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HIF-1 at the crossroads of hypoxia, inflammation, and cancer

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Abstract

The complex cross-talk of intricate inter-cellular signaling networks between the tumor and stromal cells promotes cancer progression. Hypoxia is one of the most common conditions encountered within the tumor microenvironment that drives tumor progression. Most responses to hypoxia are elicited by a family of transcription factors called hypoxia-inducible factors (HIFs), which induce expression of a diverse set of genes that assist cells to adapt to hypoxic environments. Among the three HIF protein family members, the role of HIF-1 is well established in cancer progression. HIF-1 functions as a signaling hub to coordinate the activities of many transcription factors and signaling molecules that impact tumorigenesis. This mini review discusses the complex role of HIF-1 and its context-dependent partners under various cancer-promoting events including inflammation and generation of cancer stem cells (CSCs), which are implicated in tumor metastasis and relapse. In addition, the review highlights the importance of therapeutic targeting of HIF-1 for cancer prevention.

Keywords

hypoxia; inflammation; HIF-1; microenvironment; cancer stem cells; drug resistance

Introduction

Low oxygen levels (hypoxia) play a key role in physiological conditions such as development and wound healing.[1,2] However, deregulated hypoxia signaling results in the development and progression of a variety of diseases including cancer, ischemic heart disease, advanced atherosclerosis, stroke and chronic lung disease, which are responsible for the majority of deaths worldwide. [3]

Hypoxic adaptation is largely mediated by a family of transcriptional regulators called hypoxia-inducible factors (HIFs), which induces a panel of specific target genes.[3] HIFs act as heterodimers, which are composed of an oxygen-regulated α subunit, and an oxygen-independent β subunit (also called aryl hydrocarbon receptor nuclear translocator (ARNT)).[4] There are three HIF-α family proteins identified in humans: HIF-1α, -2α and -3α. Under normal oxygen conditions, HIF-α subunits are tightly regulated by a set of enzymes called

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HIF prolyl hydroxylases (PHDs). PHDs are non-heme Fe (II)- and 2-oxoglutarate-dependent dioxygenases that hydroxylate HIF-α subunits at specific prolyl residues. The hydroxylated HIF-α subunits are recognized by the von-Hippel Lindau (VHL) tumor suppressor E3 ligase for degradation through the proteasome pathway.[3,4] In addition, factor inhibiting HIF (FIH) hydroxylates HIFs at Asn803, leading to its decreased transcriptional activity. Diminished PHD and FIH activity during periods of hypoxia stabilizes HIF-α and results in its translocation to the nucleus where HIF-α heterodimerizes with HIF-β.[3,4] The HIFα/β complex binds to the promoter regions of target genes containing hypoxia-responsive elements (HREs; 5′-RCGTG-3′, where R=A or G) and transactivates the expression of genes involved in diverse signaling pathways.[1–4]

Among the HIF-α proteins, the functions of HIF-1α and HIF-2α vary depending on the tumor and cell type.[5] In contrast, HIF-3α, and its splice variant HIF-3α4, act as dominant negative regulators of both HIF-1-, and HIF-2-mediated transcriptional activity by competing for HIF-1β.[6,7] However, recently HIF-3α was also shown to function as a transcriptional activator promoting a distinct transcriptional response to hypoxia in zebrafish embryos, suggesting the complexity in biological systems.[8] Among HIF-α factors, the role of HIF-1 in cancer and inflammatory diseases is best understood.[5,9] This review summarizes the role of HIF-1in cancer signaling and inflammation and highlights the key partners of HIF-1 in these contexts. Further, given the important role of HIF-1 in cancer progression, this article emphasizes inhibition of HIF-1 as a promising therapeutic strategy for the management of patients with cancer and cancer-associated inflammation.

HIF-1 levels are elevated in tumors

Hypoxia is one of the most common characteristics of the tumor microenvironment that drives aggressiveness of tumors.[10,11] In solid tumors, about 60% of the tumors exhibit less than 1% O_2 with a partial oxygen pressure (pO_2) of less than 10 mm Hg compared to pO_2 of ~40–65 mm Hg in adjacent normal tissues. Whereas transient or acute hypoxia occurs in tumors with inadequate blood perfusion, chronic hypoxia limiting oxygen diffusion occurs in enlarged tumors.[10] Intratumoral hypoxia activates both HIF-1 and HIF-2, with overexpression of HIF-1α documented in several human cancers with strong association to increased metastasis and mortality.[11,12] In particular, high HIF-1α expression is seen in glioblastoma multiforme, hemangioblastoma, colonic adenocarcinoma, and subtypes of lung, prostate and breast cancer.[12] HIF-1α overexpression in these cancers may result from factors other than hypoxia. These include, insulin, insulin-like growth factor (IGF) -1 or IGF-2, v-Src, lactate, pyruvate, and genetic alterations such as oncogene activation or tumor suppressor gene inactivation [13–16] Upregulation of HIF-1α has a central role in tumor progression by activating various hallmarks of cancer such as angiogenesis, migration and invasion, pH regulation, and glucose metabolism (Figure 1).[3–5,9–12]

The role of HIF-1 in inflammatory responses

HIF-1 plays an essential role in execution of an optimal inflammatory response by immune cells. [9,17–20] Like tumor cells, infiltrating immune cells are also exposed to a hypoxic environment as they extravasate from the oxygen rich bloodstream to the site of

inflammation, thus activating HIF-1 in immune cells.[9,17] The deletion of HIF-1α in myeloid cells causes a reduction in the cellular ATP pool and severe impairment of myeloid cell aggregation, motility, invasiveness, anti-bacterial activity, and survival.[17,18] Likewise, T cell-specific HIF-1α knockouts show severe colonic inflammation due to impairment of Th1 and Th17 responses.[19,20] In dendritic cells (DCs), HIF-1α promotes their maturation and subsequent functions under inflammatory conditions.[21] HIF-1α regulates lymphatic regeneration during wound repair and inflammatory lymphangiogenesis by regulating the expression of lymphangiogenic cytokines. [22] In addition, HIF-1 regulates immune checkpoint receptors by directly activating the expression of their ligands such as programmed death ligand 1 (PD-L1), which contributes to myeloid-derived suppressor cells (MDSC)-mediated T cell activation.[23] Additionally, HIF-1 exacerbates experimental colitis through the regulation of macrophage migration inhibitory factor (MIF), which in turn facilitates inflammatory cell infiltration and generation of edema in the colon.[24] Furthermore, conditional deletion of HIF-1α in the myeloid lineage protects mice against lipopolysaccharide (LPS)-induced mortality and blocks sepsis-associated hypotension and hypothermia.[25] The diverse and complex roles of HIF-1 in inflammatory responses indicate that HIF-1 is not simply a bystander and should be expected to have a major impact on the progression of inflammatory-related diseases and cancer through its actions in both immune and non-immune cells.

The role of HIF-1 in linking inflammation and cancer

HIF-1 is involved in both intrinsic and extrinsic activation of tumor-associated inflammatory signaling.[26,27] The growth of solid tumors eventually outpaces the supply of oxygen and nutrients, leading to necrosis.[9,10,27] Hypoxic and necrotic areas of a tumor in turn produce proinflammatory mediators that recruit more immune cells resulting in suppression of the immune response at the tumor site as well as tumor cell proliferation, angiogenesis and metastasis.[27,28] HIF-1 serves as a critical mediator in the signaling events culminating in lymphangiogenesis and lymphatic metastasis.[29]

Chronic inflammation results in the activation of the transcription factor nuclear factor-kappa B (NF-κB), a key coordinator of innate immunity and inflammation.[30] A large body of evidence suggests that NF-κB and HIF-1 link inflammatory signaling to hypoxia.[31] In response to inflammation, inhibitory IκB proteins are dissociated from NF-κB allowing its nuclear translocation and activation of tumor-promoting genes including interleukin-6 (IL-6), cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (NOS2), platelet endothelial cell adhesion molecule-1 (PECAM-1) and matrix metalloproteinase 9 (MMP9).[30,31] NF-κB and HIF-1 coordinate the activation of these genes' promoters. Furthermore, pro-survival genes such as *BCL2*, *CXCR1*, and *CXCR2* are induced by NF-κB and HIF-1.[32,33]

In addition to NF-κB, the signal transducer and activator of transcription 3 (STAT3), one of the seven members of the STAT family of transcription factors, also serves as a partner for HIF-1 in cancer-associated inflammatory signaling.[34] Phosphorylation of STAT3 by Janus kinases (JAKs) leads to its dimerization, nuclear translocation, DNA binding, and activation of genes involved in survival (e.g. survivin, mcl-1), proliferation (e.g. c-myc, cyclin D1),

invasion (MMP2), and angiogenesis (vascular endothelial growth factor (VEGF)).[35] STAT3 cooperates with HIF-1 and NF-κB in the regulation of these genes.[36,37] In addition, STAT3 interacts physically with HIF-1α, which is essential for activation of HIF-1 target genes under hypoxic conditions as demonstrated in MDA-MB-231 human breast cancer and RCC4 renal carcinoma cells.[38] Furthermore, a cooperative induction of HIF-1 and STAT3 contributes to hypoxia-mediated immunoresistance in lung cancer cells.[39] Of note, STAT3 and NF-κB activation promotes chemoresistance and radioresistance in various cancer cell lines, which is akin to that of HIF-1.[40–44]

HIF-1 regulates tumor-associated inflammatory responses in part through its target gene Toll-like receptor 4 (TLR4).[25,45] TLR4 belongs to the pattern recognition receptor family of proteins and recent studies have indicated its role in tumor progression and chemoresistance in addition to its function in innate immunity.[46] In glioblastoma tumorigenesis, a feed-forward loop between TLR4-HIF-1α sustains inflammatory signaling, and both HIF-1 and TLR4 have synergistic functions in the development of pancreatic adenocarcinoma.[47,48] Together, these findings provide compelling evidence for cooperative relationship between NF-κB, STAT3, TLR4 and HIF-1-dependent tumor-associated signaling events.

The transcription factors c-Jun and AP-1 cooperate with HIF-1 to allow fine-tuned regulation of gene expression during hypoxia.[49,50] HIF-1 also mediates the activation of several genes in response to IGF-1 that promote cell survival and motility.[51,52] In summary, these studies reiterate the fact that HIF-1 links both hypoxia and inflammation through context-dependent partners to drive tumor promoting signaling.

HIF-1: a key mediator of tumor metabolism

HIF-1 is an important mediator of the tumor-associated metabolic switch, Warburg effect, in which tumor cells generate energy mainly by non-oxidative breakdown of glucose rather than conventional oxidative phosphorylation.[14,53,54] HIF-1 drives the expression and activity of isoforms of glycolytic enzymes that differ from those found in non-malignant cells, thereby potentiating energy production as well as macromolecular biosynthesis pathways to support the Warburg effect.[53,54] For instance, the expression of pyruvate kinase isoform M2 (PKM2), but not PKM1, is necessary for the Warburg effect, because PKM2 physically interacts with HIF-1 and stimulates HIF-1 activity.[55,56]

The targets of HIF-1in the glycolytic pathway include glucose transporters 1 and 3 (GLUT1, GLUT3) and enzymes such as hexokinase 1 (HK1) and HK2, phosphofructokinase liver type (PFK-L), aldolase A and C (ALD-A, ALD-C), phosphoglycerate kinase 1 (PGK1), enolase alpha (ENO-alpha), PKM2, lactate dehydrogenase A (LDH-A) and fructose 2, 6 bisphosphatase (PFKFB-3).[54,55] Some of these genes, including, Glut1, HK2, and LDH-A are also direct targets of the oncogenic MYC transcription factor.[57] In addition, recent studies point to mammalian target of rapamycin (mTOR) as another important regulator of the Warburg effect, which may in part be due to its effect on HIF-1α.[58,59] By analogy, both Myc and mTOR in co-operation with HIF-1“-serve the cancer cell’s metabolic needs-” by providing high glycolytic flux. Additionally, HIF-1 activates catabolite transporters such as monocarboxylate transporter 4 (MCT4) in cancer-associated fibroblasts (CAFs), a major

cellular component of the tumor stroma.[60–62] Such activated CAFs provide metabolic coupling, which enables anabolic tumor cells to survive in their hypoxic environment.[60,61] HIF-1α also regulates the metabolic fate and multipotency of human mesenchymal stem cells (hMSCs).[63]

An important consequence of the glycolytic switch is acidosis of the tumor microenvironment.[64] Enhanced glycolysis leads to an acidic microenvironment due to the increase in the levels of lactate and H^+ that are actively expelled from tumor cells through the functions of many intracellular pH (pHi)-regulating proteins that include, MCT1, MCT4, and Na^+/H^+ exchanger 1 (NHE1).[64] Hypoxia promotes acidosis because HIF-1 induces expression of NHE1, MCT4, and carbonic anhydrase IX (CAIX).[62,65,66] NHE1 directly manages free intracellular H^+ when the buffering capacity of intracellular proteins is exhausted.[64] Tumor cell-specific expression of MCT1 and stromal cell-specific expression of MCT4 optimizes lactate utilization and is associated with the progression of prostate cancer.[67] In addition to lactate, carbon dioxide production by CAIX also causes acidosis in the tumor environment.[66,68] Acidosis also modulates the inflammatory response and immune cell functions to attenuate anti-tumor immunity and the efficacy of drug uptake by tumors.[69,70] Together, the acidic microenvironment and shift in the metabolism provides many metabolic intermediates that drive progression and aggressiveness of the cancers.[53,54,64,69]

Like tumor cells, immune cells such as activated M1 macrophages or DCs generate ATP and essential components for survival by metabolic reprogramming through activation of HIF-1 regulated genes.[71,72] Evidence is also emerging that the Warburg effect is important in adaptive immunity by regulating Th17 and Treg cells.[73] A recent study demonstrated that mTOR-HIF-1α pathway is critical for the metabolic basis of epigenetically reprogrammed myeloid cells (also called trained immunity).[74] These findings indicate that HIF-1 serves as a crucial mediator of Warburg metabolism, -which is not only relevant to cancer progression but also inflammation.

Tumor microenvironment and cancer progression: “HIF-1 in the Driver’s Seat”

The behavior of the tumorigenic cells is highly influenced by their microenvironment.[53,75] Under hypoxia and nutrient-deprived conditions, cancer cells have to dramatically re-wire their metabolism to survive and proliferate.[53,75] Tumors are heterogeneous, composed of numerous cell types such as tumor-associated endothelial cells (TAECs), CAFs, adipocytes, MDSCs, tumor-associated macrophages (TAMs) and other immune cells.[75] Hypoxia is a critical parameter that modulates stromal and/or endothelial/tumor cell interactions.[29,76] Under hypoxia, breast cancer cells secrete HIF-1-induced factors such as angiopoietin 2 (Ang2), angiopoietin-like 4 (ANGPTL4), L1 cell adhesion molecule (L1CAM), platelet-derived growth factor B (PDGFB), stem cell factor (SCF, or kit ligand), stromal-derived factor 1 (SDF1), and VEGF.[77–81] These factors directly mediate functional interactions with blood endothelial cells (BECs), lymphatic endothelial cells (LECs), and other bone marrow-derived cells (BMDCs) that promote angiogenesis, lymphangiogenesis, and metastasis.[77–81]

The balance between suppressive and cytotoxic responses of the tumor immune microenvironment has a direct effect on the treatment and prognosis of cancers.[26,28,75] Tumor immune suppression is due to impaired release of granular cytosolic content, decreased presentation of tumor-associated antigens as well as inhibition of T and B cell response.[82–84] Intratumoral hypoxia leads to release of factors that recruit TAMs, MDSCs and other immune cells to the tumor site, and induce angiogenesis, and metastasis as well as immune suppression through the secretion of pro-inflammatory cytokines and other mediators.[26,28,29,82–84] TAMs promote angiogenesis, and the presence of TAMs correlates with increased metastasis and mortality.[85,86] TAMs require HIF-1 activity to promote angiogenesis, because most of the pro-angiogenic factors (VEGF, IL-6, TNFα, and tyrosine kinase receptor Tie2)[85–88] and pro-angiogenic enzymes (iNOS, MMP-9, and Cox-2)[86,89,90] expressed in TAMs are regulated by HIF-1. In addition, HIF-1-dependent production of colony stimulating factor-1 (CSF-1) in tumor cells recruits TAMs, which in turn provide epidermal growth factor (EGF) to the tumor cells, leading to a paracrine partnership that supports tumor metastasis.[91,92] Furthermore, HIF-1α expression in the myeloid lineage promotes the differentiation of MDSCs, which contribute to tumor progression.[93] A recent study points to a role of the HIF-1/CAIX system in the production of soluble mediators such as G-CSF, which are required for the recruitment of MDSCs to the lungs and thereby generate premetastatic niches.[94] In a mouse model of triple negative breast cancer, HIF1-dependent secretory factors recruit MSCs, TAMs and MDSCs, which in turn potentiate the invasion and metastasis of tumor cells.[92]

HIF-1 also plays a key role in the activation of CAFs, which promotes persistent chronic inflammation within the tumor microenvironment.[60,61] The markers of chronic inflammation in the tumor microenvironment include Cox-2, NF-κB, IL-6, IL-8, S100 calcium binding protein A8 (S100A8), and VEGF.[26,27,29,37,86,89] In pancreatic cancer, tumor hypoxia triggers HIF-1-dependent and hedgehog (SHH)-mediated tumor-stromal interactions that amplify a desmoplastic reaction, leading to a dense fibroinflammatory microenvironment, which limits cancer drug delivery due to decreased blood perfusion.[95]

In addition, HIF-1 promotes changes in the extracellular matrix (ECM) that contribute to tumor cell invasion and metastasis.[96,97] HIF-1 activated CAFs secrete ECM remodeling proteins such as collagen prolyl hydroxylases (P4HA1 and P4HA2) and lysyl hydroxylases (PLOD2), which promote cancer cell invasion and metastasis.[96,97] As more pieces of the puzzle are put together, HIF-1-mediated activation of MDSCs, CAFs, MSCs, TAECs, TAMs and ECM remodeling takes on a central role in the modifications of the tumor microenvironment that promote tumor aggressiveness and immune suppression (Figure 2).

Role of HIF-1 in the epithelial to mesenchymal transition (EMT): a pre-requisite for metastasis

EMT, by which epithelial cells lose their polarity and acquire a mesenchymal phenotype, is a major facilitator of tumor metastasis, which is induced by the tumor microenvironment.[99] Repression of epithelial-specific proteins such as E-cadherin, desmoplakin, plakoglobin and zona occludens-1 (ZO-1) in the tumor cells is a crucial step of EMT, which is accompanied by an increase in mesenchymal markers and cell motility.[99–101] HIF-1 activates the

expression and activity of several EMT-inducing factors including SNAIL, SLUG, TWIST and ZEB1, and inhibits the expression of E-cadherin.[102–105] HIF-1 activation of CAFs and its target gene CAIX in CAFs leads to EMT-inducing conditions for tumor cells.[106,107] Additionally, HIF-1 promotes EMT under inflammatory conditions.[108,109]

Members of the TGF-β family of growth factors are major inducers of EMT.[99] Both HIF-1 and TGF-β promote each other's expression and trigger hypoxia-induced EMT in many cancer cell types.[110–113] In addition, Wnt/β-catenin signaling can play an important role in EMT.[99,114] Some studies have shown that the Wnt/β-catenin signaling pathway has an important role in HIF-1-induced EMT in human prostate and hepatocellular carcinoma cell lines.[115,116] In pancreatic cancer cells, HIF-1 mediated EMT requires NF-κB activity[117]. Furthermore, the Notch signaling pathway also plays a role in hypoxia/HIF-1-induced EMT of several cancer cell lines.[118] These studies provide compelling evidence for the role of HIF-1 and its cross talk with other factors in EMT.

HIF-1 and Cancer Stem Cells (CSCs): "the core of the enemy"

EMT is associated with the emergence of stem-like characteristics in cancer cells, which in recent times have received great attention.[119] The current CSC hypothesis suggests that a small subset of cancer cells possess extended self-renewal properties that drive tumorigenesis, promote metastasis, and contribute to treatment resistance.[120] Dick and coworkers first demonstrated the stem cell concept in leukemia, which was later shown in breast cancer. [121–123]

Microenvironmental factors of the CSC niche provide cues that are important for the maintenance of the CSC state.[120,124] However, the mechanisms regulating CSC generation and maintenance are poorly understood. Notably, hypoxia and the HIF-1 signaling pathway are known to be important for the regulation and sustenance of CSCs and the EMT phenotype.[125] HIF-1α-mediated EMT results in the enrichment of stem-like side population cells in thyroid and prostate cancer cells.[126,127] The hypoxic and/or necrotic areas of tumor tissues, which are considered a niche for CSCs, promote the induction of HIF-1 regulated CSC-signature genes such as Oct4, Sox-2, Nanog, Myc, CD44, and CD133.[128] The role of hypoxia and of HIF-1 in the control of the tumorigenic capacity of CSCs has been demonstrated in glioblastoma.[129] In pancreatic cancer, gastric cancer, and neuroblastoma cells, intermittent hypoxia enhances stem-like characteristics in cancer cells along with the upregulation of HIF-1α. [130–132] HIF-1α also plays a key role in promoting mammary tumor growth and metastasis, in part through regulation of CSCs.[133] The interplay between HIF-1 and Notch appears to be important for stem cell maintenance under hypoxia in a variety of cancer cell lines.[127, 134,135] These studies highlight the important role of HIF-1 in CSC maintenance as one of the mechanisms by which HIF-1 promotes tumorigenesis and metastasis.

HIF-1 and reactive oxygen species (ROS): "an intimate relationship"

ROS are elevated in many cancer types and have emerged as critical signaling stimuli in tumorigenesis.[136] ROS can drive the de-differentiation of tumor cells leading to EMT and metastasis.[108,136] Chronic hypoxia causes an increase in the levels of intracellular ROS at

the Q_0 site of complex III of the mitochondrial electron transport chain.[137] In addition to affecting the mitochondrial electron transport chain, hypoxic conditions also increase ROS levels through NADPH oxidase, xanthine oxidase, and eNOS.[138] The increase in ROS stabilizes the redox sensitive factor HIF-1α and thereby activates its downstream pathways.[137–139] For instance, the HIF-1 target lysyl oxidase enables tumor cells to acquire invasive competence.[139] Additionally, the endotoxin LPS induces TLR4/myeloid differentiation factor (MyD) 88-dependent ROS generation and HIF-1 activation, which is required for monocyte–macrophage differentiation in inflamed tissues.[140] A ROS/STAT3/HIF-1α/TWIST1/N-cadherin signaling cascade is involved in prostate cancer progression.[141] Furthermore, ROS and HIF-1 enhance the development of resistance to chemotherapeutics such as Doxorubicin and etoposide in lung, cervical carcinoma and melanoma cell lines.[142,143] However, attenuation of ROS by antioxidants suppresses hypoxia-induced EMT and metastasis in pancreatic cancers.[144] In summary, these findings demonstrate that both ROS and HIF-1 mutually benefit from each other for their generation and activation, respectively, which heightens aggressiveness of the tumors.

Concluding remarks

“-Hitting several birds with one stone-”: combating cancer and cancer-associated inflammation through HIF-1

Understanding the precise mechanisms underlying tumor progression is key to effective therapeutic interventions. Among the pro-oncogenic factors, HIF-1 plays a pleiotropic role in augmenting many biological processes associated with tumorigenesis. HIF-1 exerts this effect through collaboration with many factors including, but not limited to, STAT3, NF-κB, TLR4, Myc, mTOR, AP-1, IGF-1, Wnt, TGF-β, and Notch1 (Figure 3). Besides the functions discussed in this review, in support of its central role in mediating cancer progression, HIF-1 also regulates other aspects of cancer biology such as miRNAs, epigenetic alterations and autophagy as discussed elsewhere.[128,145,146] Given the critical role of HIF-1 in tumor progression including its role in CSC maintenance, it is apparent that HIF-1 signaling contributes significantly to metastasis and treatment resistance.[12,80,92,144] Accordingly, efforts have been made to target various HIF-1-regulated pathways (see also Figure 1). For instance, the VEGF-neutralizing antibody Avastin (bevacizumab) is an approved anti-angiogenic cancer therapeutic. However, some reports show that anti-angiogenic agents indeed increase tumor invasiveness and metastasis in xenograft models due to increased tumor hypoxia and HIF-1α expression.[147–149] These findings emphasize the need to explore the possibilities of targeting HIF-1 directly to solve the problem of resistance and relapse. Interestingly, the therapeutic effects of HIF-1 inhibition by small molecules have already been demonstrated in preclinical mouse models. Therefore, this area of research promises to lead to significant advances in the near future.[134,150–154] Targeting HIF-1 directly could potentially resolve the primary hurdle associated with treatment-refractory cancers and simultaneously overcome the problems associated with cancer-related inflammation.

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Abbreviations

AP-1	Activator protein-1
BECs	Blood endothelial cells
BMDCs	Bone marrow-derived cells
CAIX	Carbonic anhydrase IX
CAFs	Cancer-associated fibroblasts
CSCs	Cancer Stem Cells
COX-2	cyclooxygenase 2
CTL	Cytotoxic T lymphocytes
DCs	Dendritic cells
EMT	Epithelial-mesenchymal transition
FIH	Factor inhibiting HIF
HIFs	Hypoxia-inducible factors
HREs	Hypoxia-responsive elements
IL-6	Interleukin-6
LECs	Lymphatic endothelial cells
MIF	Macrophage migration inhibitory factor
mTOR	Mammalian target of rapamycin
MMPs	Matrix metalloproteinases
MSCs	Mesenchymal stem cells
MCT4	Monocarboxylate transporter 4
MDSCs	Myeloid-derived suppressor cells
NHE1	Na^+/H^+ exchanger 1
NOS2	inducible nitric oxide synthase
NF-κB	Nuclear factor-κB
PECAM-1	Platelet endothelial cell adhesion molecule-1
PD-L1	Programmed death ligand 1
PHDs	Prolyl hydroxylases

ROS	Reactive Oxygen Species
STAT3	Signal transducer and activator of transcription3
TAECs	Tumor-associated endothelial cells
TAMs	Tumor-associated macrophages
TGF-β	Transforming growth factor-β
TLR4	Toll-like receptor 4
VEGF	Vascular endothelial growth factor
VHL	von-Hippel Lindau

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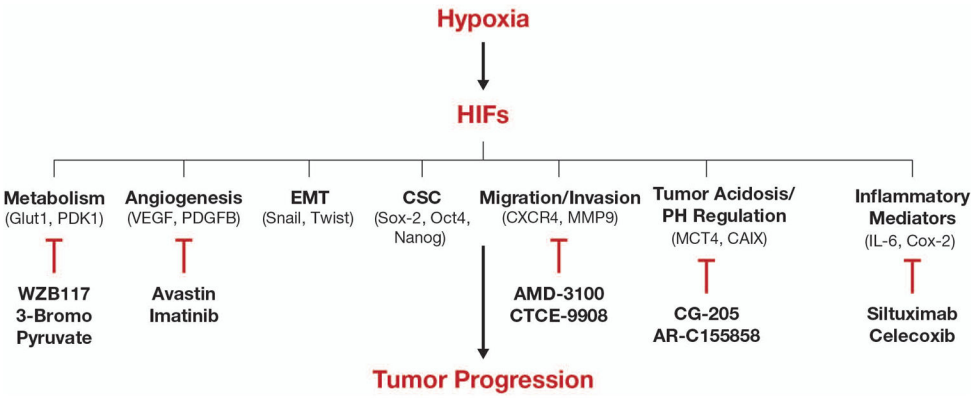

Figure 1. Hypoxia/HIF-1 links several pathways involved in tumor aggressiveness

Scheme representing cellular functions regulated by HIF-1 and showing examples of direct target genes involved in various signaling pathways. Examples of existing inhibitors and/or FDA-approved drugs, which are specific to various HIF-1 regulated genes/pathways, are shown. CXCR4, Chemokine receptor 4; Nanog; Homeobox transcription factor; Oct-4, Octamer-binding transcription factor 4; Snail, Zinc finger transcriptional repressor; Sox-2, Sex determining region Y box-2; Twist, Basic helix-loop-helix transcription factor.

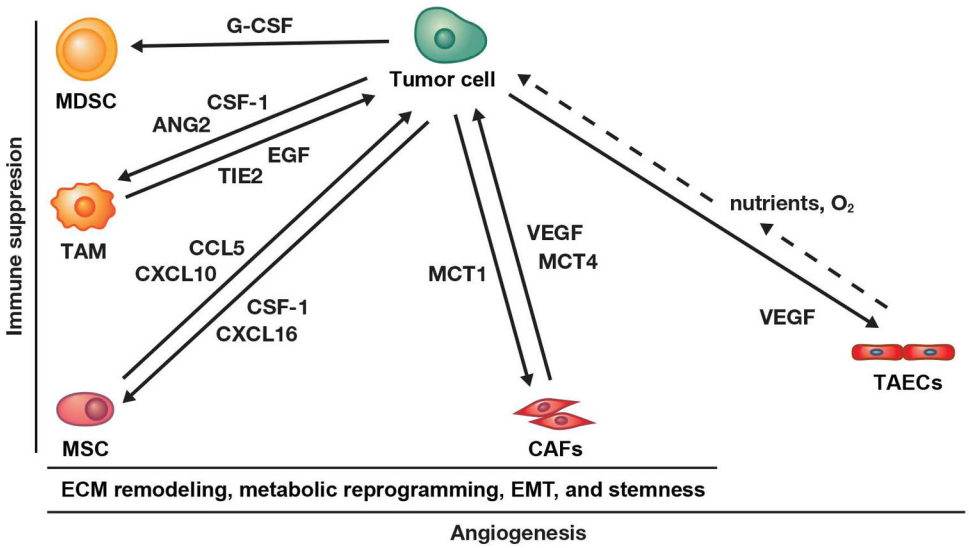

Figure 2. Simplified illustration showing tumor promoting cell-cell interactions within the tumor microenvironment supported by HIF-1 activity

Hypoxia, inflammatory conditions and genetic alterations activate HIF-1 that mediates cross-talk between tumor and multiple stromal cell types through specific factors, only a few of which are shown (for details see text). Details about role of MSCs in immune suppression, EMT, and stemness can be found in this recent review.[98]

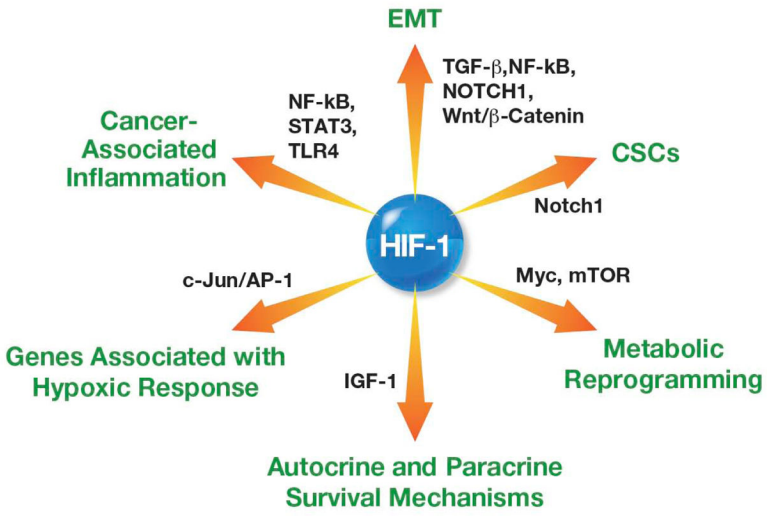

Figure 3. Partners in Crime

Scheme summarizing the collaborators of HIF-1 in the signaling pathways associated with hypoxia adaptation, cancer progression and cancer-associated inflammation (see text for details).