].

Hypoxia-inducible factors (HIFs) are responsible for regulating gene expression in response to reduced oxygen levels in both normal tissues and cancer cells. Their activation can facilitate the advancement of tumors through the modulation of cellular metabolism and the promotion of blood vessel formation [25]. HIFs are composed of oxygen-sensitive α-subunits and stable β-subunits, with the primary regulation of their activity being controlled by the stability of the α-subunits. Under normoxic conditions, HIF-α interacts with the von Hippel-Lindau (VHL) protein, triggering the activation of the ubiquitin ligase system and subsequent proteasomal degradation of HIF-α. Conversely, under hypoxic conditions, the inactivation of prolyl hydroxylase (PHD) inhibits the PHD-dependent binding of HIF-α to VHL, stabilizing HIF-α. This stabilized form then binds to HIF-β subunits to form heterodimers that regulate gene expression by binding to hypoxia response elements (HREs) on DNA [26]. The HIFs family comprises HIF-1, HIF-2, and HIF-3, which regulate various biological processes through their target genes, such as angiogenesis, erythropoiesis, metastasis through EMT, autophagy, and the modulation of metabolic pathways. These alterations are associated with the maintenance of tumor stemness.

Hypoxia promotes stemness by regulating glucose metabolism

Under low oxygen conditions, cancer cells, including CSCs, shift from oxygen-dependent mitochondrial oxidative phosphorylation (OXPHOS) to oxygen-independent glycolysis to maintain ATP production [27, 28]. Hypoxia primarily regulates glucose metabolism by influencing the expression of glucose transporters and glycolytic enzymes and suppressing the tricarboxylic acid (TCA) cycle pathway. The increase in glycolytic activity has been associated with the characteristics of tumor stemness.

In hypoxic conditions, the glucose transporter (GLUT) family members GLUT1 [29], GLUT3 [30] and GLUT5 [31] have increased expression levels, facilitating increased intracellular glucose transportation to fuel the energy demands of cancerous cells. HIF-1 directly interacts with HREs in the promoter regions of genes encoding glycolytic enzymes, increasing the expression of key enzymes such as M2 pyruvate kinase (PKM2) [32],

aldolase A [33], enolase (ENO) [33] and lactate dehydrogenase A [33]. NF-κB, FOXO4, and numerous non-coding RNAs are significant contributors to the modulation of glucose metabolism under hypoxic conditions [29, 34–39]. Hypoxia impedes OXPHOS by decreasing the influx of metabolites into the TCA cycle via the activation of pyruvate dehydrogenase kinase 1 (PDK1) in a HIF-1-dependent manner [40]. Additional pathways through which HIF-1 suppresses oxidative metabolism have been reported, such as the inhibition of fatty acid oxidation [41], the induction of selective autophagy in mitochondria [42], and the suppression of activity in electron transport chain (ETC) complex I [43].

Alterations in glucose metabolism under hypoxic conditions are associated with elevated levels of CSC markers and improved capacity for self-renewal [40, 44–46]. The precise mechanism by which alterations in glucose metabolism impact the maintenance of stemness remains uncertain. One hypothesis posits that CSCs suppress the generation of ROS within cells by enhancing the flow of glucose metabolism, thereby preserving REDOX balance and promoting cell viability. Reducing glucose uptake and glycolysis in primary glioblastoma stem cells (GSCs) elevates ROS levels, impairing proliferation and stemness, while ROS elimination reverses these effects [47]. In hepatocellular carcinoma, the accumulation of ROS is increased through the targeting of glutaminase 1, leading to a decrease in the stem cell-like properties of CSCs [48]. Various branches of glycolysis, such as the pentose phosphate pathway, serine pathway, and folic acid pathway, are interconnected with the intracellular antioxidant system [49, 50]. These pathways are selectively upregulated to varying extents in response to hypoxic conditions. In breast CSCs, HIF-1 promotes the expression of phosphoglycerate dehydrogenase (PHGDH) and the serine synthesis pathway, along with five enzymes in the folate cycle, supporting CSC proliferation and enrichment [51]. Glucose hexaphosphate, produced from glycogen breakdown, is processed through the pentose phosphate pathway, regulating ROS levels via the NADPH-glutathione system [44]. The reliance of CSCs on ROS exhibits variability across distinct cancer types [52]. In the case of liver CSCs, there is a reduction in mitochondrial ROS production facilitated by *NANOG* activity, which in turn promotes stemness [53]. Conversely, in aggressive triple-negative breast CSCs, elevated levels of ROS are sustained through the upregulation of mitochondrial biogenesis. This process is regulated by MYC and MCL1, which facilitate mammosphere formation by stabilizing HIF1α [54]. This challenges the theory that uses ROS to explain the link between hypoxic metabolism and stemness, though no superior alternative explanation exists at present. Also, there has been no comprehensive research conducted to substantiate this theory.

In summary, hypoxia influences tumor cell metabolism by upregulating glucose transporters, enhancing glycolytic enzymes, inhibiting the TCA cycle and fatty acid oxidation, suppressing ETC complex I activity, and inducing selective mitochondrial autophagy. However, the connection between hypoxia-induced metabolic alterations and tumor stemness has been explored primarily through correlation studies rather than direct mechanistic investigations. The reduction in intracellular ROS production may be the underlying mechanism. Inhibiting glycolysis is linked to increased ROS levels, and the upregulation of ROS scavenging systems has been observed in CSCs. Further research is needed to comprehensively elucidate the interplay among hypoxia, glucose metabolism, and stemness.

Hypoxia promotes stemness by regulating EMT

EMT is a phenomenon characterized by the reversible transformation of epithelial cells into mesenchymal cells. This process involves alterations in the expression of cell adhesion molecules and cytoskeletal components [55]. The suppression of epithelial markers, such as E-cadherin, and the increased expression of mesenchymal markers, such as vimentin and N-cadherin, represent common alterations in genetic expression associated with EMT [56, 57]. Hypoxia has been shown to facilitate the progression of EMT in cancer cells, leading to increased acquisition of mesenchymal and stem cell-like properties [58]. The primary regulatory mechanism governing EMT involves the suppression of the E-cadherin promoter by transcription factors [59]. The E-cadherin promoter in humans is characterized by the presence of three regulatory elements known as "e-box". Transcription factors associated with epithelial-mesenchymal transition (EMT-TFs), including SNAIL, SLUG, ZEB1, ZEB2, and TWIST, are capable of binding to the e-box elements, thereby suppressing the transcription of E-cadherin [60–63].

HIF-1 triggers EMT by increasing the expression of EMT-associated transcription factors or reducing the expression of inhibitory factors. This process involves the activation of EMT-related signaling pathways and the modulation of EMT-associated inflammatory cytokines. HIF-1 induces EMT by directly controlling the expression of E-cadherin, SNAIL, ZEB1, TWIST, and TCF3 [64, 65]. In breast cancer cells, hypoxia can lead to the degradation of the biological clock gene *Period2*, triggering the activation of EMT-related genes such as *TWIST1* and *SNAIL* [66]. HIF-1 may also regulate EMT through long non-coding RNAs (lncRNAs), microRNA [67–69], and calcium signaling pathways [70]. Multiple signaling pathways are involved in the EMT process, and hypoxia can activate NF-κB [71], Notch signaling [72], β-catenin signaling [73] and Hh signaling [74] to promote EMT. Tumor-associated macrophages (TAMs), the primary

pro-inflammatory cells within tumors, exhibit increased secretion of IL-1β in response to moderate hypoxia. This leads to the up-regulation of HIF-1α synthesis and EMT in hepatocellular carcinoma cells via cyclooxygenase-2 [75].

The process of EMT has the potential to confer self-renewal capabilities to cancer cells, leading to the transformation of non-CSCs into CSCs [76]. In breast cancer, elevated expression of *Twist*, *Snail*, or *FOXC2* is associated with increased CD44+/CD24- markers linked to breast CSCs and improved breast globule formation [77, 78]. Disseminated cancer cells demonstrate characteristics of a mesenchymal phenotype and possess properties akin to those of stem cells [79]. The connection between EMT and CSCs at the molecular level is unclear. One possible explanation is that EMT-induced changes in cancer cell secretory proteins establish autocrine signaling loops involving key pathways like TGF-β and Wnt-β-catenin, which are crucial for maintaining stem cell characteristics [80]. It has been proposed that transcription factors involved in regulating EMT may also influence the maintenance of stem cell properties. For example, ZEB1 has been shown to promote the splicing of the CD44 subtype (CD44s) in pancreatic cancer by suppressing the epithelial splicing regulator ESRP1, leading to elevated ZEB1 levels. This newly identified interaction between CD44s and ZEB1 impacts various aspects of cancer cell behavior, such as enhanced tumor sphere formation and increased metastatic potential [81]. Also in pancreatic cancer cells, the absence of ZEB1 impedes stemness and colonizing capabilities [82]. ZEB1 suppresses the activity of the miR-200 family, which strongly promotes epithelial differentiation. Additionally, its potential targets include stemness-associated factors such as SRY-box 2 (SOX2) and Klf4 [82]. In human colorectal cancer tissue, *Snail* plays a role in controlling the expression of IL-8 and stimulating the activity of CSCs [83]. These findings provide evidence of an intricate relationship between the stemness and metastatic properties of tumors. CSCs play a significant role in the EMT process, and the activation of EMT in tumor cells enhances their stem-like characteristics, invasiveness, and ability to metastasize.

In summary, hypoxia influences the regulation of EMT-TFs through various mechanisms including transcriptional control and the modulation of microRNA and lncRNA processing. While pathways like Notch, NF-κB, and Hh signaling pathways have not been definitively linked to EMT-TFs in this context, EMT-TFs are crucial in mediating the interplay among hypoxia, EMT, and stemness. These factors not only serve as significant transcriptional regulators of EMT but also function as modulators of stem cell-like properties.

Hypoxia promotes stemness by inducing tumor angiogenesis

When a solid tumor grows beyond a certain volume where diffusion can no longer adequately supply oxygen and nutrients to the cells, a deprived and hypoxic TME will develop [84]. Hypoxia has the potential to stimulate the reformation of blood vessels within the tumor in response to environmental conditions, thereby ensuring the continued provision of essential nutrients and oxygen.

HIFs are widely recognized as significant regulators of angiogenesis, a process closely linked to the preservation of tumor stemness [85]. HIF-1 induces the expression of a series of pro-angiogenic factors inside tumor cells. These factors include vascular endothelial growth factor (VEGF), placenta growth factor (PGF), angiopoietin-2 (ANGPT-2), chemokine C-X-C motif ligand-12 (CXCL-12), and stem cell factor (SCF) [86–90]. These factors are crucial for promoting tumor angiogenesis by interacting with receptors on the surfaces of endothelial cells, pericytes, and vascular smooth muscle cells to stimulate angiogenesis. In addition to regulating the secretion of factors that activate endothelial cells, HIF-1 also controls the intrinsic expression of numerous genes in hypoxic endothelial cells. A significant portion of these genes encode cell surface receptors that enable endothelial cells to react to angiogenic cytokines induced by hypoxia [89]. The expression of miR-23a is notably increased in exosomes derived from lung cancer cells exposed to hypoxic conditions. This upregulation leads to the direct suppression of proline hydroxylase 1 and 2 by miR-23a, resulting in the accumulation of HIF1α in endothelial cells [90]. Furthermore, research has demonstrated a strong correlation between EMT and angiogenesis. In particular, the process of epithelial-endothelial transformation (EET) in CSCs is notably enhanced in hypoxic environments [91]. Studies conducted in three-dimensional cell cultures have revealed that melanoma cells exhibiting angiogenic mimicry express the CD133 marker associated with CSCs. Notably, the suppression of this marker leads to a substantial decrease in the capacity of cells to form an angiogenic mimicry network [92].

Angiogenesis generates vascular niches to support and maintain the stemness of CSCs. The proximity of CSCs to the vascularized area underscores the importance of vascular niches in supporting CSC function [93–95]. A reduction in vascular endothelial cells has been shown to increase the self-renewal capacity of $CD133^{+}$ brain CSCs in vivo by suppressing the ERBB2 or VEGF signaling pathways. This depletion also leads to a decrease in the number of CSCs and effectively hinders the growth of xenograft tumors [93]. The unique metabolic conditions in the perivascular niche, marked by concentrated mTOR activity in glioblastoma, play a key role in shaping

the gene expression of GSCs and promoting GSC-specific traits [96]. Furthermore, endothelial cells increase the expression of genes associated with CSCs, including *Olig2*, *Bmi1*, and *Sox2* [95]. The Notch signaling pathway in GSCs can be activated by nitric oxide from endothelial cells via the NO/cGMP/PKG pathway, enhancing glioma stem cell traits and accelerating tumor progression in murine models [97].

In brief, hypoxia stimulates the formation of new blood vessels in the tumor area through its effects on both tumor cells and endothelial cells. When exposed to low oxygen levels, cancer cells trigger the production of angiogenic factors that interact with specific receptors on cell surfaces, thereby facilitating angiogenesis. Additionally, endothelial cells respond directly to hypoxia signals by upregulating the expression of diverse angiogenic genes. These hypoxia-induced signals contribute to the establishment of vascular niches within the tumor microenvironment, which support the maintenance of CSC stemness properties.

Hypoxia promotes autophagy and thus maintains CSC activity

Autophagy serves as a stress response mechanism that cancer cells utilize to endure nutrient scarcity or hypoxia during advanced stages of tumor development. The autophagy process is governed by over 40 autophagy-related genes (ATGs), whose proteins initiate the process upon receiving signals associated with autophagosome formation. Methylation of ULK, an oxygen-sensitive process, promotes the assembly of the initiation complex ULK-1-ATG13-FIP200, which is essential for autophagy induction in hypoxic environments [98]. Autophagy-associated proteins, including ATG2A, ATG5, ATG7, ATG9A, ATG14, and Beclin1, exhibit increased expression levels in response to hypoxic conditions, thereby facilitating the induction of autophagy in cancer cells [99–103]. Furthermore, Beclin1 has been identified as a crucial intermediary protein involved in the control of apoptosis and autophagy pathways within cancer cells. Beclin1 plays a pivotal role in determining the cellular response by interacting with proteins associated with autophagy or apoptosis. Under hypoxic conditions, tumor apoptosis is inhibited through the HIF-1α/BCL2/adenovirus E1B 19 kDa protein-3/Beclin 1 signaling pathway, while tumor autophagy is promoted [104].

Mitochondrial autophagy plays a crucial role in maintaining the self-renewal capacity of human stem cells. This mechanism involves the turnover of respiratory mitochondria to support the maintenance of hematopoietic stem cells in a glycolytic state with reduced levels of oxidative metabolism [105]. Suppression of mitochondrial autophagy in esophageal squamous cell carcinoma cells leads to a decrease in the presence of CD44, a recognized marker of CSCs [106]. One study reported that in contrast to cancer cells cultured in a two-dimensional environment, mammary spheres enriched with CSCs had notably elevated expression levels of Beclin1 and increased autophagy flux [107]. Investigating the impact of autophagy on stem cell characteristics is a significant research area, yet there is limited empirical support available. Studies in gliomas using transcriptomics and proteomics have revealed that chaperone-mediated autophagy (CMA) and its primary receptor LAMP2A, located on the lysosomal membrane, modulate CSC behavior through mechanisms such as extracellular matrix interactions, mitochondrial metabolism, and immune system pathways [108]. In addition, autophagy plays a role in regulating the secretion of IL-6 [109], and the IL-6-Jak2-STAT3 signaling pathway is important in the process of transforming non-CSCs to CSCs [110]. CD44 serves as an indicator of various CSCs and plays a crucial role in controlling the stem cell properties of CSCs [111]. Autophagy may contribute to the upregulation of CD44 and ADAM17, the latter being responsible for the cleavage of exomeric domain of CD44. This process involves extracellular matrix remodeling, cancer invasion, and metastasis [112]. When mitochondrial autophagy is increased, p53 localizes to mitochondria and is subsequently eliminated in a mitochondrial autophagy-dependent manner. This process may represent a mechanism through which autophagy influences CSC stemness [113]. In a murine model, autophagy was shown to play a role in CSC regulation through the EGFR/STAT3 and TGF-β/Smad signaling pathways in two distinct populations of breast cancer stem-like cells [114]. Autophagy is associated with angiogenesis, as evidenced by the autophagy-induced activation of KDR/VEGFR-2, facilitating the development of vasogenic mimicry in GSCs [115].

In summary, autophagy is a significant link between hypoxia and stem cell characteristics. Numerous ATGs are elevated in hypoxic environments, and intermediary molecules that connect autophagy and apoptosis exist. Increased autophagy levels in cancer cells are associated with increased apoptotic tendencies. Research has demonstrated that autophagy enhances the stemness of CSCs, although the underlying mechanism remains to be explored in mouse and cellular models.

Hypoxia promotes key transcription factors in stemness-related pathways

The effects of hypoxia on cell stemness are interconnected, and many genes such as *NANOG* [116, 117], EGF-like domain 7 (*EGFL7*) [118], Krüppel-like factor 5 (*KLF5*) [119], *SOX2* [120], and *OCT4* [121], are up-regulated under hypoxia conditions and affect the stemness of CSCs through multiple mechanisms (Fig. 1).

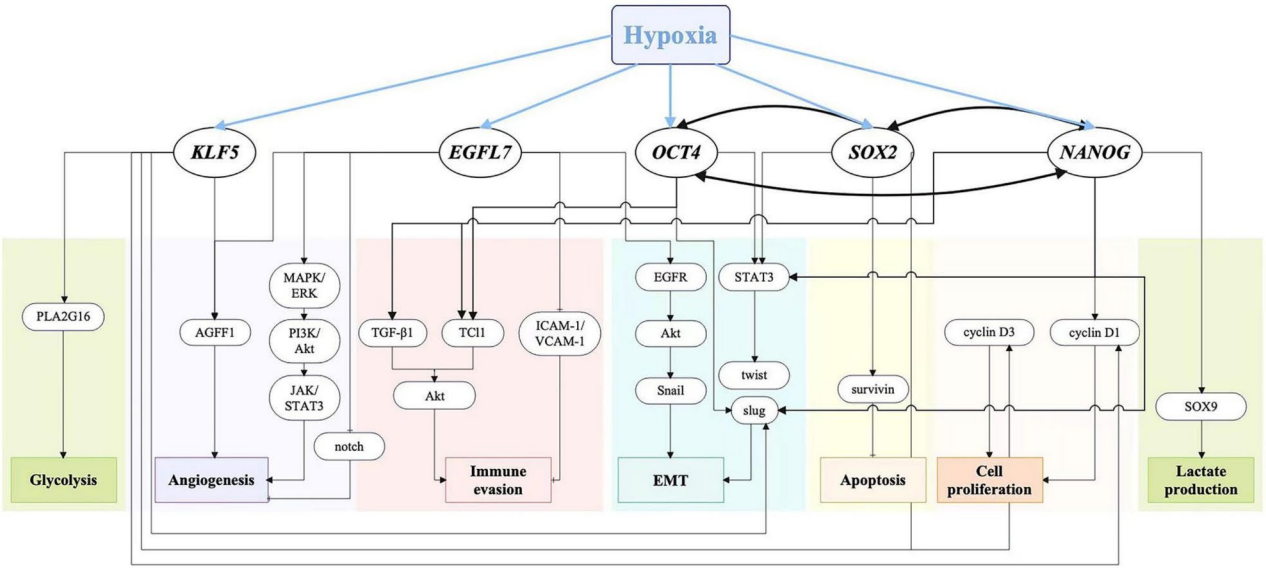

Fig. 1 Hypoxia promotes key transcription factors in the stemness-related pathways. Under hypoxia conditions, the expression of *KLF5*, *EGFL7*, *OCT4*, *SOX2*, and *NANOG* are up-regulated, and these genes act on multiple target genes, which have effects on EMT, immune escape, metabolic changes, apoptosis, proliferation, and other aspects. Abbreviation: EGFL7, EGF-like domain 7; KLF5, Krüppel-like factor 5; OCT4, octamer-binding transcription factor 4; SOX2, SRY-box 2

NANOG, KLF5, and SOX2 proteins promote cell proliferation, with NANOG exerting its effects through cyclin D1, whereas KLF5 is influenced by both cyclin D1 and cyclin B1 [122–124]. Additionally, SOX2 is responsible for the upregulation of cyclin D3 expression [125]. In terms of metabolism, the hypoxia-induced NANOG/SOX9 pathway enhances lactic acid production [126], and KLF5 promotes the expression of phospholipase PLA2G16 and thus promotes glycolysis in pancreatic cancer [127]. NANOG, EGFL7, KLF5, OCT4 and SOX2 have also been demonstrated to promote the EMT process in cancer cells, thereby affecting tumor metastasis and invasion [128–134]. As a key angiogenic factor, EGFL7 promotes angiogenesis by activating the MAPK/ERK, PI3K/Akt, and JAK/STAT3 pathways, while also inhibiting Notch signaling and its target genes to further facilitate angiogenesis [118]. SOX2 and NANOG function as significant regulators of autophagy [135]. NANOG plays a crucial role in facilitating the immune evasion of cancer cells by activating the TGF-β1 and Tcl1a/Akt signaling pathways, thereby allowing tumor cells to evade immune surveillance and avoid destruction by the immune system [136, 137]. Similarly, OCT4 can facilitate evasion of the immune system through the Tcl1a/Akt signaling pathway [138]. EGFL7 suppresses intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, which are crucial endothelial adhesion molecules facilitating the attachment and infiltration of immune cells [139]. In lung cancer cells, SOX2 has been shown to increase the expression of survivin, a protein that suppresses the apoptosis of cancer cells by acting as an inhibitor of programmed cell death [140]. Additionally, OCT4, NANOG, and SOX2 interact to form a self-sustaining network that maintains CSC characteristics by promoting self-renewal genes and suppressing differentiation genes [141].

Cancer stem cells have the potential to drive resistance to various cancer therapies.

The development of resistance to both conventional chemotherapeutic agents and targeted therapies is a significant contributor to mortality associated with cancer [142]. Cells that endure therapeutic interventions possess the capacity for proliferation, which may result in disease recurrence or metastatic dissemination. Both outcomes significantly diminish the overall survival rates of patients [143]. CSCs are frequently identified as a major contributing factor to the development of multi-drug resistance and the recurrence of cancer [14]. Detailed mechanisms for CSC-induced chemoresistance, radioresistance, and resistance to immunotherapy will be introduced in the following sections.

Mechanisms of stemness-related resistance to conventional cancer treatments

Chemotherapy drugs are genotoxic agents that cause DNA damage directly or indirectly. Similarly, radiotherapy, which employs ionizing radiation, affects the DNA structure by inducing breaks in the DNA strands, particularly double-strand breaks. Resistance to radiotherapy has been consistently noted in solid tumors and leukemia-derived CSCs [144]. Clinical research has demonstrated a notable increase in the presence of CSC markers

in small-cell lung cancer patients following chemotherapy treatment [145]. The effectiveness of chemotherapy was found to be linked to multidrug resistance mediated by ATP-binding cassette (ABC) transporters. The resistance of CSCs to radiation primarily arises from mechanisms such as reactive oxygen species (ROS) scavenging, DNA repair, and cell cycle arrest (Fig. 2).

Enriched quiescence and slow-cycling

Cell quiescence refers to the state in which stem cells enter a reversible G0 phase where they neither undergo cell death nor actively proliferate [146]. CSCs typically exist in dormant or slowly proliferating conditions, rendering them less responsive to therapies designed to attack rapidly dividing cells. As a key angiogenic factor, EGFL7 promotes angiogenesis by activating the MAPK/ERK, PI3K/Akt, and JAK/STAT3 pathways, while also inhibiting Notch signaling and its target genes to further facilitate angiogenesis [147]. In murine models, after chemotherapy, CSCs can be activated and their process of moving toward a proliferative state can be accelerated [148]. The precise mechanisms of the quiescence and drug resistance of CSCs remain to be elucidated; however, existing evidence suggests an association with Notch signaling [149], SET domain-containing protein 4 (SETD4) [150], and the c-Yes/YAP axis [151]. Advances in techniques for isolating and identifying CSCs are expected to enhance research into the dormant characteristics and drug resistance mechanisms of CSCs.

Increased efflux pump activity

CSCs exhibit elevated levels of efflux pumps, which expel chemotherapy drugs from the cell, reducing their efficacy by lowering intracellular drug concentrations [152]. ABC transporters, a diverse family of membrane proteins that can extrude a variety of chemotherapy drugs from the cell, are of particular interest [153]. Within this family, 12 glycoproteins have been identified as potential drug transporters, including P-glycoprotein encoded by *ABCB1*, multidrug resistance-associated protein 1 (MRP1) encoded by *ABCC1*, and ABC subfamily G member 2 (ABCG2) encoded by *ABCG2* [154]. Their expression levels exhibit a significant correlation with various aspects of cancer cell behavior, including

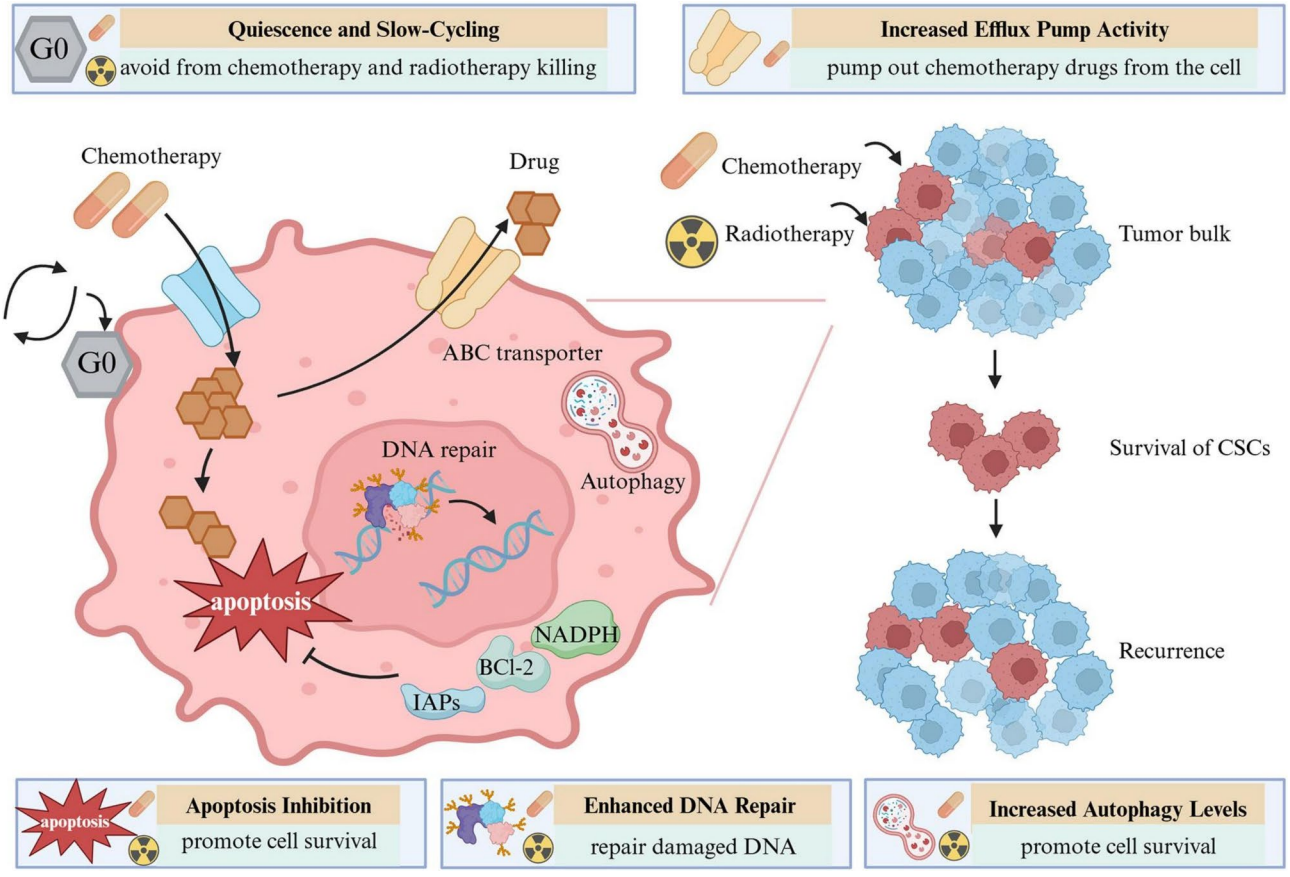

Fig. 2 Mechanism of drug resistance and relapse of CSCs. Chemotherapy and radiotherapy primarily target specialized cells and decrease tumor size in the immediate period. Nevertheless, CSCs can acquire resistance to chemoradiotherapy and radiotherapy via various mechanisms, including ABC transporter activity, cellular quiescence, upregulated DNA repair mechanisms, increased autophagy, and decreased apoptosis rates. Abbreviation: ABC, ATP-binding cassette; ROS, Reactive oxygen species

Table 1 DNA-repair proteins related to CSCs and their therapeutic resistance

Mechanisms	DNA-repair proteins	Functions	Cancer types	References
BER	APE1	Apurinic/apyrimidinic endonuclease	Colon	[332]
			Breast	[333]
	ERCC1	endonuclease	Colon	[334]
			Esophageal	[335]
	MTH1	hydrolase	Glioblastoma	[336]
NER	RPA2	binding ssDNA	Glioma	[337]
PRR	RAD6	Ubiquitin-conjugating enzyme	Ovarian	[338]
	PAF	PCNA-related protein	Glioma	[339]
			Breast	[340]
	RAD18	E3 ubiquitin-protein ligase	Breast	[341]
			Gastric	[342]
NHEJ	RIF1	Replicase	Lung	[343]
	SETMAR	Transposase, methylase	Colon	[344]
	SETMAR-1200	Transposase	Glioblastoma	[345]
	PARP1	NAD + ADP-ribosyl-transferase 1	Colon	[346]
			Glioblastoma	[347]
HRR	RAD51	Homologous pairing	Colon	[346]
			Glioma	[166]
			Breast	[348]
	BRCA1	Recombinase and E3 ubiquitin ligase	Breast	[349]
			Oral	[350]
	RAD52	Homologous pairing	Oral	[350]
	NBS1	Homologous pairing	Glioblastoma	[351]
	RAD50	ATPase	Breast	[352]
	ATM	Kinase	Breast	[290]
			Glioma	[353]
	CHK1	Checkpoint kinase	Ovarian	[169]
			Nasopharyngeal	[354]
			Lung	[355]

Abbreviation: CSCs, cancer stem cells; BER, base excision repair; NER, nucleotide excision repair; PRR, post replication repair; NHEJ, non-homologous end joining; HR, homologous recombination repair

tumorigenicity, proliferation, drug resistance, and metastasis [155]. The expression levels of ABC transporters are elevated in CSCs in vivo [156, 157]. For example, ovarian CSCs have elevated levels of *ABCB1* [158], whereas *ABCB5* is prominently expressed in the initial cells of malignant melanoma [159]. The small interfering RNA (siRNA) treatment suppressed ABCG2 expression in CD133 + colorectal CSCs, leading to reduced self-renewal capacity of CSCs and increased apoptosis induced by chemotherapy [160]. A research investigation established a vesicle co-delivery system utilizing non-ionic surfactants, designed to concurrently siRNA targeting *ABCG2* and the anti-apoptotic gene *BCL2*, in conjunction with doxorubicin, to CSCs [161]. The findings indicated a marked enhancement in the cytotoxic efficacy of doxorubicin against CSCs.

In addition to expelling chemotherapy drugs, ABC transporters act as efflux pumps for various signaling molecules, including hormones, offering CSCs an additional survival mechanism [162]. Importantly, while some ABC transporters can eliminate specific drugs, not all chemotherapy agents are substrates for these transporters. Furthermore, targeting a single ABC transporter may be insufficient to address multidrug resistance in tumors. For instance, tepotinib can reverse multidrug resistance caused by ABCB1, but not by ABCC1 or ABCG2 [163]. Hence, owing to limited knowledge of mutual compensation among ABC transporters and the regulatory pathways governing their expression, no specific inhibitor targeting all ABC transporters is currently available in clinical settings.

Enhanced DNA repair mechanisms

CSCs have effective DNA repair mechanisms [164], enabling them to recover from DNA damage caused by treatments. As a result, drugs that target cell DNA that induce tumor cell death, including cisplatin, oxaliplatin (DNA crosslinking agent), methotrexate (DNA synthesis inhibitor), doxorubicin and daunorubicin (topoisomerase inhibitor), have limited effectiveness in killing CSCs. The enhanced DNA repair process in CSCs involves various mechanisms, such as base excision repair (BER), nucleotide excision repair (NER), post-replication repair (PRR), non-homologous end joining (NHEJ), and homologous recombination (HR). Numerous DNA repair genes are overexpressed in CSCs (Table 1). Most target proteins are overexpressed in the HR pathway, which is the primary mechanism through which CSCs develop drug resistance by repairing DNA damage. The central player in HR is the strand-exchange protein, Rad51, which is highly expressed in clinical samples and patient-derived GSCs [165, 166]. The HR system includes additional elements for genetic recombination, such as the MRE11-RAD50-NBS1 (MRN) complex, which triggers the activation of

ataxia-telangiectasia mutated (ATM) kinase, early checkpoint response kinases, and BRCA-related proteins [167].

Increased anti-apoptotic pathways

CSCs have the potential to enhance the activation of anti-apoptotic pathways, thereby reducing their vulnerability to programmed cell death induced by stress from therapeutic interventions [168]. CSCs can evade apoptosis signals through various mechanisms, including alterations in cell cycle regulation, an imbalance in pro-apoptotic and anti-apoptotic proteins, down-regulation of death receptors coupled with up-regulation of c-FLIT, heightened capacity for clearing oxygen free radicals, and elevated expression of inhibitors of apoptosis family proteins (IAPs). Additionally, CSCs extend the G2/M phase of the cell cycle by increasing the expression of the checkpoint proteins checkpoint kinase 1 (CHK1) and CHK2. This extended phase is linked to DNA repair and resistance to programmed cell death [169].

The B lymphoblastoma-2 (Bcl-2) protein family comprises two main categories: anti-apoptotic members, such as Bcl-2, Bcl-XL, and Mcl-1, and pro-apoptotic proteins such as multi-domain proteins (e.g., Bax and Bak), and BH3-only molecules (e.g., Bim, Noxa, and Puma) [170]. The direct regulation of apoptosis is mediated by high levels of anti-apoptotic proteins which predominate [171, 172]. Hepatic CSCs show increased expression of the anti-apoptotic protein Bcl-2 and activation of the PI3K and ERK signaling pathways, which contribute to resistance to radiotherapy [173]. Death receptors, which belong to the TNF receptor superfamily, can induce cell death upon activation [174]. These receptors are distinguished by an intracellular death domain that aids in the transmission of cell death signals from the cell membrane to intracellular signaling molecules [175]. The reduced expression of death receptors and elevated levels of c-FLIP in CSCs impede the activation of the death receptor pathway and block apoptosis progression [176, 177]. An increased capacity for eliminating free radicals may confer increased resistance to cancer therapy in CSCs. In a study of breast CSCs in mice, researchers found that these cells resisted genotoxic stress by reducing ROS production and efficiently clearing existing ROS after treatment [178]. CSCs can increase the production of the antioxidant NADPH by increasing the expression of ALDH, a recognized marker of CSCs. This process aids in the removal of ROS generated along with oxidative stress. Following the inhibition of ALDH with disulfiram, the apoptotic response triggered by cisplatin notably intensifies [179]. The gene expression products involved in ROS clearance, including superoxide dismutase, glutathione peroxidase, and catalase, are increased in breast CSCs [178]. IAP proteins encompass a group of natural caspase inhibitors that impede apoptosis signaling pathways at critical junctures. In addition to the documented role of various IAP proteins in inhibiting cell death, elevated expression levels of IAP protein expression have been observed in CSCs. For example, the Baculoviral inhibitor of apoptosis repeat containing 5 (BIRC5), an inhibitor of the apoptosis protein family, is highly expressed in lung CSCs and GSCs, suggesting its potential as a therapeutic target [180].

CSCs possess a strong ability to evade programmed cell death induced by detachment (known as anoikis), allowing them to survive under adverse metastatic conditions characterized by extracellular matrix (ECM) deprivation, which is promoted during chemotherapy or radiotherapy [181]. The amplified expression of breast CSC markers ALDH1 and CD44+/CD24− can induce STAT3-mediated anoikis resistance [182]. CSCs acquire mesenchymal characteristics by promoting the EMT process, which is closely related to anoikis resistance [183]. A separate study demonstrated that CSCs exhibit elevated expression of β1 integrin, which confer protection against anoikis through the activation of the survivin signaling pathway [184].

Overall, CSCs have evolved mechanisms to evade apoptosis signals, thereby bolstering their resistance to therapeutic agents and radiation. Targeting the apoptosis pathway may prove to be a promising approach to overcoming drug resistance in CSCs.

Increased autophagy levels

Investigations into breast CSCs have revealed that the maintenance of autophagy homeostasis is a fundamental feature of their capacity to differentiate into diverse cell phenotypes under varying pathological states [185]. Comprehensive research suggests that increased autophagy not only promotes the life of tumors but also contributes to their resistance to drugs across various types of tumors [186]. Autophagy functions by removing damaged macromolecules or organelles caused by chemotherapy and radiotherapy, thereby shielding cancer cells from apoptosis. In estrogen receptor (ER)-positive breast cancer, inhibiting autophagy enhances the sensitivity of resistant tumors to tamoxifen-induced cell death [187]. Combined treatment of epidermal growth factor receptor-tyrosin kinase inhibitor and autophagy inhibitor inhibits the stemness and restored the toxicity of osimertinib [188]. Similarly, in prostate cancer, autophagy inhibition can overcome resistance to enzalutamide [189]. Salinomycin by inhibiting autophagy has also been reported to reduce the proportion of breast CSC population [190].

Nevertheless, the precise mechanism underlying resistance to autophagy is not fully understood. Research has indicated that the inhibition of autophagy leads to the accumulation of the autophagy-regulating transcription

factor FoxO3a in cancer cells. This accumulation results in increased expression of the pro-apoptotic target gene *Puma*, ultimately triggering programmed cell death [191]. Autophagy also triggers an intensified DNA damage response through the HR repair pathway, which is a primary mechanism for mending double-strand breaks (DSBs) [192]. Additionally, in oral CSCs, autophagy has been demonstrated to stimulate the upregulation of the drug efflux protein ABCB1 [112]. Another study on gastric cancer revealed that autophagy plays a role in controlling the resistance of gastric CSCs to chemotherapy via the Notch signaling pathway [193]. Autophagy-mediated drug resistance represents a multifaceted phenomenon that involves a range of factors, such as gene repair mechanisms, the replenishment of cytoplasmic components, alterations in drug concentration and metabolism, as well as modifications in the activity and expression of essential proteins [186]. The increased sensitivity of GSCs to radiotherapy can also be achieved through the suppression of autophagy [194]. Further comprehensive experiments are needed to clarify the mechanisms underlying autophagy, its role in CSC resistance, and potential therapeutic targets related to autophagy and CSCs.

Mechanisms of stemness-related resistance to immunotherapy

The ongoing advancements in immune checkpoint inhibitors and cellular immunotherapy have led to the development of novel approaches for target tumors. Since the identification of CSCs, numerous studies have investigated their immunological properties extensively. These findings indicate that CSCs possess immune-privileged characteristics that contribute significantly to the three phases of immunoediting, namely elimination, equilibrium, and escape [195, 196]. The inherent low immunogenicity and quiescent nature of CSCs enable them to evade immune surveillance within their microenvironment, thus protecting them from elimination by the immune system. Studies of melanoma cell lines reveal that the immunogenic tumor-associated antigen MART-1 is exclusively present in differentiated melanoma cells and not in melanoma CSCs [197]. CSCs possess distinct immune privileges and exhibit enhanced immune evasion capabilities through various mechanisms. The antigen processing and presentation processes involving the interaction between cytotoxic T lymphocyte (CTL) receptors and major histocompatibility complex class I (MHC-I)/antigen complexes are impaired in CSCs. CSCs can increase the level of CD47 expression. CD47, in turn, can bind to the inhibitory immune receptor SIRPα found on myeloid cells, leading to a "do not eat me" signal. This mechanism serves to protect CSCs from being engulfed by macrophages and dendritic cells [198, 199]. Inhibition of CD47 has been demonstrated to enhance the process of macrophage-mediated phagocytosis of CSCs in pancreatic ductal adenocarcinoma, acute myeloid leukemia, and hepatocellular carcinoma, consequently aiding in their eradication [198–200]. CSCs derived from melanoma, glioblastoma multiforme, and breast cancer have been demonstrated to reduce the expression of MHC-I molecules, consequently evading detection by T cells [201–203]. A reduction in the number of components involved in the antigen processing machinery, including low-molecular-weight proteins, antigen processing-related transporters, and beta-macroglobulin, has been observed in GSCs [202]. These findings indicate that CSCs can interfere with antigen processing mechanisms.

In several types of cancer, including glioblastoma, lung cancer, and breast cancer, M1 macrophages, which are classically activated and pro-inflammatory, are recruited to the tumor site through chemotaxis in response to cytokines released by CSCs. Upon arrival at the tumor microenvironment, these M1 macrophages undergo a transformation into M2 macrophages, which secrete factors such as TGF-β, IL-10, IL-23, and arginase 1, thereby contributing to the establishment of an immunosuppressive microenvironment that facilitates tumor growth [204–206]. CSCs facilitate the evasion of the immune system by suppressing immune-related signaling pathways, including toll-like receptor 4 (TLR4) [207] and the signal transducer and activator of transcription 3 (STAT3) pathway [208]. Furthermore, breast CSCs can specifically avoid elimination by natural killer (NK) cells and antibody-dependent cell-mediated cytotoxicity (ADCC) [209]. CSCs facilitate the infiltration of regulatory T cells (Treg cells) in glioblastoma via the release of the costimulatory molecule PD-L1, soluble Galectin-3, and TGF-β [94]. An increasing body of research has shown that CSCs play an important role in immune avoidance by altering the phenotypes of Dendritic cells (DCs) and inhibiting their recruitment to TME [210]. CSCs are not optimal targets for immune surveillance because of their ability to impede immune responses through the diverse expression of immune checkpoint molecules. The immune checkpoint protein CD276 (B7-H3) is significantly upregulated in the CSCs of head and neck squamous cell carcinoma, aiding in the evasion of host immune responses [211]. The EMT/β-catenin signaling pathway can induce significant PD-L1 expression in CSCs, thereby enabling CSCs to evade detection by T cells [212]. CSCs can also upregulate the production of the immunosuppressive molecule CD200, potentially leading to a shift in lymphocyte behavior from a Th1-like immune response to a Th2-like immune response [213].

As previously noted, CSCs possess the capacity to transition between quiescent and actively dividing states, a characteristic that aids in their evasion of immune surveillance. Quiescent CSCs derived from diverse types of

cancer can suppress the antigen-presenting machinery, such as MHC class I, Tap proteins, and UL16-binding protein (ULBP) ligands. This modulation helps avoid the detection of CSCs by cytotoxic T lymphocytes and NK cells [214, 215]. In a model of tumor dormancy, leukemia cells exhibited prolonged survival by upregulating the expression of B7-H1 and B7.1, thereby evading CTL-mediated destruction [216]. Moreover, inactive cancer cells evade T-cell-mediated cell death by disrupting the suppressor of cytokine signaling 1 (SOCS1) cascade and increasing the expression of the oncogenic factor IL-3 [217].

The immune resistance of CSCs is enhanced by their limited immunogenicity, enabling them to evade detection and destruction by the immune system through various mechanisms. In conjunction with resistance to chemoradiotherapy, the drug resistance exhibited by CSCs is influenced by multiple factors and pathways. The similarity of the defense mechanisms of CSCs and normal stem cells highlights the potential of CSC-targeted treatments. The ability of CSCs to exhibit plasticity and regenerate highlights the importance of employing CSC-specific therapies alongside traditional treatments to inhibit their regeneration, replenishment, and redistribution.

Key pathways of cancer stem cells involved in resistance to conventional treatment

The potential mechanisms of CSC-related drug resistance include activation of growth signaling pathways such as the Wnt/β-catenin, Hedgehog, Notch, PI3/AKT, and Hippo pathways [204, 218].These pathways contribute to CSC drug resistance by inducing quiescence, enhancing DNA damage repair and ROS clearance, and promoting multidrug resistance (MDR).

Wnt pathway

The WNT/β-Catenin signaling pathway, known for its participation in a range of physiological functions and pathological conditions, is conserved across evolutionary lineages [219]. Hypoxia is a significant factor in the maintenance of stemness through the Wnt signaling pathway. A study demonstrated that Wnt/β-catenin signaling facilitates the hypoxia-induced self-renewal capabilities of colorectal CSCs by reactivating the expression of Id2 [220]. Under conditions of hypoxia, there is an observed overexpression of BCL9, which serves as a significant co-activator in the Wnt/β-catenin signaling pathway [221]. HIF-1-regulated miR-1275 directly interacts with several antagonists of the Wnt/β-catenin signaling pathways, such as DKK3, SFRP1, GSK3β, and RUNX3. This interaction leads to the activation of signaling pathways and the preservation of stem cell characteristics [222]. In liver cancer, the increased expression of EPH receptor B2 in CSCs plays a crucial role in regulating cancer stemness and resistance to drugs, facilitated by the initiation of the SRC/AKT/GSK3β/β-catenin signaling pathway cascade [223]. In cases of ovarian cancer, the c-Kit receptor associated with stem cell factors, triggers the activation of the Wnt/β-catenin and ABCG2 pathways, leading to chemotherapy resistance [224]. The Wnt signaling pathway is also linked to the upregulation of ABC transporters, facilitating drug efflux and contributing to drug resistance [225].

Notch pathway

The Notch signaling pathway plays a crucial role in regulating the survival and self-renewal of CSCs. Similarly, hypoxia plays a significant role in the maintenance of stemness via the Notch signaling pathway. MiR-1275, which is regulated by HIF-1, directly engages with various antagonists of the Notch signaling pathway, including NUMB. This interaction facilitates the activation of downstream signaling pathways, thereby maintaining the characteristics associated with stem cell-like properties [222]. The Notch pathway inhibitor L685-458 was found to counteract the overexpression of HIF-2α, which is associated with the development of paclitaxel resistance and the transformation towards a stem-like phenotype [226]. Also, hypoxia stimulates the expression of the Notch ligand Jagged2 in cancer cells, which subsequently triggers EMT and enhances stemness characteristics, thereby contributing to tumor resistance [72]. In colorectal cancer, Notch1 is highly expressed in chemotherapy-resistant cells that are rich in the CSC markers CD133 and CD44 [227]. In gliomas, genes associated with the Notch and Hedgehog pathways are significantly upregulated in $CD133^+$ CSCs and are resistant to temozolomide [228]. The Notch signaling pathway, particularly the Notch3 pathway, plays a crucial role in regulating the maintenance of CSCs and their resistance to cisplatin in ovarian cancer [229]. In the context of lung adenocarcinoma, cisplatin treatment results in the enrichment of $CD133^+$ cells, thereby promoting MDR through the activation of the Notch signaling pathway [230].

Hedgehog pathway

The Hedgehog pathway is associated with the regulation of CSCs [231]. Suppression of the Hedgehog pathway results in a decrease in the expression of stemness-associated genes, including *NANOG*, *SOX2*, and octamer-binding transcription factor 4 (*OCT4*), in glioma cells [232]. The activation of the Hedgehog signaling pathway contributes to the development of resistance to sorafenib in organoids derived from individuals with hepatocellular carcinoma [233]. The expression of GLI-1, a constituent of the Hedgehog signaling pathway, is increased in cancer cells that have developed resistance to 5-FU. Conversely,

the decreased expression of GLI-1 can mitigate resistance to 5-FU [234]. In the gas-fluid organoids derived from colon cancer, the efficacy of 5-FU, irinotecan, and oxaliplatin is enhanced by hedgehog signaling inhibitors through the suppression of GLI-1 expression, thereby reducing drug resistance [234].

PI3K/AKT pathway

The PI3K/AKT signaling pathway is significantly involved in the development of resistance to chemotherapy. Studies have demonstrated a strong association between metastasis-associated colon cancer 1 (*MACC1*) and stem cell-like properties as well as resistance to 5-FU in CSCs. Furthermore, *MACC1* expression is modulated by the PI3K/AKT pathway [235]. One of the functions of the PI3K/AKT pathway is to regulate ABCG2 activity by targeting it to the plasma membrane [236], thereby facilitating the efflux of drugs. In breast cancer, PD-L1 plays a role in controlling the activation of CSCs by influencing the expression of genes associated with stemness, such as *OCT-4*, *NANOG*, and *BMI1*, through the PI3K/AKT signaling pathway [237]. This interaction has been linked to the development of tumor immunoresistance.

Hippo-YAP/TAZ pathway

The activation of the YAP/TAZ signaling pathway causes cancer cells to revert to a less differentiated state. These cells exhibit CSC-like properties, such as self-renewal ability and resistance to chemotherapy. The Hippo coactivator YAP1 plays a role in promoting the overexpression of EGFR in esophageal cancer, leading to enhanced resistance to chemotherapy [238]. Colon cancer cells were found to evade cell death induced by 5-FU chemotherapy by transitioning into a state related to stemness and dormancy, which is linked to the c-Yes/YAP axis [151]. In hepatocellular carcinoma, the YAP/TAZ signaling pathway plays a significant role in suppressing ferroptosis, thereby serving as a crucial factor in resistance to sorafenib treatment [239]. Similarly, Yap1 has been identified as a mediator of trametinib resistance in head and neck squamous cell carcinoma [240].

Biomarkers of Cancer stem cells

CSCs are responsible for resistance to chemotherapy, radiotherapy, and immunotherapy [14]. The survival of CSCs enables the replenishment of tumor cell populations and contributes to cancer recurrence [9]. One of the most effective methods for detecting CSCs within tumors is the use of CSC-specific biomarkers. Based on their cellular distribution, CSC markers can be classified into intracellular markers and cell-surface markers. Intracellular markers include transcription factors that function in the nucleus and markers found in the cytoplasm. Current studies have reported various molecules as CSC markers in solid tumors as outlined in Table 2.

A diverse array of cell-surface proteins serve as potential markers for CSCs in solid tumors. Among these, C-X-C Chemokine Receptor Type 4 (CXCR4), also referred to as CD184, is a CXC chemokine receptor that is encoded by the *CXCR4* gene [241]. CXCR4 plays a significant role in cancer progression by activating various signaling pathways, such as the PI3K/AKT, PLC, hedgehog, ERK1/2, and JAK/STAT pathways [242]. LGR5, also known as G-Protein Coupled Receptor 49 (GPR49) or G-Protein Coupled Receptor 67 (GPR67), is encoded by the *LGR5* gene. LGR5 has been identified as a part of the WNT signaling complex that potentiates WNT/β-Catenin signaling [243]. The significant involvement of the WNT signaling pathway in the maintenance of CSC properties has led to the recognition of LGR5 as a cell-surface marker in various types of solid tumors. CD24, alternatively referred to as Heat Stable Antigen (HSA), is encoded by the *CD24* gene and serves as a cell-cell adhesion molecule [244]. CD24 is involved in various signaling pathways that have the potential to increase the stemness of tumor cells [245]. Similarly, CD44, also known as Homing Cell Adhesion Molecule (HCAM) and Phagocytic Glycoprotein-1 (Pgp-1), induces cell-cell adhesion and interactions [246]. Additionally, it participates in the activation of the PI3K/AKT and Src/MAPK signaling pathways and functions as a co-receptor for c-Met [246]. Both CD24 and CD44 can individually or in combination mark CSCs in several solid tumor types. Additionally, the presence of the CD44+/CD24 – combination serves as a marker for CSCs in breast cancer, prostate cancer, head and neck squamous cell carcinoma, and ovarian cancer. Additional cell surface markers for CSCs are presented in Table 1, which is not elaborated upon in this discussion.

OCT4, SOX2, and Nanog are fundamental transcription factors responsible for governing the embryonic stem cell phenotype [247]. Through cooperative interactions, they facilitate the upregulation of their respective promoters, thereby initiating the expression of genes crucial for preserving embryonic stem cell identity while concurrently suppressing the activation of lineage-specific transcription factors. The presence of these transcription factors in cancer cells confers stem-like characteristics, thereby establishing them as conventional markers for CSCs [248–250].

Hypoxia induces drug resistance in tumors

Studies have indicated an increase in drug resistance in hypoxic tumors, with the activation of HIFs associated with tumor resistance and reduced survival rates [251]. Although the role of HIFs in tumor drug resistance has been recognized, the specific molecular pathways leading

Table 2 Cancer stem cell markers for solid tumors

Biomarker	Full name and alternative name(s)	Expression in cancer types	Function(s)	References
Cell surface markers				
CD24	Heat Stable Antigen (HSA)	HNSCC, hepatocellular, prostate, colorectal, gastric and bladder	Mediating the WNT/β-Catenin, MAPK, PI3K/AKT/mTOR, Notch, and hedgehog pathways	[356]
CD44	Homing Cell Adhesion Molecule (HCAM) Phagocytic Glycoprotein-1 (Pgp-1)	Breast, bladder, cervical, colorectal, gastric, HNSCC, liver, pancreatic, prostate and ovarian	Recruiting ezrin/radixin/moesin (ERM) proteins to interact with VEGFR and to actiavte the PI3K/Akt and Src/MAPK pathways Co-receptor of c-Met	[246, 356]
CD133	Prominin-1 PROM1	Breast, cervical, colorectal, esophageal, liver, lung, prostate, pancreatic, and glioblastomas	A member of pentaspan transmembrane glycoproteins Activating the PI3K/AKT, Src, and β-Catenin	[357, 358]
CXCR4	C-X-C Chemokine Receptor Type 4 Fusin CD184	Breast, colorectal, gastric, glioma, and pancreatic	A chemokine receptor that contributes to HIV infection and triggers activation of several signaling pathways that supports cell proliferation, migration, and survival	[242, 356]
EpCAM	Epithelial Cell Adhesion Molecule CD326	Breast, colon, HNSCC, lung, pancreatic and liver	Homotypic cell adhesion Epithelial mesenchymal transition	[356, 359]
LgR5	Leucine Rich Repeat Containing G Protein-Coupled Receptor 5 G-Protein Coupled Receptor 49 (GPR49) G-Protein Coupled Receptor 67 (GPR67)	Intestinal, colorectal, cervical, hepatocellular, pancreatic and glioblastoma	A member of the WNT signaling pathway	[356, 360, 361]
Intracellular markers				
ALDH	Aldehyde dehydrogenase	Breast, ovarian, brain, bone, prostate, colorectal, lung, cervical, renal, endometrial, pancreatic, esophageal, hepatobiliary and melanoma	A polymorphic enzyme that oxidates aldehydes to carboxylic acids	[362]
BMI-1	B Lymphoma Mo-Mlv Insertion Region 1 Homolog Polycomb Group RING Finger Protein 4 (PCGF4) RING Finger Protein 51 (RNF51)	Oral, esophageal, gastric, thyroid, prostate, pancreatic, hepatocellular, neuronal, colorectal, lung and breast	Negatively regulating $p16^{INK4a}$ and $p14^{ARF}$/$p19^{ARF}$ expression at the transcriptional level Inhibiting E-cadherin expression	[363]
Musashi-1/2	RNA-Binding Protein Musashi Homolog 1/2	Breast, colorectal, endometrial, esophageal, hepatocellular and lung	RNA-binding protein involved in post-transcriptional mRNA editing	[364]
Nanog	Nanog Homeobox	Breast, colorectal, esophageal, gastric, hepatocellular, lung, ovarian, pancreatic and prostate	A transcription factor that maintains pluripotency of stem cells	[136]
OCT4	Octamer-Binding Transcription Factor-4 POU Domain, Class 5, Transcription Factor 1 (POU5F1)	Breast, endometrial, gastric, glioma and HNSCC	A homeodomain transcription factor of the POU family that maintains self-renewal of stem cells	[365]
SOX2	Sex determining region Y-box 2	Bladder, breast, cervical, colorectal, esophageal, gastric, glioma, hepatocellular, HNSCC, lung, melanoma, pancreatic, ovarian, renal cell carcinoma and sarcoma	A transcription factor that maintains self-renewal and pluripotency of stem cells	[120, 248]

Abbreviation: HNSCC, head and neck squamous cell carcinoma

to reduced drug efficacy are still under investigation. This review summarizes the current knowledge of HIF activation and the regulation of tumor drug resistance and focuses on mechanisms, including enhancing drug efflux, preventing cell death, promoting cell survival, and repairing DNA damage (Fig. 3; Table 3).

Hypoxia can induce tumor resistance directly

Hypoxia is a key driver in the development of drug resistance in tumors. Like resistance facilitated by CSCs, hypoxia can contribute to drug resistance by directly influencing various cellular processes. These include the upregulation of drug efflux proteins, the modulation of apoptotic pathways, the initiation of autophagy, the

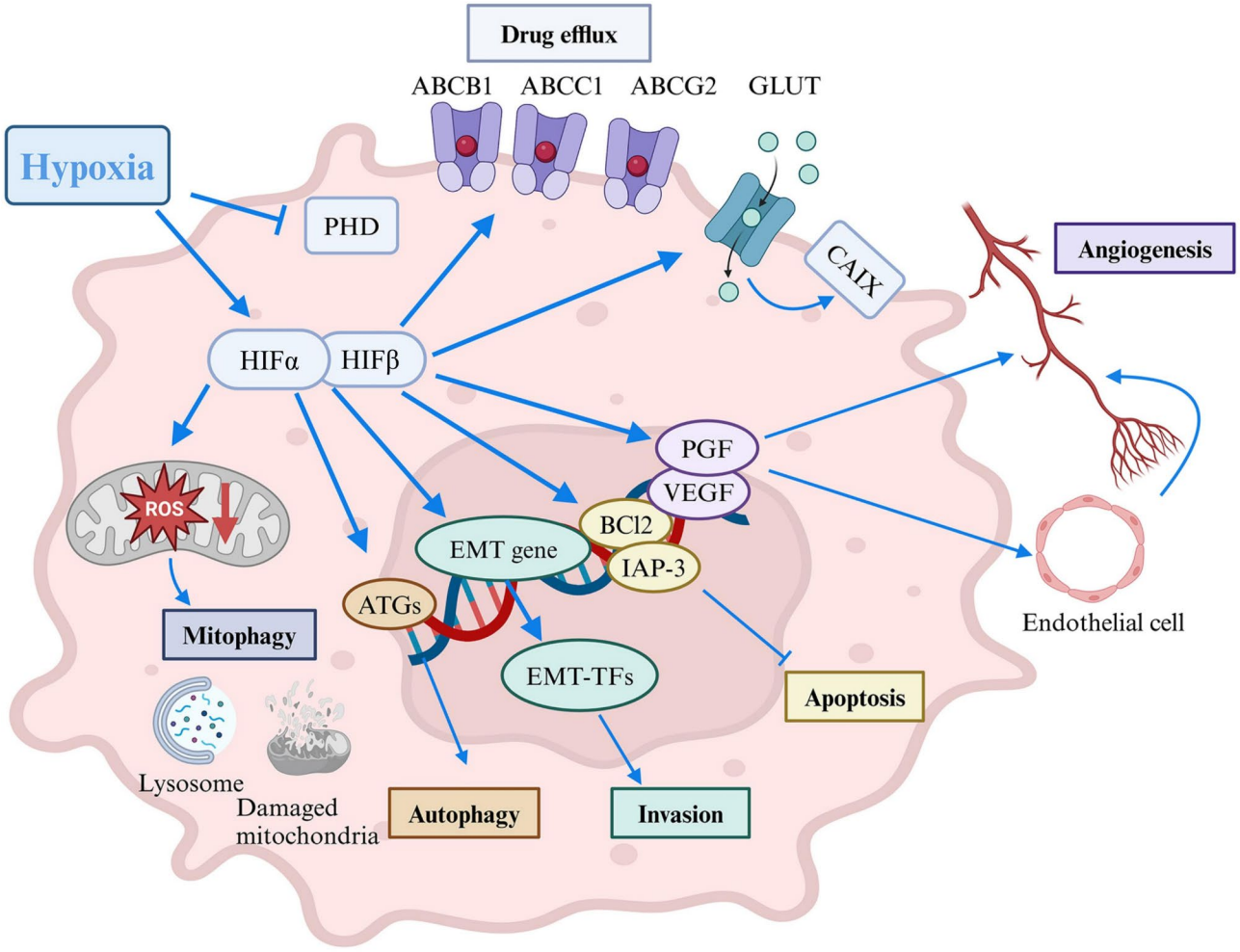

Fig. 3 Hypoxia induces chemoradiotherapy resistance through a pleiotropic mechanism. Reduced oxygen levels in the TME inhibit the enzymatic function of PHDs, which normally hydroxylate the oxygen-sensitive HIF-α leading to its heterodimerization with the HIF-β subunit. This process induces the expression of GLUTs and glycolytic enzymes, promoting anaerobic glycolysis, intracellular acidification, and acidification of the TME, which is regulated by the coordinated expression of CAIX. The decrease in oxidative phosphorylation metabolism and increase in mitochondrial autophagy during hypoxia reduce the levels of ROS. Under anoxic conditions, drug efflux is facilitated through ATP-binding cassette transporters such as ABCB1, ABCC1, and ABCG2. Upregulation of anti-apoptotic proteins Bcl-2 and IAP-3 leads to decreased apoptosis, while genes associated with EMT enhance the invasiveness of apoptotic cells. Additionally, increased expression of VEGF promotes new angiogenesis, which is a key characteristic of chemotherapy resistance in hypoxic tumors. Abbreviation: TME, tumor microenvironment; PHDs, proline hydroxylase dioxygenase; GLUTs, glucose transporters; CAIX, carbacylase IX; ROS, reactive oxygen species; Bcl-2, B-cell lymphona 2; IAP-3, inhibitor of apoptosis protein 3; EMT, epithelial mesenchymal transformation; VEGF, vascular endothelial growth factor

control of mitochondrial function, and the detoxification of ROS.

Hypoxia induces drug resistance in tumors by activating specific pathways. Like that of CSCs, hypoxia can influence the expression of various members of the ABC transporter family, thereby facilitating the efflux of drugs. The transporter genes directly regulated by HIF-1α are *ABCB1*, *ABCC1*, and *ABCG2*, and their promoters contain HREs sensitive to HIF-1α transcriptional regulation. ABCB1 and ABCC1 are linked to unfavorable outcomes in human non-small cell lung cancer in a HIF-1-dependent fashion with resistance to cisplatin and docetaxel [252]. In the case of pancreatic cancer, hypoxic conditions can stimulate HIF-1α binding to a specific gene sequence within the ABCG2 promoter, resulting in increased HIF-1α expression levels [253].

Apoptotic malfunctions contribute to the development of resistance to hypoxia-induced tumors, which is crucial for the efficacy of anti-cancer treatments that rely on the activation of apoptosis through various members of the caspase protease family [254]. The initiation of the intrinsic caspase cascade is intricately linked to components of the Bcl-2 protein family. Under hypoxia, the balance of Bcl-2 family proteins in tumors is disrupted, and the pro-apoptotic proteins BIM [255] and Bax [256] are inhibited, whereas the antiapoptotic proteins Bcl-2 [257], Bcl-xl

Table 3 Overview of HIF-1-mediated mechanisms in drug resistance

Resistance phenotype	Cancer type	Resistant chemotherapy drug	Molecular basis	Reference
Overexpression of drug efflux proteins	Colorectal	5-fluorouracil	MDR1/ P-glycoprotein	[366]
	NSCLC	Cisplatin, docetaxel	ABCB1, ABCC1	[252]
	Pancreatic	Gemcitabine	ABCG2	[253]
Apoptosis inhibition	NSCLC	EGFR tyrosine kinase inhibitors	BIM	[255]
	GBM	Radiotherapy	BAX	[256]
	Colon	Radiotherapy	Bcl-2, Bcl-xl	[257]
	Breast	Her2 inhibitor	Mcl-1	[258]
	Ovarian	Cisplatin	HDAC4	[259]
Apoptosis inhibition and stemness maintenance	Breast, Prostate, cervical	2-DG	Hexokinase 2	[270]
DNA damage inhibition	Breast	Paclitaxel, adriamycin, mitoxantrone and	SOD2	[265]
	Breast	Fulvestrant	miR-137	[367]
	NSCLC	Cisplatin	exosomal PKM2	[368]
	NSCLC	Gemcitabine	ABCB6	[266]
DNA damage inhibition and stemness maintenance	Breast	Cisplatin	Aldolase A	[272]
DDR	Colon		ATR kinase	[263]
DDR and stemness maintenance	HepG2 cell	Doxorubicin	GLUT1	[267]
	Pancreatic, gastric	Radiotherapy	6-phosphofructo-2-kinase/fructose-2,6-bisphosphates	[271]
	EC	Cisplatin	Phosphoglycerate kinase 1	[273]
Stemness maintenance	Colorectal	Oxaliplatin	GLUT5	[269]
	Gastric	Cisplatin	Enolase 1	[274]
	Ovarian, HCC	Cisplatin, sorafenib	Pyruvate dehydrogenase, pyruvate dehydrogenase kinase	[40, 277, 278]
Autophagy induction	HeLa cell	N-(4-Hydroxypheny) retinamide (4-HPR)	Beclin1	[369]
	Gastric	Vincristine	ATG12 and HMGB2	[370]
	Breast	Tamoxifen	ATG5, ATG7	[100, 101]
Autophagy induction and stemness maintenance	Breast	Tamoxifen	Lactate dehydrogenase A	[276]
Overexpression of drug efflux proteins, DNA damage inhibition and stemness maintenance	NSCLC, Pancreatic	Paclitaxel	Snail	[286, 288]
Overexpression of drug efflux proteins, DDR and stemness maintenance	Colorectal	Oxaliplatin	Twist	[284, 291]
	Breast	Radiotherapy	Zeb1	[285, 290]

Abbreviation: DDR, DNA damage response; EC, Endometrial carcinoma; GBM, Glioblastoma multiforme; HCC, hepatocellular carcinoma; NSCLC, Non-small cell lung cancer

[257], and Mcl-1 [258] are upregulated, thus increasing the apoptotic threshold and reducing the efficacy of chemotherapy and radiotherapy. The inhibition of apoptosis induced by hypoxia also involves the P53 and Ras signaling pathways [259].

When cancer cells are subjected to hypoxia, they activate processes that suppress DNA damage and enhance repair mechanisms, leading to resistance to anticancer treatments. Among the various types of DNA damage, DSBs are the most severe and serve as the molecular foundation for the efficacy of radiotherapy in eradicating cancer cells [260]. DSBs are identified through the action of ATM kinase, which regulates the cascade of signal transduction processes that follow [261]. ATM and ATR enzymes are responsible for phosphorylating numerous substrates that play crucial roles in the DNA damage response (DDR) and subsequent DNA repair processes [260, 262]. DSB repair predominantly takes place during the S and G2 phases of the cell cycle through either the NHEJ or HR pathway. The relationship between the DDR under hypoxic conditions and signaling pathways involving HIF-1, ATR, and ATM is well established [263], and cells lacking HIF-1α exhibit reduced expression of numerous DSB receptor proteins [264].

The intracellular removal of ROS plays a crucial role in preventing DNA damage in cancer cells. HIF-2α stimulates the transcription of superoxide dismutase 2 (SOD2) in low-oxygen environments, leading to a decrease in mitochondrial ROS levels [265]. Additionally, in response to the HIF-1α signal, the production of heme is elevated, resulting in increased activation and buildup of catalase, which in turn effectively reduces the levels of ROS [266].

Hypoxia can induce tumor resistance indirectly through stemness

Hypoxia has a regulatory effect on the stemness of CSCs. In the process of maintaining the stemness of tumors through cellular metabolic reprogramming, EMT, and autophagy induction, hypoxia imparts drug resistance to tumors.

Numerous compounds within the glycolysis pathway have been demonstrated to engage in an intricate network involving hypoxia, stem cell characteristics, and resistance to pharmaceutical agents. Among glucose transporters, GLUT family members, including GLUT1 [267], GLUT4 [268], and GLUT5 [269] have been shown to induce antitumor resistance. In terms of glycolytic enzymes, Hexokinase (HK) [270], 6-fructose-2-phosphate kinase (PFKFB) [271], aldolase A [272], phosphoglycerol kinase 1 (PGK1) [273], enolase [274], pyruvate kinase (PK) [275], and lactate dehydrogenase (LDH) [276] are involved in inducing antitumor resistance. Furthermore, enzymes that indirectly influence glycolysis metabolism are linked to drug resistance. The pyruvate dehydrogenase (PDH) complex, which mediates the glycolytic to tricarboxylic acid cycle pathway, is inhibited by overexpressed PDK1 under hypoxic conditions [40], and PDH inhibition [277] and PDK overexpression [278] have also been found to induce antitumor resistance. Importantly, resistance can arise from the direct influence of glucose transporters and glycolytic enzymes or from the promotion of glycolytic metabolism. The process of drug resistance caused by glycolysis and its intermediary elements encompasses a wide range of mechanisms associated with hypoxia, including antiapoptotic effects [271, 273, 279], the induction of autophagy [276, 280], and the promotion of drug effectiveness [281]. The increased glycolytic activity observed in cancer cells is believed to be linked to the initiation of EMT [282].

Hypoxia regulates drug resistance through EMT, a process linked to the tumor stemness phenotype. The increased genetic expression typically in stromal cells is closely linked to therapeutic resistance. This transcriptional upregulation is partially driven by the activation of the EMT program in cancer cells [283]. EMT-TFs play roles in the development of acquired resistance. Numerous promoters of ABC transporter genes contain EMT-TF binding sites. Proteins such as SNAIL, Twist, and ZEB1 are known to trigger EMT and are linked to the regulation of P-glycoprotein and other ABC transporters [284–286]. EMT-TFs also induce drug resistance independently of ABC transporters by increasing cell resistance to drug-induced apoptosis. Furthermore, following conventional treatment, CSCs may undergo EMT, leading to distant metastasis and the subsequent reacquisition of self-renewal capabilities after a certain duration, a phenomenon referred to as recurrence [287]. This occurrence poses a significant challenge to the efficacy of therapeutic interventions.

The SNAIL protein suppresses the transcription of cyclin D2, slowing cell cycle progression. This action results in enhanced resistance to both internal and external apoptotic pathways, ultimately contributing to cellular resilience against DNA damage responses [288]. EMT-TFs play crucial roles in the cellular response to DNA damage repair [289]. For example, Zeb1 plays a role in safeguarding cells against genotoxic stress induced by chemotherapy by activating CHK1 and facilitating DNA repair through recombination mechanisms [290]. The activation of P53 through phosphorylation has been demonstrated to phosphorylate TWIST, thereby controlling the expression of various genes associated with cell cycle arrest (such as *p21*) and apoptosis (including *BAX* and *Puma*) [291]. The increased expression of SNAIL, in conjunction with EMT, triggers metabolic reprogramming in cancer cells, which is characterized by increased glucose absorption and lactate generation, as well as decreased mitochondrial respiration [292, 293].

Autophagy has been demonstrated to increase the survival of tumor cells and contribute to treatment resistance. In preclinical studies of breast cancer, autophagy has been found to support the survival of quiescent disseminated cells and is essential for metastasis following the dormant phase [294]. Regulatory processes control hypoxia and autophagy, as well as the mechanisms by which autophagy is upregulated, and drug resistance is induced in CSCs. However, the current literature lacks a comprehensive analysis that fully integrates the pathways of hypoxia, autophagy, and drug resistance.

The process of developing drug resistance under hypoxic conditions can be succinctly described as involving the upregulation of drug efflux proteins, the modulation of apoptosis signaling pathways, the initiation of autophagy, and alterations in DNA damage and repair pathways. Furthermore, tumor stemness is intricately linked to drug resistance, with hypoxia playing a crucial role in maintaining stemness and contributing to tumor drug resistance. Alterations in hypoxia-induced stemness, such as modifications in glucose metabolism, EMT, and autophagy, have been shown to result in drug resistance. These processes operate through various mechanisms that can directly affect pathways associated with

drug resistance or be modulated by the stemness of tumors. The relationship between hypoxia and stemness involves a complex interaction network involving multiple pathways implicated in tumor drug resistance.

Hypoxia leads to the development of immune resistance in tumors

Hypoxia has been shown to impact the efficacy of immunotherapy through various mechanisms. Specifically, a decrease in oxygen levels can lead to a diminished proportion of antitumor immune cells relative to immune-tolerant or immunosuppressive cells. Furthermore, hypoxia upregulates the expression and function of immune checkpoints (ICPs) and their ligands (ICPLs) in both immune and cancer cells. The concurrent presence of immunosuppressive cells, anergic effector cells, and immune evasion cancer cells significantly limits the effectiveness of immune checkpoint inhibitors (ICPIs).

The hypoxic conditions within the TME significantly modulate the function of immunosuppressive cell populations. Through mechanisms like increased lactate secretion and carbonic anhydrase-driven carbonic acid production, hypoxia lowers extracellular pH to between 5.8 and 6.5, creating an acidic environment. Vascular irregularities associated with hypoxic regions impede the influx of circulating T lymphocytes. Moreover, increased collagen levels in the hypoxic tumor stroma hinder the outward movement and penetration of CD8 + T lymphocytes [295]. In instances where tumor cells persist under acidic conditions, the presence of lactic acid diminishes the functionality of CD8 + T cells by reducing their viability, proliferation rate, cytolytic activity, and secretion of proinflammatory cytokines [296–298]. Furthermore, the development of dendritic cells crucial for facilitating the proliferation of CD8 + T lymphocytes is impeded within an oxygen-deprived environment abundant in lactic acid [299]. Conversely, elevating the pH within the TME has the potential to relieve the suppression of T cells and increase the expression of IFN-γ in CD8 + T cells, thereby substantially enhancing the effectiveness of both active and adoptive immunotherapy strategies [300]. In instances of tumor hypoxia, continuous T cell receptor (TCR) activation expedites the transformation of effector CD8 + T cells into a state of exhaustion, facilitating the upregulation of immunosuppressive effector molecules [301].

Furthermore, in addition to its impact on T lymphocytes, HIF-1α hinders the functionality of NK cells by inhibiting the upregulation of key receptors involved in NK cell activation, including NKp46, NKp30, NKp44, and NKG2D [302]. Myeloid-derived suppressor cells (MDSCs), a distinct subset of immunosuppressive cells abundant in the hypoxic TME, diminish the activation of CD8 + T lymphocytes through the secretion of the inhibitory cytokines IL-10 and IL-6. Concurrently, the transcription factor HIF-1α upregulates the expression of the immune checkpoint molecules PD-L1 and PD-L2 on MDSCs, thereby transforming these cells into a central hub of immunosuppression [303]. M2-polarized TAMs are prevalent in hypoxic tumor environments and are driven by HIF-1α transcriptional programs that promote the transition from M1 to M2 polarization [304].

Treg cells present metabolic advantages in low-glucose, high-lactate environments. This metabolic advantage facilitates the promotion of peripheral immune tolerance and aids cancer cells in evading immune destruction within the TME [305]. Furthermore, hypoxia induces the build-up of the suppressive metabolite adenosine in Treg cells by facilitating the HIF-1α-mediated expression of the extracellular ATP-degrading enzymes CD39 and CD73 on Treg cells. The limitation of extracellular ATP restricts the activation of T cell receptors, whereas elevated levels of free adenosine suppress cytotoxicity by interacting with A2AR and A2BR receptors [306–308]. HIF-1α also regulates the degradation of the transcription factor forkhead box P3 (FoxP3), which physiologically converts effector T cells into Treg cells, thereby reducing the anticancer activity of tumor-infiltrating lymphocytes (TILs) [309].

Hypoxia directly regulates the expression and activity of ICP and its ligands. The PD-L1 promoter contains HREs and is a specific target of HIF-1α, which may be upregulated in hypoxic environments [303]. Research has demonstrated an increase in PD-L1 expression during the process of EMT, with PD-L1 signaling playing a role in sustaining EMT [310]. These findings indicate a reciprocal regulation between EMT and PD-L1, with EMT serving as a bridge between stemness and hypoxia. Furthermore, multiple investigations have revealed diverse interactions between PD-L1 and HIF-1α-dependent pathways, including the PI3K/mTOR [311] and NF-κB pathways(reviewed in [312]). Hypoxia impacts the structure and binding of ICP by inducing posttranslational modifications or modifying the lipid environment in which ICP is located. Additionally, various pathways influence the localization of ICP between the plasma membrane and endosomes, as discussed in a previous review [313].

In brief, hypoxia recruits and activates immunosuppressive cell subsets; elevates PD-1 expression on cancer, stromal, and immune cells; and facilitates the development of an immunosuppressive microenvironment within tumors. Consequently, tumors exhibit resistance to immune checkpoint inhibitor therapies under hypoxic conditions [314, 315].

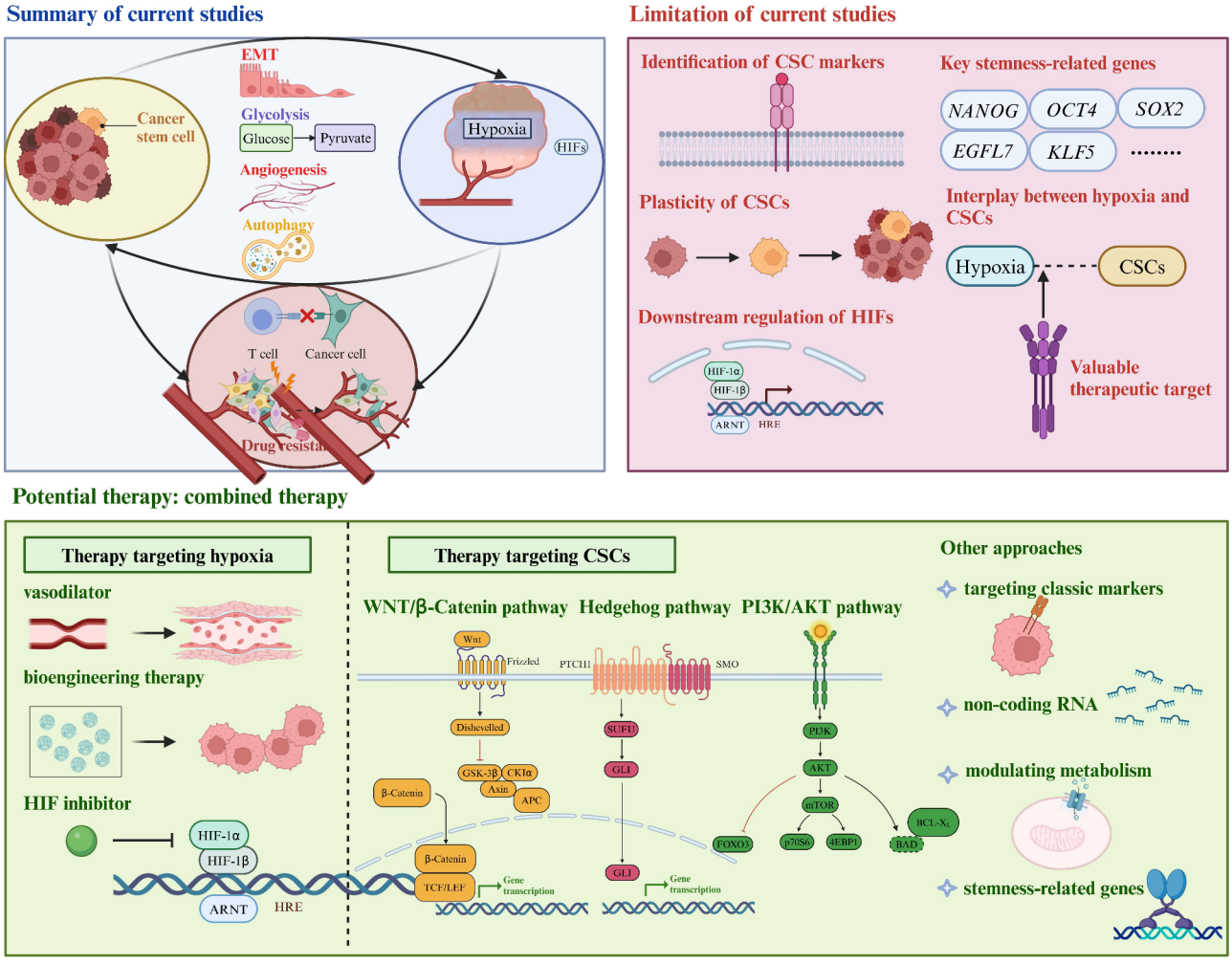

Fig. 4 The cross-relationship between hypoxia, stemness, drug resistance, current research deficiencies, and potential treatment therapy. The interplay between hypoxia and stemness is intricate, and both elements play significant roles in influencing drug resistance. Current research in this field is constrained by several factors, including the absence of optimal biomarkers, insufficient investigation into associated mechanisms, and the necessity to identify more appropriate therapeutic targets. There exist targeted therapies aimed at addressing hypoxia and CSCs; however, the majority of these therapies are still undergoing clinical trials. Notably, the most promising interventions tend to be combined therapy. Abbreviation: CSCs, cancer stem cells; EMT, EMT, epithelial-mesenchymal transition; HIFs, hypoxia-inducible factors

Perspective

Hypoxia triggers aggressive tumor traits, including metabolic reprogramming, apoptosis inhibition, autophagy initiation, enhanced migration, and angiogenesis. Additionally, hypoxic tumors exhibit increased resistance to chemotherapy and radiotherapy (Fig. 4). The impact of hypoxia on tumors extends beyond cancer cells to encompass other tumor-associated entities such as endothelial cells and immune infiltrating cells. The reactions of each constituent are intricately interconnected and collaborate to engender tumors that are more aggressive and resilient to standard treatments. Endothelial cells respond to hypoxia by releasing angiogenic factors, which contribute to the establishment of new vascular environments and sustain tumor stemness. Immune infiltrating cells exhibit reduced antitumor cytotoxicity, increased immune checkpoint protein expression, and increased levels of immunotolerant or immunosuppressive cells. Alterations in the immune microenvironment represent significant mechanisms underlying tumor immune evasion and immune resistance. Particularly in advanced or metastatic cancer, a hypoxic TME is frequently established and plays a pivotal role in cancer progression. Investigations on hypoxia have offered novel perspectives on its mechanisms and set the groundwork for targeted therapies with potentially improved outcomes. Nevertheless, owing to the intimate association between hypoxia and tumor stemness, achieving optimal outcomes solely with targeted therapies for hypoxia or stemness remains challenging [13].

Hypoxia impacts tumor cell behavior, initiating or exacerbating stemness-associated traits. Numerous targets

of HIFs have been identified, with alterations in glucose metabolism, angiogenesis, increased autophagy, and activation of the EMT program being extensively linked to tumor stemness. Conversely, increased tumor stemness increases cancer cell survival, as increased metabolism and self-renewal can lead to local hypoxia. The reciprocal stimulation of hypoxia and CSCs establishes a positive feedback loop, rendering the tumor more resilient to conventional treatments. With respect to drug resistance mechanisms, hypoxia and CSCs comparably contribute to tumor resistance. ABC transporters facilitate drug efflux, whereas the modulation of apoptosis pathways, autophagy induction, and ROS clearance are common drug resistance mechanisms. Within the hypoxia regulatory network, molecules such as glycolytic enzymes, GLUTs, Snail, Twist, Zeb1, and other transcription factors are linked to drug resistance. This occurs either by reinforcing glycolytic and EMT pathways to enhance tumor stemness or through direct involvement in resistance mechanisms.

Given the significant impact of hypoxia on cancer development, interest in increasing oxygen levels within the TME as a potential therapeutic approach is increasing. However, the direct intravenous delivery of oxygen to cancer lesions is hindered by systemic exposure to ROS and the limited solubility of oxygen in the bloodstream. One proposed strategy to increase the oxygen supply involves augmenting blood flow to the tumor via vasodilatory drugs; however, practical challenges exist in how to effectively modulate blood perfusion to the tumor tissue [316]. To address this obstacle, researchers are utilizing nanoscale and bioengineering methodologies to facilitate the targeted delivery of oxygen to specific tumor sites, thereby increasing the efficacy of chemotherapy, radiation therapy, and immunotherapy [317, 318]. However, nearby healthy cell destruction is an inevitable consequence. Another effective approach is to block the activation of HIFs and their associated genes. Compounds that inhibit HIF-1α, such as topotecan and bortezomib (PS-341), as well as HIF-2α inhibitors, such as PT239, PT2385, and PT2977, have been shown to suppress the activity of HIF1/2α and the expression of their downstream genes. Clinical trials are also investigating the inhibition of downstream targets of HIF to achieve anticancer effects (Supplementary Table 1). The aggressive biological characteristics of CSCs are supported by a complex interplay of various signaling pathways, suggesting the potential importance of focusing on traditional pathways in the treatment of CSCs. Preclinical studies have confirmed the viability of targeting signaling pathways within CSCs. ICG-001, an inhibitor of the WNT signaling pathway, effectively diminishes the stemness and metastatic characteristics of colorectal cancer cells by inhibiting the expression of the downstream target gene of the WNT pathway, Myeloid Ecotropic Viral Insertion Site 1 (MEIS1) [319]. In a similar vein, pharmacological agents that target the Notch, hedgehog, PI3K/AKT, and NF-κB signaling pathways have demonstrated potential utility in addressing tumor resistance [320–323]. Cell surface markers, including CD13, CD44, and CD133, as well as intracellular markers, such as Nanog, ALDH1, and SOX2, serve as effective indicators for the identification of rare populations of CSCs. These markers are significant targets for the eradication of the diverse malignant biological behaviors exhibited by CSCs [324, 325]. In addition to focusing on the markers, signaling pathways, and niches associated with CSCs, alternative strategies for the eradication of CSCs may involve the modulation of genes related to stemness, the alteration of aberrant metabolic processes, and the manipulation of non-coding RNAs, among other approaches [326, 327]. Further research is required at the genetic, epigenetic, proteomic, and metabolic levels to identify potential targets for CSCs, helping to develop new therapies that are more effective to the existing challenge of cancer drug resistance [328].

The identification of CSC-specific antigens or biomarkers remains a challenge. Cell surface markers, especially transport proteins and signaling receptors, have attracted considerable interest because of their potential to enhance diagnostic capabilities and enable the targeted delivery of therapeutic agents to CSCs [329]. However, the non-specificity and low abundance of these markers present substantial barriers to their practical application. Currently identified surface markers do not exhibit specificity for any particular CSC type, as they are also expressed on non-CSCs or healthy cells, albeit at reduced levels [330]. Despite extensive research on the relationship between hypoxia and tumor stemness in recent years, the expected broad use of medical drugs aimed at these factors has not occurred as anticipated. Many studies have focused only on establishing correlations between hypoxia and tumor stemness rather than delving into the underlying mechanisms involved. For example, the key regulators of hypoxia, HIFs, govern a multitude of target genes, prompting inquiries about the potential presence of additional regulators in addition to HIFs. Similarly, while numerous stemness-related genes are actively expressed in CSCs, the intricate interactions among them that ultimately contribute to the stemness phenotype remain unclear. Furthermore, the possibility of undiscovered stemness-related genes and understanding the full functions of known stemness-related genes necessitates further investigation. Moreover, tumor stemness and hypoxia mutually reinforce each other. Therapies focused solely on hypoxia often fail to achieve optimal outcomes because they neglect the regulatory influence of local tumor hypoxia. Conversely, treatments

that focus on tumor stemness often overlook the importance of regulating hypoxia. Hypoxia in tumors is highly heterogeneous and lacks a sensitive detection method, posing challenges in identifying potential patient populations for hypoxia-targeting drugs. Recent investigations have revealed that CSCs exhibit plasticity, allowing for phenotypic alterations under particular conditions. Nevertheless, contemporary research concerning the microenvironment and CSCs predominantly depends on tumor implantation studies in murine models. These models are unable to accurately mimic the microenvironment of primary tumors or the interactions between human CSCs and their respective microenvironments, thereby imposing certain constraints on the findings [14]. Consequently, addressing these complexities is crucial for advancing the development and efficacy of therapies targeting hypoxia and tumor stemness.

The divergent findings presented in numerous studies underscore the necessity for further exploration of the interplay between hypoxia, CSCs and drug resistance. For example, the variability in ROS levels among different types of CSCs raises questions about whether diminished ROS levels can entirely explain the preservation of the stem cell phenotype, particularly in light of the altered glucose metabolism characteristic of these cells [53, 54]. Indeed, numerous conclusions remain to be substantiated across various types of CSCs, as their characteristics are not entirely uniform. Furthermore, the function of autophagy in the drug resistance exhibited by CSCs remains ambiguous. Some viewpoints propose that autophagy may serve a dual role in this context, prompting inquiries into the observed elevation of autophagy levels in hypoxic environments [331].

Emerging technologies such as organoids, three-dimensional (3D) printing technology, AI-driven drug discovery, single-cell transcriptomics, and CRISPR/Cas9 gene editing are significantly advancing the ability to target both hypoxia and CSCs, two key factors driving tumor progression and therapy resistance. The simulation of TME and the interactions between CSCs and the TME present significant challenges that impede current research efforts. Organoids and 3D printing technology hold considerable potential for accurately replicating the in vivo environment. These advanced methodologies can yield critical insights into the impact of hypoxia on CSCs and offer a platform for the development of personalized therapeutic strategies. AI-driven drug discovery accelerates the identification of compounds that can simultaneously target hypoxia-induced signaling pathways and CSCs, while single-cell transcriptomics enables the detailed profiling of gene expression at the single-cell level, revealing new molecular drivers of stemness under hypoxic stress. Furthermore, the advancement of single-cell transcriptomics and associated cell isolation methodologies has made it possible to explore more efficient approaches for the isolation and identification of CSCs, as well as to discover additional significant protein markers. The CRISPR/Cas9 gene editing technology is especially valuable for elucidating the molecular mechanisms that govern the relationship between hypoxia and cancer stem cells. This approach facilitates the identification of novel therapeutic targets and potential mechanisms of resistance. These advancements are paving the way for more effective, targeted therapies that address the complexities of hypoxia and CSCs, with the potential to overcome resistance and reduce tumor relapse.

Conclusions

This review highlights the complex interplay among hypoxia, stemness, and drug resistance. The induction of tumor stemness within a hypoxic microenvironment complicates the efficacy of tumor treatments, while the mechanism by which hypoxia triggers tumor stemness offers insights for targeted therapeutic approaches. As HIFs serve as primary regulators of oxygen homeostasis under hypoxic conditions, targeting HIFs and their downstream pathways has emerged as a promising strategy in cancer treatment. The stabilization of HIFs in hypoxic cancer cells prompts the expression of specific target genes encoding proteins involved in processes such as angiogenesis, metabolic alterations, EMT, metastasis, and autophagy, thereby influencing tumor stemness. These proteins play crucial roles as mediators of hypoxia and stemness, and inhibiting their activity through targeted therapies has the potential to overcome tumor resistance. It is essential to utilize emerging technologies to model the interactions between the hypoxic TME and CSCs. Furthermore, it is viable to investigate novel markers and genes associated with CSCs, as well as to explore regulatory targets related to hypoxia or identify new hypoxia-inducible factors.

Abbreviations

ABC	ATP-binding cassette
ABCG2	ATP-binding cassette subfamily G member 2
ADCC	Antibody-dependent cell-mediated cytotoxicity
AGGF1	G-patch and FHA domains 1
ANGPT-2	Angiopoietin-2
ATGs	Autophagy-related genes
ATM	Ataxia-telangiectasia mutated
BER	Base excision repair
BIRC5	Baculoviral inhibitor of apoptosis repeat containing 5
CAFs	Cancer-associated fibroblasts
CD44s	CD44 subtype
CHK1	Checkpoint kinase 1
CMA	Chaperone-mediated autophagy
CSCs	Cancer stem cells
CTL	Cytotoxic T lymphocyte
CXCL-12	Chemokine C-X-C motif ligand-12
CXCR4	C-X-C Chemokine Receptor Type 4
DC	Dendritic cell
DDR	DNA damage response
DSB	Double strand breaks

ECM	Extracellular matrix
EGFL7	EGF-like domain 7
EMT	Epithelial-mesenchymal transition
EMT-TFs	Transcription factors associated with epithelial-mesenchymal transition
ENO	Enolase
ER	Estrogen receptor
ETC	Electron transport chain
5-FU	5-fluorouracil
FoxP3	Forkhead box P3
GLUT	Glucose transporter
GPR49	G-Protein Coupled Receptor 49
GPR67	G-Protein Coupled Receptor 67
GSCs	Glioblastoma stem cells
HCAM	Homing Cell Adhesion Molecule
HIFs	Hypoxia-inducible factors
HK	Hexokinase
HNSCC	Head and neck squamous cell carcinoma
HR	Homologous recombination
HREs	Hypoxia response elements
IAPs	Inhibitors of apoptosis family proteins
ICP	Immune checkpoints
ICPI	Immune checkpoint inhibitors
ICPLs	The ligands of immune checkpoints
JAK	Janus Kinase
KLF5	Krüppel-like factor 5
LDH	Lactate dehydrogenase
lncRNAs	Long non-coding RNAs
MACC1	Metastasis-associated colon cancer 1
MDR	Multidrug resistance
MDSCs	Myeloid-derived suppressor cells
MHC-I	Major histocompatibility complex class I
MRN	MRE11-RAD50-NBS1
MRP1	Multidrug resistance-associated protein 1
MSCs	Mesenchymal stem cells
NER	Nucleotide excision repair
NHEJ	Non-homologous end joining
NK	Natural kill
OCT4	Octamer-binding transcription factor 4
OXPHOS	Oxygen-dependent mitochondrial oxidative phosphorylation
PDH	Pyruvate dehydrogenase
PDK1	Pyruvate dehydrogenase kinase 1
PFKFB	6-fructose-2-phosphate kinase
PGF	Placenta growth factor
PGK1	Phosphoglycerol kinase 1
Pgp-1	Phagocytic Glycoprotein-1
PHGDH	Phosphoglycerate dehydrogenase
PK	Pyruvate kinase
PKM2	M2 pyruvate kinase
PRR	Post-replication repair
ROS	Reactive oxygen species
SCF	Stem cell factor
SOCS1	Suppressor of cytokine signaling 1
SOD2	Superoxide dismutase 2
SOX2	SRY-box 2
STAT3	Signal transducer and activator of transcription 3
TAMs	Tumor-associated macrophages
TCA	Tricarboxylic acid
TCR	T cell receptor
TILs	Tumor-infiltrating lymphocytes
TME	Tumor microenvironment
Treg cells	Regulatory T cells
ULBP	UL16-binding protein
VEGF	Vascular endothelial growth factor
VHL	Von Hippel-Lindau

Supplementary Information

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Supplementary Material 1

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Author contributions
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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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