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Review article

Hypoxia inducible factors in the tumor microenvironment as therapeutic targets of cancer stem cells

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ABSTRACT

Cancer stem cells (CSC) constitute a small area of the tumor mass and are characterized by self-renewal, differentiation and the ability to promote the development of secondary chemo-resistant tumors. Self-renewal of CSCs is regulated through various signaling pathways including Hedgehog, Notch, and Wnt/β-catenin pathways. A few surface markers have been identified, which provide a means of targeting CSCs according to tumor type. Depending on the proximity of CSCs to the tumor hypoxic niche, hypoxia-inducible factors (HIFs) can play a critical role in modulating several CSC-related characteristics. For instance, the upregulation of HIF-1 and HIF-2 at tumor sites, which correlates with the expansion of CSCs and poor cancer prognosis, has been demonstrated. In this review, we will discuss the mechanisms by which hypoxia enhances the development of CSCs in the tumor microenvironment. Targeting HIFs in combination with other common therapeutics is pre-requisite for effective eradication of CSCs.

1. Introduction

The tumor microenvironment consists of cancer, perivascular, endothelial and other cells that provide immunosuppressive signals that compromise the activity of tumor-infiltrating leukocytes by various mechanisms [1]. Cancer cells use various mechanisms to evade anti-tumor immune responses. It has been shown that the lack of efficient oxygenation within the tumor center induces hypoxia and hypoxia-related factors, which correlate with tumor progression [2]. Although hypoxia is one of the important escape mechanisms within the tumor microenvironment, it should be noted that hypoxia generation is a function of tumor growth and it is a physiological effect of fast growth and not enough circulation. Hypoxia extensively shapes the tumor microenvironment by modulating the transcription of hundreds of genes, which regulate tumorigenesis, angiogenesis, invasion, metastasis, drug-resistance, and immune suppression. Hypoxia-inducible factor-1 (HIF-1) is an important transcription factor induced in tumor cells following oxygen deficiency, which plays a critical role in several tumor-promoting processes regulating cancer cell survival and cancer progression. HIF-1 consists of two subunits, HIF-1α and HIF-1β; HIF-1β is constitutively expressed, whereas expression of HIF-1α is oxygen-dependent and induced in response to acute hypoxic conditions. There are two HIFα subunits, HIF-1α and HIF-2α. Although they are homologous and bind to similar hypoxic response elements (HREs), there are some structural differences between isoforms. For example, the N-terminal transactivation domain (N-TAD) is variable between HIF-1α and HIF-2α and increases the expression of target genes which are specific in each subunit, however, (C-TAD) contributes to target genes that are common between HIF-1α and HIF-2α [3]. On the other hand, HIF-1α preferentially increases the expression of genes that are involved in the glycolytic pathway, and HIF-2α is contributed to the regulation of genes crucial for cell cycle progression, tumor growth, and maintaining stem cell pluripotency, like stem cell factor OCT-3/4 and the proto-oncogene c-Myc [4,5]. HIF factors are involved in several

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tumor-promoting processes such as survival, proliferation, angiogenesis, invasion, metastasis and tumor recurrence via differentiation of cancer stem cells (CSCs) [6,7]. CSCs (also known as tumor-initiating cells) are present in various cancers and can enhance tumor onset, progression, and metastasis [8]. Expression of various embryonic factors such as Sox2, Nanog, and Oct4 by CSCs enhances properties such as embryogenesis, pluripotency, and self-renewal [9]. There is evidence that indicates the role of HIF-1α and HIF-2α in CSC-induced cancer-growth and recurrence. Accordingly, it has been demonstrated that direct binding of HIF-2α to the HRE located in the promoter regions enhances expression of Sox2, Nanog and Oct4 [10]. CSCs can be discriminated from other cells by expression of some surface molecules such as CD133, CD24, and CD44. Consequently, HIFs control CD133 promoter activity and increase the proliferation of CD133-expressing CSCs [11]. Although the precise molecular mechanisms that drive the development of CSCs by HIFs are not completely understood, targeting hypoxia-related factors is a potential strategy for inhibiting CSC-associated cancer recurrence and chemo-resistance. In this review, we will discuss the role of hypoxia and HIFs in the growth and development of CSCs and their potential as therapeutic targets for the eradication of CSCs and suppression of cancer recurrence. (see Table 1)

2. HIF and cancer progression

Tumorigenesis is a complex and multi-step process, which is related in part to the interplay between several tumor-driving metabolic pathways, factors, and cells and the development of the tumor microenvironment. The rapid proliferation of cancer cells in combination with inefficient blood supply leads to oxygen deficiency in the tumor center. To compensate oxygen deficiency and adaptation within the tumor microenvironment, cancer cells use various metabolic pathways such as activation of HIF factors, which are the most prominent regulators of oxygen homeostasis [12,13]. HIF factors consist of HIF-α and HIF-β subunits in which expression of the α-subunit is oxygen-dependent, whereas β-subunit is constitutively expressed [14,15]. In response to decreased oxygen levels, cancer cells in solid tumors express the HIF-1 transcription factor that induces expression of several factors involved in cancer progression: processes including extracellular matrix remodeling, angiogenesis, cell migration, metastasis, epithelial-mesenchymal transition (EMT), drug resistance, and maintenance of CSCs [16].

Angiogenesis is a prerequisite for tumor development and is robustly promoted by the upregulation of vascular endothelial growth factor (VEGF) at the tumor site. The expression of VEGF is strictly induced by HIF-1 upon the onset of hypoxia in the tumor microenvironment. This relationship has been confirmed by using a HIF-1α-deficient experimental model, which is associated with significant downregulation of VEGF expression. Moreover, HIF orchestrates the migration of endothelial cells to hypoxic areas to facilitate the generation of blood vessels to overcome oxygen deficiency [17,18].

In hypoxic tumors, anaerobic metabolism pathways are more prominent compared to oxidative phosphorylation to maintain ATP generation [19]. On the other hand, glucose metabolism is regulated in the hypoxic tumor microenvironment by HIF-1 as tumor cells express several HIF-1-regulated genes involved in glucose metabolism to adapt to oxygen deficiency [20]. Concomitantly, HIF-1 upregulates GLUT1 and GLUT3 glucose transporters, facilitates the conversion of glucose to pyruvate, and induces enzymes responsible for clearance of pyruvate [21,22]. In addition to the regulation of metabolic pathways, HIF can also modulate tumor-infiltrating immune cells. It has been shown that HIF-1α recruits and increases the function of suppressive cells including tumor-associated macrophages and myeloid-derived suppressor cells (MDSCs) in the hypoxic tumor microenvironment [23,24]. This recruitment is in part through upregulation of chemokines such as CCL5, CXCL12, and the cytokine VEGF, which attracts myeloid cells [25,26]. Induction of hypoxia-related signaling in MDSCs and tumor-associated macrophages by HIF leads to their recruitment into the tumor site and increases their suppressive function [27]. Following recruitment, tumor-associated macrophages secrete MMP-9, which upregulates VEGF in the tumor region and promotes tumor angiogenesis, metastasis and subsequently progression [25]. The suppressive effect of hypoxic tumor region on immune cells, particularly by HIF-1α, is associated with the upregulation of adenosine levels in tumor sites and adenosine receptors on tumor-infiltrating immune cells. Signaling of A2AR on T cells inhibits their proliferation and cytokine production [28,29]. HIF-1α also induces the expression of immunosuppressive molecules including programmed death-ligand 1 (PD-L1) on cancer cells and CTLA-4 on $CD8^+$ T cells, which reduce T cell-mediated anti-tumor responses [30]. Tregs are other hypoxia targets present in the tumor microenvironment. HIF-1α induces FoxP3 expression in T cells, thereby increasing the frequency and function of Tregs in the tumor microenvironment. Cancer cells secrete Treg-specific chemo-attractants such as TGF-β and CCL28, which recruit CCR10-, neuropilin-1- and CXCR10-expressing Tregs into the tumor microenvironment.

Intriguingly, cancer cells not only induce HIF signaling following hypoxic stress, but also they use various oxygen-independent pathways for promoting HIF expression, stability, and downstream signaling pathways. For example, the constitutive expression of oncogenes or mutation of tumor suppressor genes can activate HIF-1α in an oxygen-independent manner in the tumor microenvironment [31]. One of the HIF-regulating tumor suppressors, von Hippel-Lindau protein (vHL), regulates HIF expression via proteasomal degradation and ubiquitination in normoxic conditions. The hydroxylation of proline 402 and 564 in the human HIF1α is involved in its degradation. vHL in complex with elongin B and C recognizes hydroxylated prolines and then acts with neDD8 as an E3 ubiquitin ligase that alters HIF1α and targets it for degradation. Since Prolyl hydroxylases (PHDs) has low affinity to O2, HIF1α is not hydroxylated under O2 tension condition and becomes stabilized [32]. vHL ubiquitin ligase complex cannot undergo HIF-1 ubiquitination under hypoxic conditions; instead, it is translocated to the nucleus, where it forms a complex with HIF-1β. This is followed by upregulation of target genes via binding to the HRE in the promoter. The binding of C-TAD and co-activators CBP/p300 is mandatory for the expression of HIF-1α target genes. Loss of vHL expression in renal cancers leads to constitutive expression of HIF1α and HIF2α (even in normoxia) resulting in stimulation of target genes and loss of VHL-mediated tumor suppression [33]. Under normoxic conditions, factor inhibiting HIF-1 (FIH-1) promotes hydroxylation of C-TAD and blocks transcription of HIF-1α. On the other hand, hypoxic conditions inhibit hydroxylation and enhance transactivation of HIF-1α [34]. Therefore, the expression of HIF by CSCs under both hypoxic and normoxic conditions is considered advantageous, due to its ability to promote tumorigenesis and regulate the expression of over 100 tumor-associated genes.

3. Biological properties of cancer stem cells

CSCs constitute a small group of cells in tumors, which are mainly involved in cancer recurrence, metastasis, and chemo-resistance. CSCs exhibit various characteristics including self-renewal, asymmetric division, promotion of EMT and chemo-resistance. Based on cancer type, CSCs can be discriminated from other cells via expression of surface molecules including CD44, CD24, CD133, Lgr5, and CD166, which can be used to specifically target these cells [35]. Despite several hypotheses on the origin of CSCs, their precise origin remains elusive. However, it is assumed that they originate from normal tissue progenitor cells, differentiated somatic cells, or even from tumor cells. They were first detected in human acute myeloid leukemia (AML), and subsequently identified in several hematopoietic and solid tumors such as breast, colon, brain, lung, pancreas, liver, ovarian, melanoma, prostate, bladder, and head and neck [36].

CSCs can generate differentiated clones *in vitro*, and also regenerate

Table 1
Studies related to the role of HIFs in the induction and development of CSCs.

HIF	Molecular mechanism	Type of study	Cell lines	Major findings	Ref.
Induction of cancer stem cell markers					
HIF-2α	Hypoxia induces stem cell markers, including NANOG, c-MYC and OCT4.	In vitro In vivo	T4121 non-stem glioma cells BALB/c nu/nu mice	HIF2-α solely induces a CSC phenotype in glioblastoma.	[49]
HIF-1α HIF-2α	Hypoxia upregulates Sox-2, CD133, Bmi-1, nestin, and podoplanin	In vitro	SJ-1 and U87 cells	Hypoxia promotes stem-like tumor cell phenotype.	[51]
HIF-1α	HIF-1α regulates dedifferentiation of.$CD133^{-}CD15^{-}NESTIN^{-}$ cell into tumorigenic $CD133^{+}CD15^{+}NESTIN^{+}$GSCs.	In vitro In vivo	GL261 and U87 cells C57 female mice	Hypoxic microenvironment plays an important role in maintaining the GSCs stemness.	[52]
HIF-1α	Long-term hypoxia increases expression of CD133 and nestin.	In vitro	Spheroid culturesT78(mesenchymal subtype), T86 (classical subtype),T87 (proneural subtype)and T111 (mesenchymal subtype)	Hypoxia promotes the self-renewal of cancer stem cells.	[53]
HIF-2α	1. $CD133^{+}$ cells express higher HIF-2α levels compared to HIF-1α. 2. Growth at 7% oxygen increases the expression of the neural stem cell markers Oct4, CD133, nestin, and Sox2.	In vitro	Neurosphere-forming cultures MDNSC11, MDNSC20, and MDNSC23	7% O_2 induces the stem cell–like phenotype of CD133 + GB cells.	[54]
HIF-1α	Hypoxia increases stem cell marker CD133, Sox2 and Klf4.	In vitro	The GBM neurosphere lines HSR-GBM1 and HSR-GBM2	Hypoxia induces the stem-like population and increases the frequency of CD133-expressing cells.	[55]
HIF-2α	1. Hypoxia upregulates ABCG2 expression 2. Hypoxia upregulates stem cell factors, Oct4, CD133 and CD34 through the stimulation of the TGF-β/Smad2 signaling pathway.	In vitro	K562 (K562/WT) cell	Hypoxia promotes stemness properties and enhances multidrug resistance in leukemia cells	[56]
HIF-1α	1. Hypoxia increases the expression of stem cell markers on GRPs. 2. Exposure to hypoxic condition promotes IGF1R activation 3. HIF-1 increases the expression of IGF1 on GRPs.	In vivo In vitro	PC9 and HCC827 NOD/Shi-scid/IL-2Rcnull (NOG) mice	Activation of IGF1R has an important role in hypoxia-mediated resistance of NSCLC to gefitinib.	[58]
HIF-1α and HIF-2α	1. Under hypoxic condition HIF-1 and HIF-2 induce expression of OCT4 and sox2 2. Hypoxia-induced expression of OCT4 and SOX2 increases the promoter activity of CD133	In vitro	N417, NCI–H157, NCI–H358, and A549	CD133 + cells express high amount of stem cells factors, OCT4 and SOX2.	[59]
Hypoxia	Hypoxia-induced OCT4 is associated with resistance of NSCLC cells to gefitinib	In vitro In vivo	PC9 and HCC827 Seven-week-old female NOD/Shi-scid/IL-2Rcnull (NOG) mice	OCT4 is responsible for maintenance of lung CSCs and resistance of them to gefitinib	[60]
HIF-1α	HIF-1α expression is correlated with NANOG and OCT4 expression.	In vitro	Patients with elevated serum prostate-specific antigen	NANOG and HIF-1α co-operate in prostate carcinogenesis.	[61]
HIF-1α HIF-2α	1. Hypoxia upregulates expression of NANOG and oct3/4 2. Upregulation of NANOG expression was derived from NANOGP8 genes 3. Hypoxia induced expression of ABCG2 and CD44	In vitro	PC-3 DU145	Prostate cancer cells exhibit stem-like properties under hypoxia.	[62]
HIF-1α HIF-2α	Acute and chronic exposures to hypoxia induce SOX2 expression.	In vitro	PC-3, DU145 and LNCaP	SOX2 is a key mediator of hypoxia-mediated metastasis for prostate cancer.	[63]
HIF-1α	1. HIF-1α regulates the expression of LIF 2. Nanog, SOX2, GBX2 and OCT3/4, are modulated by LIF.	In vitro	Primary melanoma cell lines Mel Wei, Mel Juso and Mel Ho. Metastatic cell lines, Mel Im, Mel Ju, SKMel28, KMel3 and HTZ19d	LIF plays an important role in progression of melanoma.	[64]
Hypoxia	1. Hypoxia-induced Nanog can modulate expression of TGF-β 2. Nanog can regulate the immunosuppressive phenotype of Tregs and macrophages	In vitro In vivo	B16–F10 melanoma cell line C57BL/6 mice	Nanog has a critical role in hypoxia-mediated immunosuppression	[65]
CD44 and ALDH					
HIF-1α	HIF-1α increased the percentage of CD44 positive cells	In vitro	SUM-149 cells MDA-MB-231	CD44 expression is associated with stem-like breast cancer cells.	[68]
HIF-1α HIF-2α	1. Hypoxia induces the expression of CD44 2. CD44bright cells express high levels of Oct3/4 and Sox2	In vitro	ES-2 and OVCAR-3 ovarian cancer cell lines	Ovarian cancer cells upgrade their stem-like properties through up-regulation of stemness-related factors and behave more aggressively in hypoxic environment.	[69]
HIF-1α	1. HIF-1α activates Notch and TGF-β signaling in ALDH + cells. 2. HIF-1α upregulates Slug and Snail. 3. HIF-1α correlates with expression of OCT4 and Nanog stem cells factor in ALDH + cells.	In vivo	Female C57BL/6J mice	High ALDH activity is correlated with stem cell-like features such as self-renewal activity and metastasis.	[71]
HIF-2α	ALDH expression was correlated with the HIF-2α	In vitro In vivo	4T1, 67NR, 4TO7, TS/A EMT6, BT-474, MCF-7, ZR-75B, T-47D, SK-BR3, MDA-MB-435, 119 MDA-MB-231 and Hs578T Balb/c mice	Suppression of HIF-2α expression reduced self-renewal ability in ALDH-positive cells.	[72]

(*continued on next page*)

Table 1 (*continued*)

HIF	Molecular mechanism	Type of study	Cell lines	Major findings	Ref.
HIF-1α HIF-2α	HIF-dependent ALKBH5 overexpression resulted in reduced m6A modification of NANOG mRNA.	In vitro	MCF-7 MDA-MB-231, MDA-MB-435, T47D	ALKBH5 enriches BCSCs in the hypoxic tumor microenvironment	[73]
Adenosine/STAT3/IL-6 pathway					
HIF-1α	Hypoxia increased expression of A2BR and enhanced expression of NANOG and IL-6 by phosphorylation and activation of PKCδ and STAT3.	In vitro In vivo	MCF-7 MDA-MB-231 SUM149 SUM159 SCID mice	A2BR stimulates PKCδ–STAT3 signaling, which is essential for hypoxia-mediated enrichment of BCSC.	[80]
HIF-1α	1. HIF-1α activates STAT3 in JAK-mediated manner. 2. Hypoxia-induced VEGF release is essential for activating STAT3	In vitro In vivo	FVB-NJ mice HGG tissue derived from CNS tumors in S100β-v-erbB/p53 − / − mice	STAT3 induces glioma stem cell self-renewal under hypoxic condition.	[83]
HIF	IL-6 induces stem cell markers such as Nanog, Oct4 CD133, and ALDH, by upregulating the HIF transcription factor.	In vitro	Cisplatin-resistant NSCLC cell lines, A549CisR and H157CisR	IL-6-induced HIF expression enhances stemness during cisplatin resistance development.	[84]
HIF-1α	1. HIF-1α regulates the expression of Nanog 2. Nanog increases the phosphorylation of STAT3	In vitro	IGR-Heu lung carcinoma cell line	Nanog is an important factor which is related to hypoxia-mediated resistance of cells to Ag-specific lysis	[85]
IL-6 and HIF-1α	Hypoxia and IL-6 signaling enhances the expression of C/EBPδ	In vitro In vivo	MDA-MB-231 MDA-MB-468 SUM159	C/EBP δ promotes cancer cell dedifferentiation, mesenchymal transition, and stem cell-like features.	(139)
Hypoxia	Hypoxic microenvironment induces the expression of STAT3	In vitro	MDA-MB-231	Hypoxia-induced STAT3 has an important role in the acquisition of stem cell properties in RU cells	(140)
MAPK/ERK signaling pathway					
HIF-1α	Hypoxia and EGFR signal upregulate SCF through HIF-1α	In vitro	MCF-7	HIF-1α-induced expression of SCF promotes angiogenesis.	[86]
HIF-1α	IL-1β induces HIF-1α activation and SCF production through PI3K/ mTOR pathway	In vitro	MCF-7 THP-1 human myeloid cells	IL-1β induces the production of the major hematopoietic growth factor (SCF) via the HIF-1 transcription	[87]
HIF-1α	1. Glutathione enhances nuclear translocation of FoxO3 which upregulates NANOG 2. Glutathione can promote FoxO3 activity through inhibition of MEK1-ERK signaling	In vitro	MDA-MB-231 SUM-149	HIF-1–induced glutathione synthesis mediates chemotherapy-induced CSC enrichment.	[88]
HIF-1α HIF-2α	1. HIFs induce the expression of GSTO1 2. Overexpression of GSTO1 induces KLF4, NANOG, and SOX2 expression. 3. GSTO1 augments cytosolic Ca2 + levels via activating PYK2/SRC/STAT3 signaling	In vitro	MCF-7, HCC1954, MDA-MB-231, SUM-149	Overexpression of GSTO1 increases the percentage of ALDH + cells, expression of pluripotency factors and induced BCSC.	[89]
HIF-1	1. DUSP9 and DUSP16 regulated by HIF-1 through inactivation of ERK and activation of p38 MAPK signaling pathways. 2. Inhibition of ERK caused transcriptional induction of Nanog through decreased inactivating phosphorylation of FoxO3. 3. Activation of p38 stabilized Nanog and Klf4.	In vitro In vivo	MDA-MB-231, MCF-7, SUM-149 SCID mice	MAPK signaling contributes to chemotherapy-induced BCSC enrichment.	[90]
HIF-1α	Hypoxia activates the PI3K and MAPK pathways in the CSCs by augmenting phosphorylation of Akt, ERK and p70S6-kinase	In vitro	X01 (derived from a woman with a GBM) X02 (originated from a man with GBM) X03 (derived from a woman with anaplastic oligoastrocytoma)	HIF-1α induces the self-renewal in CD133-expressing cells.	[91]
HIF-2α	1. HIF-2 can regulate the expression of prostatic acid phosphatase (PAP) 2. PAP-derived adenosine activates A2BRs. 3. PAP also activates Akt/Erk-1/2 signaling via activating A2BR.	In vitro In vivo	GL1GSC U87GSC NT1NSC Nude rats	PAP is induced GSCs during hypoxia and promote tumorigenesis of potential of GSCs.	[92]
HIF-1α	CAFs activate the HIF-1α/β-catenin signaling pathway through regulating the expression of HIF-1α.	In vitro	LNCaP	CAFs increases aggressive potential of prostate cancer stem cells through a HIF-1α/β-catenin pathway.	[93]
HIF-1α	1. CAFs increase IL-6 receptor and CXCR4 expression and ROS content of PC3 cells. 2. CAFs regulate MAOA/mTOR/HIF-1α pathway in PC3 cells.	In vitro	PC3	Curcumin inhibits ROS production and IL-6 receptor and CXCR4 expression in PC3 cells.	[94]
HIF-1α	1. Hypoxia increases expression of VEGF, IL-6, CSC markers including Oct4, Nanog, and EZH2, 2. Hypoxia increases the expression of miR-21.	In vitro	PC-3 LNCaP	CDF targets the expression of miR-21, miR-210, HIF-1α and CSC markers. CDF also suppresses the hypoxia-mediated IL-6 and VEGF production.	[95]

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Table 1 (*continued*)

HIF	Molecular mechanism	Type of study	Cell lines	Major findings	Ref.
HIF-1α	1. MAOA stimulates HIF-1α/VEGF-A/AKT signaling pathway. 2. MAOA decreases PTEN expression in prostate cancer patients.	In vitro In vivo	Human PCa LNCaP and 22RV1 cells	MAOA expression promotes prostate cancer development by increasing cell proliferation and CSCs.	[96]
NOTCH and WNT signaling pathway					
HIF-1α	HIF-1α stabilizes NICD, and increases the expression of Notch downstream genes, including Hey2 and Hes1,and increases the Notch Delta ligand DLL1, through direct binding to NICD.	In vitro	C6 (rat) U251, A172, U87MG (human)	HIF-1α-mediated stimulation of Notch signaling is required for hypoxia-induced maintenance of GSC	[97]
HIF-1α and HIF-2α	HIF-2α interacts with NICD and suppresses Notch signaling. HIF-1α upregulates Notch-responsive genes	In vitro	Human Glioma tissues	HIF-1α and HIF-2α modulate Notch signaling in GSCs based on different oxygen tensions.	[98]
HIF-1α	HIF-1α enhanced Notch-induced Hes1 expression by preventing Hes1 from binding to the N-box of Hes1 promoter.	In vivo	B10.BR mice BALB Rag2//c mice AML patients	HIF-1α -Notch interaction is essential for maintaining CSCs.	[99]
HIF-1α	Hypoxic niches support Wnt signaling, through HIF-1α-mediated transcription of β-catenin.	In vivo	human T-ALL samples C57BL/6, NOD/Scid/Il2rg−/− (NSG) mice	HIF-1α and Wnt/β-catenin signaling promotes stem cell function in T-ALL.	[100]
HIF-1	1. NICD1 expression is increased under hypoxic condition 2. Hypoxia-induced NICD1 is associated with increasing the SOX2 promoter activity	In vitro	A2780, SKOV3, and PA-1	hypoxia-NOTCH1-SOX2 signaling pathway is responsible for induction of stem cells properties in ovarian cancer	[101]
HIF-2α	1. HIF-2α induces the expression of stem cell markers, NANOG, c-Myc, and OCT4. 2. HIF-2α activates Notch signaling and Wnt pathway	In vitro In vivo	MCF7 MDA-MB231 BALB/c (nu/nu) mice	HIF-2α promoted stem-like properties and induced resistance to PTX.	[102]
Other mechanisms					
HIF-1α	1. HIF-1α increases the expression of TAZ. 2. HIF-1α stimulates transcription of the SIAH1 and increases ubiquitination and degradation of LATS2	In vitro In vivo	MCF-7 and MCF-10A MDA-MB-231 MDA-MB-435 SCID mice	TAZ expression is essential for maintenance of BCSCs	[104]
HIF-1α	ITGA6 is a HIF-dependent target gene	In vitro	polyoma middle T(MMTV-PyMT), MDA-MB-231	ITGA6 regulates stem-like phenotypes and tumor cell invasion	[105]
HIF-1α	1. HIF-1α can regulate PAX3. 2. PAX3 represses p53 expression through binding to the its promoter.	In vitro	Human BGSCs	HIF-1α regulates PAX3/p53 axis, which is a critical mechanism for modulating migration, self-renewal, and tumorigenesis of GSCs	[106]
HIF	HIF regulates the expression of MCT4.	In vitro	HSR-GBM1 and JHH-GBM10 cell lines	MCT4 overexpression is associated with proliferation and survival of GBM stem-like cells.	[107]
HIF-2α	MLL1 regulates the expression of HIF-2α and HIF-2α targets VEGF.	In vitro	Human brain tumor patient specimens	MLL1 increases GSC self-renewal, growth, and tumorigenicity.	[108]
HIF-1α HIF-2α	HIF1α and HIF2α regulate CDH5 level in GSCs.	In vitro	Brain tumor samples	CDH5 expression was upregulated in GSCs under hypoxia and correlated with tumor grades.	[109]
HIF-1α	1. BCR-ABL upregulates HIF-1α and its downstream genes in BCR-ABL-expressing LSK cells. 2. Deletion of HIF-1α elevated expression of p16Ink4a and p19Arf in LSCs	In vivo	HIF1α flox/flox C57BL/6J, Vav1-Cre-C57BL/6J, C57BL/6J-CD45.1and C57BL/6J-CD45.2 mice	HIF-1α plays an important role in CML development and maintenance of LSCs.	[111]
HIF-1	miR-21 increases the expression of P-gp by targeting HIF-1α	In vitro	A2780 cell lines	Expression of miR-21 is associated with resistance of ovarian cancer cell lines to paclitaxel	[113]
HIF-1	1. HIF-1 induces the expression of SIRT1 through NF-κB signaling pathway	In vitro In vivo	SKOV3 and HO8910 cell lines Female athymic BALB/c nu/nu mice	HIF-1-induced SIRT1 is correlated with the promotion of cancer stem cell-like properties.	[115]

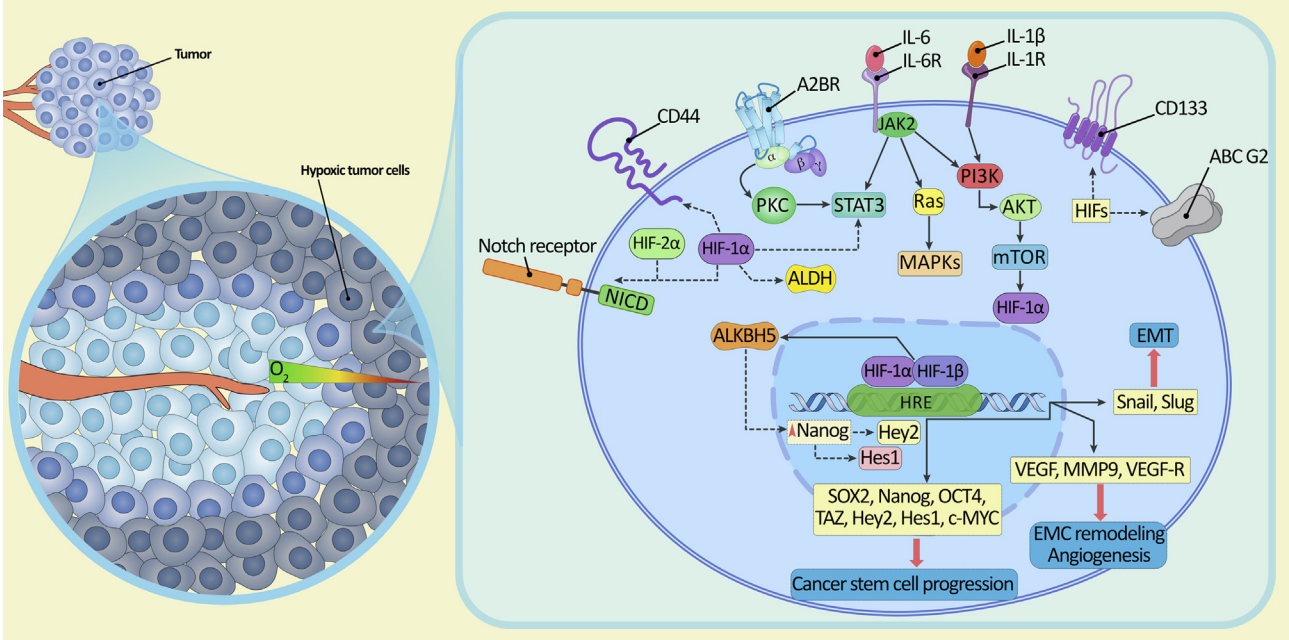

Fig. 1. Molecular pathways activated in cancer stem cells under hypoxia in tumor microenvironment. In the tumor microenvironment blood vessels often do not function properly which results in poor O_2 supply to the center of tumor region. Following activation, HIF-1α and HIF-2α translocate to the nucleus and make a complex with HIF-β in cancer cells under hypoxic condition, which leads to expression of several downstream genes involved in CSCs development, self-renewal, expression of stemness factors, induction of angiogenic factors, and upregulation of stem cell markers including CD44 and CD133. Stimulation of PI3K/Akt/mTOR pathway enhances the stabilization of HIF-α. Induction of STAT3 in a jak-mediated manner or through stimulation of adenosine receptor 2B enhances the expression of interleukin 6 and Nanog, which is associated with cancer stem cell phenotype. Stabilization of notch intracellular domain (NICD) by HIF-1α and HIF-2α leads to the upregulation of Notch-responsive genes. HIFs: hypoxia-inducible factors, PI3K: Phosphatidylinositol 3-kinase, mTOR: mammalian target of rapamycin, VEGF: vascular endothelial growth factor, ALDH: Aldehyde dehydrogenase, ABCG2/BCRP: breast cancer resistance protein, MAPK: mitogen-activated protein kinase.

tumor bulk in immunodeficient animals [37]. Signals derived from tumor microenvironment can induce differentiation of CSCs into cancer cells. Interestingly, other signals from the tumor microenvironment promote the differentiation of cancer cells into CSCs [38]. There are various factors including niche cells and cytokines in the CSC niche, which induce CSC development. T helper (Th) cells and tumor-associated macrophages release TNFα and induce NF-κB signaling in CSCs present in the inflammatory CSC niche, leading to upregulation of factors such as *Twist*, *Snail*, and *Slug*, EMT and CSC self-renewal [39,40].

Nanog, Oct4, and *Sox2* are three main transcription factors, which are critically involved in self-renewal and pluripotency of embryonic stem cells (ESCs) and CSC-like cells (CSCLCs). The upregulation of these factors has been demonstrated in various cancer types and associated with tumorigenesis, transformation, and metastasis [41]. Among these factors, *Oct4* inhibits apoptosis and increases the proliferation of CSCLCs partly via the Oct4-TCL1-AkT1 pathway [9,42]. On the other hand, *Nanog* upregulates CD44, CD133, ALDH1A1, and ABCG2 in CSCs, promoting survival and drug resistance in these cells [43]. Besides, the upregulation of *Sox2* enhances tumorigenesis and sphere formation by CSCs [44].

Notch, Wnt/β-catenin, and *Hedgehog* are the main signaling pathways involved in the regulation of CSC. Wnt/β-catenin, which is a pivotal signaling pathway for tumorigenesis, is the most critical pathway for regulating CSCs self-renewal. In the absence of ligand binding with the Wnt receptor, β-catenin generates the APC-degrading complex in the cytoplasm. On the other hand, stimulation of Wnt signaling stabilizes β-catenin and leads to its association with TCF/LEF and upregulation of target genes including *CCND1/2, Sox4, c-MYC, TCF7, Axin2, LGR5,* and *ASCL2*. Accordingly, blockade of the Wnt/β-catenin pathway leads to the downregulation of CSCs maintenance [45].

In addition to exerting critical effects on the regulation of embryogenesis, differentiation, proliferation, and apoptosis, Notch signaling is also required for self-renewal of CSCs. Following ligand binding, ɣ-secretase and metalloprotease cleave Notch receptors and deliver the active Notch intracellular domain (NICD) to the cytosol. Translocation of NICD to the nucleus and its binding with the core binding factor-1 (CBF-1) leads to the expression of downstream genes such as HES family genes, HEY family genes, and NRARP [46,47].

Constitutive signaling of the Hedgehog pathway can lead to tumorigenesis. While the Smo receptor induces the Hedgehog signaling pathway, the Patched receptor blocks it. Expression of Hedgehog target genes leads to the development of CSCs and tumor progression. Therefore, targeting these three pathways involved in the generation and development of CSCs should be therapeutic strategies for suppressing cancer recurrence.

4. Hypoxia and CSCs

Hypoxia and HIF factors can exploit various mechanisms to affect the induction and development of CSCs. These factors may promote the propagation of CSCs through induction of CSC markers, CD44 and ALDH, adenosine/STAT3/IL-6 pathway, MAPK/ERK pathway, NOTCH and WNT signaling, or other mechanisms.

4.1. Induction of cancer stem cell markers

CSCs in various cancers can be identified by the expression of various surface-expressed markers. Several studies indicate HIFs can induce the expression of CSC markers.

CSCs in glioblastoma (GBM), which are also known as GBM stem cells (GSCs), participate in tumor recurrence and progression. It has been demonstrated that hypoxic conditions can induce a GSC phenotype and enhance the expression of GSC associated markers. While both the GSCs and neural progenitor cells express HIF-1α, HIF-2α is only expressed by GSCs. Interestingly, HIF-2α is expressed in GSCs in both

acute hypoxic and normoxic conditions, which shows it can act in an oxygen-independent manner. Therefore, HIF-2α may be considered as a GSC-specific marker [48]. Consequently, transfection of non-stem glioma cells (T4121) with HIF-2α led to the induction of major stem cell markers, including Oct4, Nanog and c-MYC indicating that HIF-2α is a pivotal transcription factor for inducing a GSC phenotype [49]. $CD133^+$ cells purified from human brain tumors have stem cell features, which implies that CD133 can be used as a GSC marker (Fig. 1). $CD133^+$ cells can also induce tumor formation in the brains of NOD-SCID mice [50]. The frequency of $CD133^+$ cells and concomitant upregulation of various stem cell markers such as Klf4, nestin, Sox2, and Oct4 can also be induced in hypoxic conditions. There is evidence that HIF-1α can regulate de-differentiation of more than 95% of residual differentiated cells ($CD133^-CD15^-NESTIN^-$) to tumorigenic GSC-like cells ($CD133^+CD15^+NESTIN^+$) and play an important role in maintaining of GSCs stemness feature [51–53]. Besides, while hypoxia induces both the HIF1 and HIF2 in $CD133^+$ cells, expression levels of HIF-2α are significantly higher than HIF-1α in these cells [54]. However, self-renewal of CD133-expressing GSCs is linked to the upregulation of HIF-1α under hypoxic conditions and silencing HIF-1α suppressed expansion of these cells [55]. Moreover, the culture of multidrug resistant CML K562/DOX cells under hypoxic conditions led to the expression of stem cell markers including CD133, CD34, and Oct4 by HIF-1α in a TGF-β/Smad2/3 signaling-dependent manner [56]

Cancer stem-like cells, characterized by CD133 expression, have also been detected in patients with lung cancer. $CD133^+$ ESA^+ cells exhibited high tumorigenic potential in primary non-small cell lung cancer (NSCLC) [57]. Exposure of PC9 and HCC827 NSCLC cells to high amounts of gefitinib under hypoxic conditions for seven days led to the survival of a small fraction of cells, termed gefitinib-resistant persisters (GRPs). These cells had the high sphere-forming ability and expressed high levels of stem cell factors such as CD133, Nanog, ALDH1A1, and Oct4. Moreover, hypoxia induced the expression of insulin-like growth factor 1 (IGF1) and activated IGF1 receptor (IGF1R) on the resistant cells in the HIF-dependent manner, which was associated with the development of CSCs resistant to gefitinib. Therefore, it is likely that inhibition of HIF-1α and targeting the IGF1R pathway decreases the population of $CD133^+$ and $Oct4^+$ resistant CSCs in lung cancer [58]. Lida and colleagues also detected the increased expression of CD133 in the lung cancer cell lines A549, H358 and N417, following the culture of these cells under low oxygen conditions. They showed that the activity of the P1 promoter of the CD133 gene locus is robustly linked to hypoxia-induced promoter activity. They also demonstrated the direct binding of Oct4 and Sox2 to the P1 region using the chromatin immunoprecipitation assay. Interestingly, hypoxia-mediated expression of CD133 was related to HIF-1α- and HIF-2α-induced expression of Sox2 and Oct4. Consequently, silencing Sox2 or Oct4 in N417 cells suppressed HIF-induced CD133-P1 activity. Therefore, it seems that hypoxia (HIF-1α/HIF-2α) promotes the development of CD133-expressing CSCs through Sox2 and Oct4 in lung cancer cells by binding to the P1 region of the CD133 gene promoter [59]. In another study, overexpression of Oct4 and CD133 was observed in gefitinib-resistant NSCLC cells, PC9. Moreover, these resistant cells had CSC properties. Interestingly, it has been shown that Oct4 is one of the most important factors for maintaining resistance to gefitinib in lung CSCs, which can be further enhanced by hypoxia [60].

Stem-like cancerous cells in prostate cancer have also stemness features including differentiation, self-renewal, and tumor recurrence. Prostate CSCs express the stemness factors including Nanog, and to a lesser extent, Oct4, CD133, and NESTIN. Similarly, HIF-1α is highly expressed by prostate cancer cells and plays an important role in tumorigenesis. Moreover, hypoxia enhances the formation of prostaspheres in prostate cancer cells, which was associated with the upregulation of CSC markers including Nanog, EZH2, Oct4, EpCAM, and CD44. It has been shown that the expression of Nanog highly correlates with HIF-1α levels in prostate cancer cells, implying their cooperative action in prostate carcinogenesis [61]. Similarly, the culture of PC3 and DU145 cells under hypoxia led to overexpression of HIF-1α and HIF-2α, which was associated with the upregulation of CSC factors including CD44, Nanog, Oct3/4, and ABCG2 and stemness features [62]. Exposure of LNCaP, PC-3, and DU145 prostate cancer cells to hypoxia also led to the upregulation of another CSC marker, Sox2, which is involved in the invasion of cancer cells and sphere formation. Accordingly, the silencing of HIF-1α resulted in the downregulation of Sox2 and suppressed the invasion of tumor cells [63]. Kuphal and colleagues have demonstrated that hypoxia and HIF-1α enhance the overexpression of LIF in melanoma cells. Moreover, the expression of LIF was associated with the upregulation of CSC markers such as Nanog, Sox2, GBX2, and Oct3/4 [64]. Nanog promotes the tumorigenic potential of B16–F10 melanoma cells under hypoxic conditions, which is associated with the acquisition of CSC-like properties. Silencing Nanog in B16–F10 cells in combination with the melanocyte differentiation antigen, tyrosinase-related protein-2 peptide-based vaccination, TRP-2180–188, resulted in tumor regression [65]

4.2. CD44 and ALDH

CD44 and aldehyde dehydrogenase are two critical factors of CSCs. It has been shown that hypoxia can also promote the induction and development of CSCs through these two factors in various cancers.

Breast cancer stem cells (BCSCs) constitute a small group of cells in breast cancer with the ability to undergo self-renewal and induce chemo-resistant and secondary tumors. They show cellular heterogeneity for maintenance of tumorigenesis ability following several rounds of division. BCSCs are usually identified by aldehyde dehydrogenase $1(ALDH)^{high}$ $CD44^+$ $CD24^{dim}$ expression profile [66]. CD44 is a cell surface-expressed glycoprotein with alternatively spliced variants, which acts as a cell adhesion molecule and is overexpressed in CSCs and associated with metastasis and cancer progression [67]. Induction of hypoxia in MDA-MB-231 and SUM-149 breast cancer cells using CoCl2 was associated with the upregulation of CD44 implying the role of hypoxia in the induction of CSC associated molecules (Fig. 1). Hypoxia also regulates the expression of CD44v8 and CD44v6 isoforms of CD44 in MDA-MB-231 breast cancer cells. These reports indicate the role of the hypoxic tumor microenvironment, particularly HIF-1α, in the upregulation of CD44 and cancer progression [68]. Liang and coworkers demonstrated that the culture of ovarian cancer cell lines OVCAR-3 and ES-2 cells under hypoxic conditions enhances the expression of HIF-1α and HIF-2α, which are associated with enrichment of $CD44^{bright}$ cells with stemness characteristics [69].

High activity of ALDH is also associated with stem cell features including self-renewal, metastasis, tumorigenesis and poor prognosis in breast cancer. ALDH enzymes are involved in various processes such as oxidative metabolism, cell differentiation, and drug resistance. Therefore, BCSCs can be identified by ALDH expression [70]. Interestingly, HIF-1α can induce the expression of ALDH1A1 in breast cancer cells under hypoxic conditions. HIF-1α induced expression of Jagged-1, TGF-β, and Notch-1 in ALDH-expressing BCSCs, which was associated with EMT-related factors, such as Snail, Slug, and E-cadherin. On the other hand, silencing HIF-1α in BCSCs leads to the downregulation of Oct4 and Nanog [71]. Kim and colleagues also demonstrated that ALDH expression was associated with HIF-2α expression in breast cancer cell lines and samples. Moreover, exposure of breast cancer cells to the diethylaminobenz aldehyde (DEAB), ALDH inhibitor, suppressed HIF-2α expression and self-renewal in BCSCs derived from 4T1 cells [72]. It has also been reported that HIF can enhance the induction of CSCs by epigenetic-dependent mechanisms. HIF-mediated upregulation of ALKBH5 in MCF-7 and MDA-MB-231 cells negatively impacted m6A modification of Nanog mRNA, leading to increased Nanog mRNA demethylation, stabilization, expression and thereby upregulation of ALDH in BCSCs. Consequently, silencing ALKBH5 led to reduced HIF-mediated sphere formation and thereby reduced the frequency of BCSCs

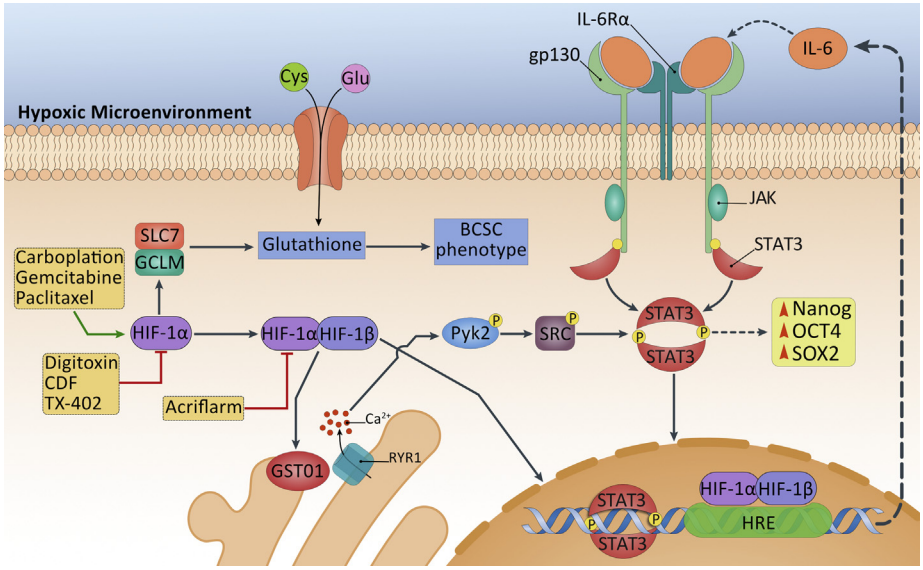

Fig. 2. Chemotherapy-dependent induction of stem cell factors. Chemotherapeutics such as Carboplatin, Gemcitabine, and Paclitaxel can enhance the expression of stem cell factors in tumor cells via inducing HIF-1α expression in the tumor microenvironment. Expression of GSTO1 in a HIF-dependent manner increases intracellular Ca^{2+} and activates PYK2/SRC/STAT3 signaling, resulting in the expression of IL-6 and stem cell factor. IL-6 can phosphorylate STAT3 in JAK-mediated manner and enhance the expression of stem cell factors in a positive feedback loop. HIF-dependent activation of SLC7A11 and GCLM increases the synthesis of glutathione, which led to the expression of pluripotency factors and the induction of breast cancer stem cells. There are different types of agents, which inhibit expression of HIF-1α and hypoxia-induced stem cell factors, including Digoxin, Acriflavine, Curcumin-derived synthetic analog (CDF) and TX-402.

under hypoxic conditions [73].

4.3. Adenosine/STAT3/IL-6 pathway

Adenosine, STAT3, and IL-6 are other hypoxia-related factors in the tumor microenvironment that can drive the induction of CSCs. Hypoxia can promote the induction and expansion of BCSCs via adenosine metabolism. Adenosine is one of the important immunosuppressive factors in the tumor microenvironment that promotes tumorigenesis via various mechanisms [74]. It is well-known that HIF-1α increases the expression of adenosine-generating enzymes including CD73 and CD39 [75–77] in association with adenosine receptors such as A2AR and A2BR [78,79]. Accordingly, silencing HIF-1α in MCF-7 cells using shRNA led to the downregulation of A2BR in these cells under hypoxic conditions. It has also been demonstrated that HIF-1α enhances the development of BCSCs through phosphorylation and activation of PKCδ in the adenosine/A2BR-dependent manner (Fig. 1). PKCδ activates STAT3 and its nuclear translocation, which leads to the upregulation of Nanog and IL-6, which are critical factors for the development and maintenance of BCSCs. Moreover, blockade of IL-6 in adenosine-stimulated MDA-MB-231 and MCF-7 cells by neutralizing antibodies can potently decrease BCSCs. Similarly, silencing A2BR in MDA-MB-231, MCF-7, and SUM149 cells, robustly decreased BCSCs. Therefore, signaling of A2BR can promote the development of BCSCs in part through the upregulation of IL-6 and Nanog [80]. Moreover, HIF-1/IL-6 and C/EBPδ exhibit a positive feedback loop in which HIF-1 and IL-6 increase expression of C/EBPδ which in turn it amplifies both IL-6 and HIF-1. This positive regulation is relevant due to the ability of C/EBPδ to promote the development and phenotype of CSCs. Accordingly, blockade of C/EBPδ has been associated with the downregulation of stem cell factors and stemness markers [81,82]. Interestingly, hypoxia also promotes cancer stemness in the MDA-MB-231 triple-negative breast cancer cell line partly through STAT3. Therefore, targeting STAT3 can also be considered as a potent therapeutic approach [17,18]. HIF-1α can induce STAT3 via the JAK pathway, which promotes the self-renewal of GSCs under hypoxic conditions. The secretion of VEGF in response to hypoxia is critical for stimulation of STAT3 and subsequent self-renewal of GSCs; inhibition of VEGF secretion by Brefeldin A and EHT-1864 agents potently suppress GSC self-renewal and tumor growth [83].

Exposure of H157 and A549 NSCLC cells to accumulating concentrations of cisplatin led to the development of resistant cell lines with CSC characteristics such as expression of CD133, Nanog, Oct4, and ALDH [84]. Moreover, the treatment of tumor-bearing mice by cisplatin resulted in enrichment of $CD133^+CXCR4^+$ and $CD133^+ABCG2^+$ cells with drug-resistant, metastatic and high mobility properties [57]. The appearance of these characteristics was partly associated with IL-6-dependent upregulation of HIFs in cancer cells. Interestingly, blockade of IL-6 or HIF could potently arrest the expression of CSC markers in these cells [84]. Consequently, targeting IL-6 or HIFs can suppress the development of CSCs and cancer recurrence in patients with lung cancer. Hasmim and colleagues demonstrated that Nanog facilitates hypoxia-mediated resistance of lung carcinoma cells to CTL-induced lysis. Nanog was overexpressed in cancer cells under hypoxic conditions. Accordingly, silencing Nanog promoted CTL-dependent killing of lung carcinoma cells and cancer cell growth arrest under hypoxic conditions. Also, the downregulation of Nanog was associated with blockade of STAT3 activation. These observations show that hypoxia-mediated Nanog expression by lung carcinoma cells enhances resistance to CTL-mediated killing [85].

4.4. MAPK/ERK pathway

MAPK/ERK signaling pathway is one of the most important mechanisms used by hypoxia to induce CSCs. HIF-1α in the hypoxic tumor microenvironment enhances the development of BCSCs and thereby cancer progression and recurrence. Downregulation of stem cell factor (SCF), in response to HIF-1α silencing in MCF-7 cells, has been demonstrated. HIF-1α binds to an HRE region in the SCF promoter as shown by chromatin immunoprecipitation (CHIP assay). It has also been demonstrated that SCF is a critical factor in cancer growth and angiogenesis. Moreover, it has also demonstrated that EGF increases SCF expression in MCF-7 cells under normoxia in a HIF-1α-dependent manner [86]. Another study showed that IL-1β also enhanced the expression of SCF in MCF-7 cells via induction of HIF-1α in a PI3K/ mTOR pathway-dependent manner. Consequently, silencing HIF-1α in these cells reduced the expression of SCF following stimulation with IL-1β [87]. HIF can also propagate BCSCs in response to chemotherapy in part through induction of glutathione via activating cystine transporter xCT and the glutamate-cysteine ligase. Blockade of xCT or glutamate-cysteine ligase reflects the importance of glutathione in the development of BCSCs (Fig. 2). Glutathione enhances FoxO3 nuclear translocation, which in turn stimulates the expression of Nanog in BCSCs. The blockade of a MEK1-ERK signaling pathway is another mechanism by which glutathione activates FoxO3. Moreover, inhibiting either FoxO3, xCT, glutamate-cysteine ligase, or Nanog can prevent chemotherapy-

mediated induction of BCSCs and tumor recurrence [88]. Culture of MCF-7, MDA-MB-231, SUM-149, and HCC1954 cells under hypoxic conditions led to the upregulation of glutathione S-transferase omega1 (GSTO1), which was associated with increased frequency of $ALDH^+$ BCSCs and upregulation of Nanog, Sox2, and KLF4 in MCF-7 and MDA-MB-231 cells. It is demonstrated that GSTO1 increases cytosolic Ca^{2+} levels, which leads to the induction of the PYK2/SRC/STAT3 signaling pathway, resulting in the upregulation of BCSCs [89]. HIF also enhances the enrichment of BCSCs via activation of the mitogen-activated protein kinase (MAPK) pathway. Treatment of SUM-149 and MDA-MB231 breast cancer cells with chemotherapeutics induced DUSP9 and reduced DUSP16 by HIF resulting in blockade of ERK and stimulation of p38, which led to upregulation of Nanog and KLF4 and enrichment of BCSCs. Inhibition of ERK blocks nuclear localization of FoxO3 and induces expression of Nanog. Stimulation of p38 stabilizes the mRNA of Nanog and KLF4 via the inactivation of ZFP36L1 [90].

HIF-1 can expand GSCs in association with growth factor signaling pathways. This has been demonstrated by blockade of ERK1/2 or PI3K-Akt pathways, which suppressed the hypoxia-induced expansion of CD133-expressing GSCs [91]. HIF-2 can upregulate prostatic acid phosphatase (PAP) in hypoxic GSCs. PAP subsequently facilitates adenosine production, which in turn binds to A2BR and enhances the expansion of GSCs and tumorigenesis through activation of Akt and Erk-1/2 pathways [92].

Cancer-associated fibroblasts (CAFs) are an important non-cancer group of cells in the tumor microenvironment. Interestingly, it is demonstrated that CAFs enhance development and EMT of prostate CSCs partly by stimulating the HIF-1α/β-catenin signaling pathway. Accordingly, blockade of HIF-1α/β-catenin signaling in LNCaP cells resulted in the downregulation of mesenchymal markers including N-cadherin, Fibronectin, and Vimentin [93]. Another pathway by which CAFs promote EMT in PC3 cells is by activating the monoamine oxidase A (MAOA)/mTOR/HIF-1α signaling pathway. CAFs can also increase oxidative stress through the same pathway, which promotes cancer progression. Moreover, they upregulate IL-6 receptor and CXCR4 in prostate cancer cells [94]. This is important because it has been shown that prostate CSCs secrete high amounts of IL-6, which enhances self-renewal [95]. Interestingly, the treatment of PC3 cells with curcumin could potently suppress EMT by enhancing E-cadherin and reducing vimentin expression. Furthermore, it prevents oxidative stress and expression of IL-6 receptor and CXCR4 by suppressing the MAOA/mTOR/HIF1α pathway [94]. It has been suggested that targeting MAOA may serve as a potent anti-CSC therapeutic strategy in prostate cancer. MAOA enhances HIF-1α/VEGF-A/AKT signaling pathways, reduces PTEN expression, increases expression of stemness markers, and promotes the development of CSCs via HIF-1α pathways in prostate cancer. Consequently, silencing MAOA in LNCaP cells can potently suppress the formation of spheroids [96].

4.5. NOTCH and WNT signaling

Hypoxia exploits NOTCH and WNT signaling pathways to regulate the development of CSCs. It has been suggested that the Notch pathway is required for HIF-1α-induced maintenance of GSCs. Accordingly, Qiang and colleagues showed that exposure of U251-derived stem-like tumor sphere cells to hypoxia-induced upregulation of HIF-1α and NICD. HIF-1α stabilizes NICD and upregulates the Notch Delta ligand (DLL1) thereby increasing expression of Notch downstream factors, such as Hes1 and Hey2. STAT3 is also involved in the maintenance of GSCs by upregulation of HIF-1α and promoting hypoxia-mediated stimulation of the Notch signaling pathway [97]. Although both HIF-1α and HIF-2α bind to NICD, HIF-1α is more stabilized in hypoxic conditions and its binding to NICD enhances expression of Notch responsive genes. On the other hand, under mild hypoxia or normoxia, HIF-2α enhances stem cell-related factors such as Oct4 and prevents the expression of Notch target genes [98]. Wang and coworkers demonstrated that HIF-1α enhances the Notch-mediated induction of Hes1, which is an important factor for LSCs stemness, self-renewal and cancer recurrence. Hes1 has an autoregulation mechanism, which is counteracted blocking binding to the N-box of its promoter by HIF-1α [99]. It has also been demonstrated that a small population of Wnt-active cells seen in T-ALL possess stem-like self-renewal properties, robustly induced by HIF-1α-mediated transcription of β-catenin under hypoxic conditions [100]. Seo and coworkers demonstrated that the hypoxia/NOTCH1/Sox2 axis are crucial factors for the development of ovarian CSCs, and can thereby serve as candidates for novel anti-CSC therapeutics for ovarian cancer. They showed that hypoxia in association with Notch signaling promotes drug resistance and self-renewal of ovarian CSCs. Indeed, Notch signaling facilitates hypoxia-induced upregulation of Sox2, which promotes drug resistance in ovarian cancer cells through the upregulation of ABCB1 and ABCG2. Sox2 can also promote sphere formation and induce CSCs characteristics. Consequently, silencing Sox2 abolishes hypoxia-mediated induction of CSC characteristics [101]. The culture of MCF-7 cells under hypoxic conditions gradually increased the expression of HIF-2α, which was associated with resistance to PTX chemotherapy and expression of stem cell markers including Nanog, c-Myc, and Oct4. HIF-2α induces Notch and Wnt signaling pathways in MCF7 and MDA-MB231 cells, which enhance the expression of c-Myc and induce phenotype of CSC [102].

4.6. Other mechanisms

In addition to the above-mentioned mechanisms, there are several mechanisms by which HIFs enhance the development of CSCs. The influence of hypoxia on BCSCs can be mediated by TAZ protein. It has been shown that the expression and function of TAZ protein, encoded by the *WWTR1* gene, is significantly increased in BCSCs from patients with advanced disease [103]. Exposure of various breast cancer cell lines including MCF10A, HCC-1954, MCF-7, MDA-MB-435, and MDA-MB-231 to both hypoxic and normoxic conditions showed that upregulation of TAZ protein is due to binding of HIF-1α to the HRE in the promoter of the *WWTR1* gene. Furthermore, HIF-1α enhances nuclear localization of TAZ by increasing the ubiquitination and degradation of LATS2 kinase, an inhibitor of TAZ nuclear localization, via binding to HRE in the ubiquitin protein ligase *SIAH1* gene. Consequently, silencing *SIAH1*, TAZ, or HIF-1α by shRNA potently decreased BCSCs under hypoxic conditions [104]. Another way by which HIF signaling promotes stemness of breast cancer cells is through induction of integrin alpha 6 (ITGA6, which is also known as CD49f). Accordingly, it has been shown that the upregulation of ITGA6 by HIF signaling modulates stem cell-like features and invasion of cancer cells in metastatic breast cancer cells such as MDA-MB-231 and polyoma middle T (MMTV-PyMT) cells [105].

The regulation of the PAX3/P53 axis is an important mechanism, which controls the development of GSCs by HIF-1α. HIF-1α upregulates PAX3, which is pivotally involved in regulating carcinogenesis, migration, and self-renewal of GSCs by binding to the promoter region of p53 and suppressing its expression [106]. Monocarboxylate transporter 4 (MCT4) is another factor induced under hypoxic conditions by HIF. Overexpression of MCT4 in GBM patients is associated with the expansion and survival of GBM stem-like cells. The knockdown of MCT4 by shRNA also reduces the frequency of $CD133^+$ cells and suppresses HIF transcriptional function [107]. GSCs express high levels of Mixed-Lineage Leukemia1 (MLL1), an epigenetic-modifying protein, which is a critical factor for growth, self-renewal, and tumorigenicity of GSCs. It has been shown that MLL1 upregulates HIF-2α and its downstream genes, such as VEGF, in glioma cells [108]. GSCs also overexpress CDH5 (also known as vascular-endothelial–cadherin or CD144) under hypoxic conditions, which enhance TGF-β-dependent tumor progression. It has also been demonstrated that HIF-1α and HIF-2α upregulate CDH5 in GSCs under hypoxic conditions [109].

Leukemia stem cells (LSCs) exhibit high self-renewal capacity, large

expansion, preferred homing to the bone marrow niche in association with robust tumorigenic features. Although several factors in tumor microenvironment help maintain multipotency and self-renewal of hematopoietic stem cells (HSCs) within the niche, hypoxia, and HIFs are also essential for this process [110]. It has been demonstrated that BCR-ABL-expressing HSCs ($Lin^{-}Sca\text{-}1^{+}c\text{-}Kit^{+}$ cells) in mouse AML overexpress HIF-1α and its downstream genes including VEGF, TGF-α, and GLUT1 and act as LSCs. HIF-1α was also a critical factor for development of CML and maintenance of LSCs, as demonstrated in HIF-1α-deficient mice used in a bone marrow transplantation (BMT) model. The lack of HIF-1α led to the induction of apoptosis and cell cycle arrest through upregulation of tumor suppressor genes such as p53, $p16^{Ink4a}$, and $p19^{Arf}$ in LSCs [111].

It has been reported that SIRT1, a member of the sirtuin family, has been detected in some cancers such as colon cancer, prostate cancer, breast cancer, and is associated with carcinogenesis, cell proliferation, EMT phenotype, and differentiation [112,113]. SIRT1 is also related to poor prognosis and chemoresistance in ovarian cancer [114]. SIRT1 is the downstream target gene of HIF-1α and can be induced by hypoxic conditions that are associated with the promotion of CSC properties in ovarian cancer cells. The NF-κB signaling pathway, which is activated by hypoxia, is involved in hypoxia-induced SIRT1 upregulation. Therefore, targeting SIRT1and HIF-1α are potential therapeutic strategies for the treatment of ovarian cancer [115].

5. Targeting HIFs as a therapeutic approach

Recent studies have shown that HIF-1 can mediate resistance to radiation and chemotherapy, therefore, inhibition of HIF-1 activity can provide a novel therapeutic opportunity for cancer. One of the molecules intervening HIF-1 expression is EZN-2698 (an RNA antagonist) which can bind specifically and hinder the expression of HIF-1α mRNA and target genes. Tumor progression and expression of HIF-1α protein is inhibited by EZN-2698 [116]. Hypoxia can promote tumor progression and induce CSCs by regulating miRNAs. Hypoxia upregulates miR-21 in prostate cancer cells, which correlates with increased self-renewal of prostate CSCs [95]. Accordingly, exposure of prostate cancer cells to curcumin-derived synthetic analog (CDF) suppressed hypoxia-mediated migration of prostate cancer cells and inhibited the formation of prostaspheres partly by downregulating HIF-1α, miR-210, miR-21, and CSC markers [95]. Similarly, treatment of PC-3 cells with another anti-cancer agent, Pristimerin, leads to suppression of hypoxia-mediated expansion and EMT and prevents sphere formation, colony formation and expression of CSC markers including CD44, Oct4, AGO2, and KLF4 [117]. Therefore, curcumin and Pristimerin are potential anti-cancer treatments for inhibition of hypoxia-mediated induction of prostate CSCs. Overall, prostate cancer cells express both HIF-1α and HIF-2α under hypoxic conditions and acquire stem-like properties and upregulate stem cell factors. Treatment with curcumin-derived synthetic analog (CDF) and Pristimerin may be a potential strategy for the suppression of hypoxia-induced CSC properties and the prevention of prostate cancer progression. Cardiac glycoside (Digoxin) is a cognitive drug for the treatment of congestive heart failure. Surprisingly, it has been shown that this drug can inhibit the expression of HIF-1α protein and HIF-2α mRNA expression [118]. Inhibition of HIF-1α by Digoxin, promoted suppression of downstream targets such as VEGF, Glut1, and CA9, which are associated with GSC properties such as self-renewal, angiogenesis, invasiveness and downregulation of CD133 [119]. It is proposed that inhibition of HIF-1α can be considered as a potent anti-LSC therapeutic strategy in CML. Consequently, the treatment of CML cells with the HIF-1 inhibitor, Acriflavine (ACF), potently suppressed the stemness capacity of CML cells and inhibited maintenance of LSC and growth of CML cells. ACF potently inhibited the expression of important stemness-promoting molecules including Nanog, Oct4, c-MYC, and Sox2 [120]. Downregulation of HIF-1α and HIF-2α expressed by CaOV3 and SKOV3.ip1 ovarian cancerous cells by TX-402 treatment, an analog of tirapazamine, leads to reduced expression of CSC markers including CD44 and CD133 and stem cell characteristics [121]. It has also been reported that interaction of Nanog with signaling axis of androgen receptor drives the development of ovarian CSCs [122] Co-treatment by ursolic acid and cisplatin can considerably reduce the resistance of ovarian CSCs to cisplatin. Under hypoxic conditions, ursolic acid can suppress the proliferation of ovarian CSCs and promote their sensitivity to chemotherapeutic drugs by downregulation of HIF-1α and ABCG2. The PI3K/Akt signaling pathway, which is activated by hypoxia, has a critical role in ursolic acid-dependent suppression of HIF-1α and ABCG2 expression [123]

6. Conclusion

Previous studies have demonstrated a profound connection between the hypoxic tumor microenvironment, HIFs, and CSC specification and maintenance [10,124]. CSCs have been detected in several cancers such as AML, colon, lung, breast, brain, liver, pancreas, ovarian, prostate, and melanoma [125,126], and characterized by expression of different cell surface glycoproteins depending on the tissue origin. Beside self-renewal, CSCs, can give rise to differentiated tumor cells and play a crucial role in tumor formation [127]. The eradication of CSCs can potentially facilitate remission, as they are the main causes of cancer recurrence and metastasis. Therefore, targeting CSCs based on their cell surface markers is a good therapeutic strategy. For instance, therapeutic-targeting of CD133 holds promise for the eradication of CSCs due to its expression by CSCs in various solid tumors, [128]. Furthermore, the use of nanomaterials has also been explored as a strategy for the targeted destruction of CSCs [129]. The use of CD133-specific peptide-coated gold nanoparticles as imaging agents facilitated the diagnosis of GBM and served as a drug carrier for therapeutic approaches [130]. However, the cellular heterogeneity, development, and interaction of CSCs with the tumor microenvironment, making it difficult to specifically target these cells in cancer patients [131]. Immunotherapeutic strategies should selectively target both CSCs and differentiated tumor cells, as CSCs can give rise to differentiated tumor cells and play a crucial role in tumor formation. On the other hand, differentiated cancer cells enhance the generation of CSCs. Therefore, immunotherapy strategies that target both CSCs and differentiated tumor cells will be more beneficial and achieve better clinical impact [127].

In addition to the identification of CSC specific markers for selective targeting of these cells, other questions in the relation between hypoxia and CSC; which one is more important for induction and development of CSCs, HIF1 or HIF-2? Various studies have been demonstrated that HIF-2α enhances expression of target genes required for the enrichment of CSCs under normoxic conditions [132], however, HIF-1 has a stronger potential for inducing CSCs under hypoxic conditions compared to HIF-2. In our opinion, the tumor microenvironment efficiently preserves the properties of CSCs and provides conditions, which are essential for the development of CSCs during tumor initiation, development, and regression (following chemotherapy) by providing HIF factors. Both HIF-1α and HIF-2α are required for the development of CSCs, as they manage different stages of development. HIF-1α is the main HIF factor during tumor growth, which is associated with the generation of the hypoxic area in the tumor center, whereas HIF-2α is active following treatment such as chemotherapy and radiation that significantly decrease tumor size and provide normoxic conditions. Although based on current knowledge this model seems to be rational, it needs to be approved by performing further precise studies.

Based on the both *in vitro* and *in vivo* results derived from preclinical studies, targeting HIFs can suppress metastasis-initiating cells and thereby inhibit tumor recurrence [119]. Blockade of HIFs in association with their signaling mediators and combined with immune checkpoint inhibitors may be effective for eradicating total tumor mass without the risk of CSC-induced cancer recurrence. HIF-1α can regulate

PD-L1 expression by directly interacting with the PD-L1 proximal promoter. Also, PD-L1 and HIF-1α co-expression in hypoxic conditions abrogate T cell function. Consequently, the inhibition of PD-L1 signaling in hypoxic conditions increases the sensitivity of cancer cells to T cell-mediated killing and abolishes the function of tumor-associated immune cells [133,134]. Therefore, combining HIF-1α blockade with negative immune checkpoint inhibitor treatment may be a more effective therapeutic strategy.

Understanding the differences between tumor-initiating and chemo/radiotherapy-induced CSCs for stemness, specificity, stability and sustained expression of CSC markers properties is relevant for future therapeutic studies. Moreover, the effect of HIF factors on different stages of CSC development is also of importance.

The development of new potent and selective HIF inhibitors is required to supplement others such as Digoxin and Pristimerin. Assessing the clinical benefits will facilitate the design and development of a new generation of drugs, which can robustly target and block the expression of HIF factors. Additionally, novel nano-based drug delivery systems can be used to increase the detection of intracellularly-expressed HIF factors at tumor sites [135]. The use of HIF-1α-specific siRNA-loaded nanoparticles can efficiently decrease the expression of HIF-1α and inhibit tumor metastasis [136]. Drug delivery systems are one of the most efficient agents to be used for targeted therapy-they can simultaneously target various pathways, decrease the side effect of traditional treatments, increase the concentration of drug in the tumor niche thereby preventing the resistance of cancer cells to current chemotherapy drugs [129,137,138].

Declaration of Competing Interest

There is no conflict of interest.

Acknowledgments

None.

Abbreviation

CSC	Cancer stem cells
HIFs	Hypoxia-inducible factors
HREs	Hypoxic response elements
EMT	Epithelial-mesenchymal transition
VEGF	Vascular endothelial growth factor
MDSCs	Myeloid-derived suppressor cells
PD-L1	Programmed death–ligand 1
VHL	Von Hippel-Lindau protein
FIH-1	Factor inhibiting HIF-1
AML	Acute myeloid leukemia
ESCs	Embryonic stem cells
CSCLCs	CSC-like cells
NICD	Notch intracellular domain
CBF-1	Core binding factor-1
BCSCs	Breast cancer stem cells
ALDH	Aldehyde dehydrogenase
SCF	stem cell factor
GSTO1	Glutathione S-transferase omega1
DEAB	Diethylaminobenz aldehyde
GSCs	GBM stem cells
DLL1	Notch Delta ligand
MCT4	Monocarboxylate transporter 4
MLL1	Mixed-lineage leukemia1
PAP	Prostatic acid phosphatase
LSCs	Leukemia stem cells
HSCs	Hematopoietic stem cells
ACF	Acriflavine
CAFs	Cancer-associated fibroblasts
MAOA	Monoamine oxidase A
CDF	Curcumin-derived synthetic analog
EGFR	Epidermal growth factor receptor
IGF1	Insulin-like growth factor 1
LIF	leukemia inhibitory factor

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