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Hypoxia-induced epithelial to mesenchymal transition in cancer

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Abstract

A common feature of many solid tumors is low oxygen conditions due to inadequate blood supply. Hypoxia induces hypoxia inducible factor (HIF) stabilization and downstream signaling. This signaling has pleiotropic roles in cancers, including the promotion of cellular proliferation, changes in metabolism, and induction of angiogenesis. In addition, hypoxia is becoming recognized as an important driver of epithelial-to-mesenchymal (EMT) in cancer. During EMT, epithelial cells lose their typical polarized states and transition to a more mobile mesenchymal phenotype. Hypoxia induces this transition by modulating EMT signaling pathways, inducing EMT transcription factor activity, and regulating miRNA networks. As both hypoxia and EMT modulate the tumor microenvironment (TME) and are associated with immunosuppression, we also explore how these pathways may impact response to immuno-oncology therapeutics.

Keywords

EMT; hypoxia; HIF; metastasis; immunosuppression; cancer

1. Introduction

1.1 Hypoxia

Given the critical role of molecular oxygen to cellular activity, physiological processes have developed to adapt to differing oxygen concentrations. This oxygen sensing occurs primarily through a highly conserved pathway that appears to function in all metazoans[1]. In this pathway, hypoxia inducible factor (HIF) serves as a transcription factor that regulates cellular adaption to low oxygen (i.e. hypoxic) conditions. HIF proteins are heterodimers formed from a constitutively expressed HIFβ subunit paired with an oxygen-regulated HIFα protein[2,3]. Though the HIFα proteins exist as three isoforms, HIF-1α, HIF-2α, and HIF-3α, HIF-1α is the primary form that regulates the hypoxia response in most tissues[4].

Conflict of Interests

We have no significant conflict of interests to disclose.

HIF oxygen sensing occurs through the hydroxylation of two distinct prolyl residues on HIFα by prolyl hydroxylase domain (PHD) proteins[5,6]. Under well-oxygenated conditions, PHD proteins hydroxylate HIFα, allowing Von Hippel Lindau protein (pVHL) to bind. pVHL recruits an E3 ubiquitin ligase that polyubiquinates HIF-1α, targeting it for proteasomal degradation[7]. Conversely, under hypoxic conditions, hydroxylation of HIF-1α is inhibited, allowing for dimerization with HIF-1β to form active HIF-1 transcription factor. Through the basic helix-loop-helix (bHLH) motif, active HIF-1 recognizes specific sequences of DNA termed hypoxia response elements (HREs) within gene loci, driving transcriptional expression of hundreds of genes[8]. Besides PHD regulation, factor inhibiting HIF-1 (FIH-1) represses HIF activity in well-oxygenated conditions by hydroxylating an arginine on HIF-α and inhibiting transcriptional activation[9]. A common technique to mimic hypoxia-induced signaling is through $CoCl_2$ treatment, which inhibits PHD function and upregulates HIF expression[10].

Uncontrolled proliferation within tumor tissue can create an oxygen-starved environment as the blood supply becomes insufficient. In response, hypoxic signaling stimulates angiogenesis, or the growth of new blood vessels, to increase oxygen delivery. However, the rapid proliferation of malignancies often outpaces angiogenesis, leading to intra-tumoral hypoxic regions and even necrosis within solid tumor cores[11]. Although hypoxia can be toxic, cancer cells adapt in various ways to allow continued tumor progression in such an environment. Activation of hypoxic signaling pathways may even be advantageous to some aspects of cancer development, as tumors have developed numerous mechanisms to increase HIF activity even in well-oxygenated conditions. This list includes the loss of pVHL in renal cell carcinomas, HIF-1α stabilization by herpesvirus in Kaposi's carcinoma, and various oncogenes and tumor suppressors identified to activate or inhibit HIF-1 activity, respectively[12]. This inappropriate stabilization of HIF-1α during normoxic conditions has been observed in numerous cancers, including breast, pancreatic, prostate, and kidney cancers[13]. Overexpression of HIF-1α correlates with worse prognosis in many solid tumors, including gastric cancer, osteosarcoma, and colorectal cancer (CRC)[14–16]. As the situations described above do not necessarily occur in a low oxygen environment, the signaling differences from authentic hypoxia and stabilization of HIF in the context of normal oxygen tension or "pseudo-hypoxia" could account for the discrepancies seen by different groups. In an effort to highlight these disparities, we will hereinafter emphasize if observations about hypoxic signaling pathways were made in normoxic conditions (e.g. *VHL* gene deletion or $CoCl_2$ treatment) versus low oxygen tension or true hypoxia.

The HIF transcription factors are perhaps best known for their role in hypoxia-induced angiogenesis, allowing for increased oxygen and nutrient delivery to the tumor. However, the role of HIFs in cancer development extends beyond angiogenesis, and includes reprograming metabolism, regulating cell proliferation and survival, and increasing therapeutic resistance[17]. HIF proteins also play a role in metastatic disease. For example, increased HIF-1α was observed in breast and pancreatic metastases relative to primary tumors[13,18]. Subsequent research has identified several hypoxia mechanisms that promote metastasis, including the promotion of an epithelial to mesenchymal transition (EMT)[19].

1.2 EMT

The EMT process is an important early step in the development of metastases in solid epithelial tumors. EMT is a reversible transition in which malignant carcinomas lose epithelial characteristics in favor of mesenchymal traits, including enhanced migratory capacity and invasiveness[20]. While occurring in normal development and physiology such as embryo formation and wound healing, for the purpose of this review, we will focus on the type of EMT that occurs in carcinomas[21]. It is worth noting that the role of EMT *in vivo* has been controversial and at times difficult to observe[22,23]. This difficulty in observing EMT in cells from *in vivo* tumors may be due to the transient and reversible nature of EMT as well as intratumoral heterogeneity. For example, some regions, such as the leading edge of invasive tumors, may have higher proportions of cells undergoing EMT than other regions[24]. Given this intratumoral hetereogeneity, it is perhaps not surprising that single cell transcriptomics have had success in identifying cell populations within tumors that exhibit EMT characteristics[25]. These studies also support that EMT is not a binary switch, but rather the transition may occur on a continuum in which hybrid epithelial/mesenchymal (E/M) cells exist. This hypothesis is supported in human malignancies, as circulating E/M hybrid breast cancer cells were found in patient blood samples[26].

Metastasis consists of several steps that are aided by increased mesenchymal traits, including invasion, migration and intravasation[27]. EMT is initiated through a loss of cell polarity, along with disassembly of cell-cell contacts, including desmosomes, tight junctions, adherens junctions, and gap junctions[28]. The transition includes the downregulation of epithelial cell markers, such as E-cadherin. Concomitantly, mesenchymal characteristics are gained, with upregulation of N-cadherin, vimentin, fibronectin, various matrix metalloproteases (MMPs), and β1 and β3 integrins[28]. Although roughly 400 genes are reconfigured in the EMT process, select transition factors have been discovered that regulate EMT (EMT-TFs)[29,30]. This list of EMT-TFs includes SNAIL1–2 (*SNAI1–2*), TWIST1–2, ZEB1–2, FOXC2, goosecoid, and others, leading to the repression of E-cadherin and other junctional proteins[31,32]. The induction of EMT also occurs through signaling pathways involving transforming growth factor β (TGFβ), Notch, and others, leading to EMT through a variety of methods[33–35]. Although the mechanisms whereby these pathways facilitate EMT remain an active area of research, all rely at least partly on the upregulation and activation of key EMT-TFs. Regulation of EMT also occurs at the post-transcriptional level by the activity of microRNA (miRNA, miR) and long non-coding RNA (lncRNA)[36]. These various pathways are explained in greater detail in their respective sections below. Outside of metastasis, EMT also aids primary tumor progression by increasing therapeutic resistance to chemo-, radio-, and immunotherapies[37,38].

Hypoxia affects EMT through several core themes: regulating EMT signaling pathways, modulating EMT-TF expression and signaling, and regulating EMT-associated miRNA and lncRNA networks. Hypoxic signaling also modulates the tumor microenvironment, including infiltrating immune cells, which potentially synergizes with EMT-mediated immunosuppression[39]. The transition from epithelial to mesenchymal lineage assists with early stages of metastasis, but may be detrimental in later stages, such as metastatic seeding and out-growth of secondary tumors. These later stages may require a reversal of EMT in a

process termed mesenchymal to epithelial transition (MET). In the context of hypoxia-induced EMT, departure of the mesenchymal-like tumor cell from its hypoxic primary tumor to a more oxygen-rich secondary site may facilitate MET by loss of hypoxic signaling[40,41].

2. EMT signaling and Hypoxia

While EMT and hypoxia are best recognized for their essential roles in the respective cancer hallmarks of metastasis and angiogenesis, a link between the two is continuingly being established (Fig. 1). Regulation of the EMT is well characterized in the context of signaling based on external stimuli and is induced in several methods, including by TGFβ, WNT-β-catenin, Notch, and Hedgehog (SHH) pathways[42]. Under hypoxia, several of these EMT signaling pathways are similarly active (Fig. 1A). The best understood connections are with the TGFβ, nuclear factor-κB (NF-κB), and Notch pathways and are discussed below. However, this section is by no means comprehensive[43,44].

2.1 TGFβ

The TGFβ signaling pathway is active in an assortment of developmental programs, including cell proliferation, differentiation, morphogenesis, tissue homeostasis, and regeneration[45]. Various diseases have dysregulated TGFβ signaling, such as cardiovascular diseases, connective tissue diseases, skeletal and muscular disorders, and cancers[46]. During cancer progression, TGFβ serves as a tumor suppressor in early stages of disease. Eventually, the cancer cell may evolve mechanisms whereby it evades these growth inhibitory effects, leaving tumor promoting properties of TGFβ unopposed. Thus, TGFβ may transition to an oncoprotein in later stages of cancer[47,48]. TGFβ signaling in cancer thus has diverse actions and was recognized early on as an inducer of EMT[49].

TGFβ family proteins are an important promoter of the EMT process, and inhibition of TGFβ binding to its receptor inhibits EMT[50]. TGFβ induces EMT by signaling through a heterotetrameric TGFβ receptor complex consisting of both type I and II serine-threonine kinase receptors. The activated receptor then phosphorylates Smad2 and 3, which form trimers with Smad4 that activate three distinct families of EMT-TFs: SNAIL, ZEB, and bHLH (TWIST) families. This activation occurs either directly in the case of SNAIL1 and SNAIL2, in which active Smad binds to their respective promoters and promotes transcription, or indirectly with the ZEB and bHLH families[33]. TGFβ also promotes EMT through Smad-independent signaling, including through RHO-like GTPases, phosphoinositide 3-kinase (PI3K), and ERK mitogen-activated protein kinase (MAPK) pathways[28,33].

The TGFβ and hypoxia signaling pathways demonstrate crosstalk at numerous levels (Fig. 1A). An early discovery of this connection was made when hypoxic fibroblasts were discovered to upregulate expression of TGFβ1[51]. In the context of cancers, a similar observation was made with increased TGFβ expression in lung carcinoma cells under long term (>10 days) exposure to hypoxia[52]. Under hypoxia, the TGFβ pathway is active, with upregulation of TGFβ type I receptor at protein level and greater levels of Smad3[52,53]. TGFβ autocrine signaling by hypoxic gastric cancer cells results in EMT, indicating the

importance of TGFβ in hypoxia-induced EMT[54]. Interestingly, while hypoxia has been shown to potentiate TGFβ signaling pathways, TGFβ was found to stabilize HIF1 through the downregulation of PHD2 expression, establishing positive feedback between the two pathways[55]. pVHL was recently discovered to poly-ubiquinate TGFβ type I receptor, marking it for proteasomal degradation and possibly indicating another level of hypoxia-TGFβ crosstalk[56].

2.2 NF-κB

The NF-κB signaling pathway is best known for its role in immune system development, but also plays roles in cell proliferation, survival, and differentiation[57]. NF-κB signaling is initiated through the pairing of a variety of ligands and receptors, including primarily the TNF receptor (TNFR), Toll-like receptor (TLR), and pattern recognition receptor (PRR) families[57]. In cancers, NF-κB is an oncogene that links chronic inflammation with disease, along with stimulating cell proliferation, survival, angiogenesis, metabolic remodeling, and EMT[58].

Huber et al. demonstrate that NF-κB is essential to the EMT process, and inhibition of NF-κB signaling reversed EMT and abrogated metastatic potential in a mouse model[34]. Since this discovery, the mechanism by which NF-κB regulates EMT is increasingly becoming clearer. Activation of the NF-κB pathway induced the expression of TWIST1 and was followed with EMT[59]. In a pancreatic cancer model, the inhibition of NF-κB signaling decreased the expression of EMT-TFs SNAIL1, SNAIL2, and ZEB1, along with mesenchymal marker vimentin[60]. Recently, Pires et al. demonstrated that NF-κB binds to the promoter regions of several EMT-TF genes, including *TWIST1*, *SNAIL2*, and *ZEB2*, upregulating their expression[61]. NF-κB signaling also indirectly upregulates EMT-TFs, as SNAIL1 was stabilized by NF-κB-induced *COPS2* expression, which blocks SNAIL1 ubiquitination and degradation[62].

Hypoxia rapidly activates NF-κB through robust crosstalk between various components of both hypoxia and NF-κB pathways (Fig. 1A)[63]. Under hypoxia, increased degradation of IκBα, an inhibitor of NF-κB, activates the signaling pathway[64]. Although the functional relevance requires further investigation, HIF asparaginyl hydroxylase (FIH-1) post-translationally modifies multiple components of the NF-κB pathway under normoxia[65]. PHD1, an enzyme regulating HIF prolyl hydroxylation, was proposed to similarly regulate a component of the NF-κB pathway under well-oxygenated conditions and inhibit its functions[66]. However, this stance has been challenged recently and requires further verification[67]. Reciprocally, NF-κB serves as transcriptional activator of HIF-1α, indicating similar crosstalk between the two factors[68]. Treatment of cell lines with TNFα, a potent cytokine inducer of NF-κB signaling, stabilizes HIF-1α protein in normoxia[69]. Given the significant crosstalk between the two pathways, hypoxia-induced EMT is abrogated by NF-κB downregulation in pancreatic and colorectal cancer models[70–72].

2.3 Notch

After binding of signaling ligand to the Notch receptor, the activated Notch intracellular domain (ICD) is cleaved and travels to the nucleus, where it directly stimulates transcription

of target genes. Although simple, the pleiotropic Notch signaling pathway plays diverse roles in development, stem cell differentiation, cell proliferation, and apoptosis[73]. The Notch pathway is deregulated in many cancers, with roles as either an oncoprotein or tumor suppressor protein depending on the context[74]. In cancers such as cervical, lung, pancreatic, renal, and colon, activating elements of the Notch signaling pathway are upregulated, suggesting an oncogenic role in these diseases[35].

Activation of Notch1 induces EMT in cancer cells[75,76]. The role Notch1 plays in EMT is complex, but can primarily be summarized to its effects to EMT-TFs SNAIL1 and SNAIL2, along with TGFβ pathway activation[35]. The activated Notch1 ICD directly upregulates the transcription of *SNAI2* by gene promoter activation[77]. Notch signaling has two distinct mechanisms to upregulate expression of SNAIL1, one of which is HIF-dependent. First, Notch directly promotes SNAIL1 expression through binding of the Notch ICD to the *SNAI1* promoter[78]. Second, Notch1 augments HIF-1 recruitment to the *LOX* promoter, enhancing expression of the *LOX* gene[78]. LOX enhances SNAIL1 protein stability and potentiates its EMT-inducing activity[78,79]. Notch and TGFβ signaling pathways have extensive crosstalk, particularly in promotion of EMT. Notch and TGFβ pathways cooperate to promote HEY1 expression, which is also required for TGFβ-induced EMT[80]. As part of this synergistic pathway, Notch ligand Jagged1, Notch1, and TGFβ signaling component Smad3 are all required for TGFβ-induced EMT[80].

The role of Notch in hypoxia is still emerging but is known to interact at multiple levels. Hypoxia and Notch signaling share similar gene signatures, suggesting a functional synergy between the two[81]. Hypoxia induces the Notch signaling pathway by stabilizing the Notch1 ICD and upregulating expression of Notch ligand, Jagged2 (Fig. 1A)[82,83]. Further, the Notch ICD binds FIH-1, the HIF asparaginyl hydroxylase, with higher affinity than does HIF-1[84]. As the Notch ICD potentially serves as a competitive inhibitor of FIH-1, this possibly accounts for the observed increase in HIF activity upon Notch activation. This synergy between the two pathways similarly applies to the EMT process. Activation of Notch signaling under hypoxia stimulated EMT in cancer[85]. Hypoxic tumor cells require Notch signaling for EMT, suggesting that in some contexts Notch is necessary for hypoxia-induced EMT[78].

3. EMT-TFs and Hypoxia

EMT-TFs, such as TWIST, SNAIL, and ZEB, alter the expression of hundreds of genes and their expression is critical for EMT. Not only does hypoxia activate signaling pathways that induce EMT-TF expression, but hypoxia also directly promotes EMT via the transcriptional activation of these factors.

3.1 TWIST1

Including HIF proteins, TWIST1 is among the bHLH family of transcription factors, which modulate target gene expression through E-box response elements[86]. During development, TWIST1 normally acts in mesoderm differentiation. In cancers, the roles of the TWIST1 transcription factor include the promotion of primary tumor growth, metastatic dissemination, and chemoresistance[86]. The expression of TWIST1 causes transcriptional

repression of E-cadherin, losing E-cadherin-mediated cell-cell adhesion and inducing EMT along with the expression of mesenchymal markers[87]. HIF-1 directly upregulates TWIST1 expression by binding to the HRE in the *TWIST1* proximal promoter (Fig. 2)[88]. Hypoxia-induced TWIST1 regulation promotes EMT, and the inhibition of TWIST1 in this context reverses the EMT process[88]. This model of hypoxia-driven TWIST1 activation for EMT has been confirmed in numerous cancer models, including pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer (NSCLC), and ovarian epithelial cancer (OEC)[89–91].

3.2 SNAIL1

The transcription factor SNAIL1 is essential for mesoderm formation during development[92]. SNAIL1 induces EMT mainly by suppressing E-cadherin expression, along with up-regulating key mesenchymal genes such as fibronectin (*FN1*) and *MMP9*[93]. In hepatocellular carcinoma (HCC), HIF-1α was found to correlate with SNAIL1 expression[40]. In an ovarian carcinoma model, hypoxia-induced SNAIL1 attenuated the expression of E-cadherin and increased the invasiveness of cancer cells[94]. Introduction of an oxygen-insensitive HIF resulted in an induction of SNAIL1 expression, indicating that the expression of SNAIL1 is HIF-dependent[95]. Since these observations, several mechanisms as to how HIF induces SNAIL1 expression have been established. One mechanism is a direct route in which HIF transcription factor activates SNAIL (*SNAI1)* promoter activity, as SNAIL1 contains two putative HREs in the *SNAI1* promoter region. Mutation of these HRE domains drastically decreased *SNAI1* expression, suggesting HIF-mediated transcriptional activation[96]. In mice, chromatin immunoprecipitation (ChIP) assays confirmed association of HIF with the *SNAI1* promoter HRE (Fig. 2)[95]. Second, the TGFβ signaling pathway is a known inducer of SNAIL1 expression[97]. Given the crosstalk between HIF and TGFβ, it is possible that hypoxia-induced TGFβ activates SNAIL1 activity, but this needs further investigation. A third mechanism is attenuated proteasomal degradation of SNAIL1 through deubiquitinating enzyme ubiquitin-specific protease 47 (USP47) activity, which is elevated under hypoxic conditions in colorectal adenocarcinoma (Fig. 2)[98]. USP47, which deubiquitinates SNAIL1, is upregulated in hypoxia via a transcription factor cascade. HIF binds to the promoter region of *SOX9*, elevating its expression. USP47 is a target gene for SOX9 transcription factor activity, and is therefore up-regulated under hypoxia[98].

3.3 ZEB1

ZEB1 is another EMT-TF that is active under hypoxia. Through its zinc-finger clusters, ZEB1 binds to E-box motifs in gene promoter regions and recruits transcription co-activators or corepressors to modulate gene expression[99]. It is in this manner by which ZEB1 alters the expression of over 200 genes, including the transcriptional repression of *CDH1*, the gene coding for E-cadherin[100]. Besides affecting classical EMT genes, ZEB1 has also been shown to suppress the expression of miR203 and miR200 stemness-inhibiting microRNA (miRNA)[101]. As both EMT and stemness inducing pathways are closely associated, decreasing expression of stemness-inhibiting miRNA is likely another mechanism whereby ZEB1 activates EMT[102]. Much like TWIST1 and SNAIL1, the ZEB1 promoter region contains an HRE that is recognized and directly bound by HIF-1 (Fig. 2)[103]. Stabilization of HIF-1 leads to transactivation of ZEB1 and subsequent EMT

induction. Inhibition of ZEB1 abrogates hypoxia-induced EMT, indicating a reliance on this factor for the EMT process[103].

3.4 Other EMT-TFs in hypoxia

While TWIST1, SNAIL1, and ZEB1 are the EMT-TFs most commonly associated with hypoxia, other EMT-TF have been implicated in oxygen-poor environments. SNAIL2 (SLUG) and TCF3 (E47), are upregulated under hypoxia in certain instances[104,105]. Whether this is a direct mechanism of HIF transcriptional activation, or a downstream result of hypoxia-induced EMT requires further investigation. HIF-1 was recently found to bind to an HRE in the promoter region of ZEB2 (SIP1), inducing its expression in podocytes[106]. ZEB2 is similarly induced in hypoxia-mediated EMT, and could therefore be another EMT-TF target of direct HIF transcriptional activation[107]. Numerous EMT-TFs are implicated in hypoxia, either as direct transcriptional targets, or as essential components in downstream processes of hypoxia induced EMT. Further work is necessary to clarify which EMT-TFs are most essential to each carcinoma.

4. Extracellular Matrix

Many aspects of EMT are influenced by extracellular cues and processes. As such, alteration of the ECM surrounding epithelial cells has been shown to induce EMT. Numerous components of the ECM affect EMT, including collagen, fibronectin, and MMPs. Likewise, hypoxia and HIF signaling is known to remodel the ECM through various means. It is likely that the effect of HIF on ECM remodeling affects hypoxia-mediated EMT.

Another component of ECM signaling occurs through cell adhesion molecules (CAMs), which are a subset of transmembrane receptors that facilitate cellular adhesion to specific components of the ECM and subsequently trigger internal signaling that affects a broad range of processes including cellular growth, differentiation, junction formation, and polarity[108]. CAM families include integrins, cadherins, selectin and immunoglobin superfamily CAMs, the majority of which have been identified to play a role in EMT.

4.1 ECM remodeling

The role of the extracellular matrix (ECM) in the modulation of the EMT process was recognized early on, when Greenburg and Hay observed that epithelial cells acquired mesenchymal traits during growth in 3D collagen gels[109]. Subsequent research has shown that in NSCLC, collagen I induces EMT through TGFbeta signaling[110]. Collagen is similarly implicated in hypoxia-induced EMT. Under hypoxia, collagen I remodeling is increased, presumably from upregulated urokinase-type plasminogen activator receptor (uPAR) expression[111]. Silencing of uPAR diminished hypoxia-mediated collagen I remodeling and subsequent EMT, indicating an importance of the ECM in hypoxia-induced EMT. Other components of the ECM, such as fibronectin, are also affected under hypoxia. HIF-1 signaling increased the abundance of extracellular fibronectin, although it did not seem to affect filament formation[112].

Hypoxia also causes broad changes to ECM composition and organization through altering expression of MMPs, the key proteolytic enzymes of the ECM. MMPs are well described as

mediators of EMT processes[113]. Under prolonged hypoxia, MMP2 is upregulated[114]. In hypoxia-induced EMT, SNAIL2 directly upregulates MMP17 expression, increasing *in vitro* invasiveness[115]. Finally, through a HIF-1-dependent manner, hypoxia increases the expression of MMP13 in tumor-derived exosomes[116]. Knockdown of MMP13 expression restored epithelial markers in nasopharyngeal carcinoma cells, indicating a reversal of EMT[116]. This complex relationship between hypoxic ECM alterations and the role of the extracellular environment on EMT is still being resolved and warrants further investigation.

4.2 Cadherins

Cadherins are classically involved in the EMT process, serving as markers of either epithelial or mesenchymal type. E-cadherin expression in epithelial cells is repressed either directly or indirectly by EMT-TFs, and N-cadherin expression is up-regulated in mesenchymal cells. Other cadherins are also regulated in EMT, including cadherin 7, cadherin 6B, and cadherin 11[117]. The contributions of cadherins to hypoxia-induced EMT warrants further investigation, especially with the recent discovery of hypoxia-activated cadherins[118,119].

4.3 Integrins

The integrin family of receptors consist of 18 α- and 8 β- subunits that comprise 24 distinct heterodimers. This family recognizes various components of the ECM, binding of which results in activation of integrin-mediated signaling pathways. ECM components including vitronectin, collagen, and fibronectin are upregulated during EMT, resulting in EMT-mediated integrin activation[120]. Similarly, β6 integrin overexpression induces EMT, indicating a significant role for integrins in the promotion of EMT[121].

Integrin expression is also regulated in EMT, with some complexes serving as essential components of the transition[122]. Maschler et al. discovered that α5β1 was central to EMT induction, inhibition of which resulted in apoptosis during TGFβ-induced EMT[123]. αVβ3, αVβ5, and αVβ6 integrins are all upregulated during EMT, presumably induced by TGFβ signaling[122]. Integrin β1 (ITGB1) was similarly shown to promote the expression of various EMT-related genes[124].

The significance of integrins to TGFβ-mediated EMT was demonstrated in the context of hypoxia. Integrin β3 (ITGB3) expression is necessary for sustained hypoxia-induced TGFβ pathway activation, and knockdown of integrin β3 reduced SNAIL1 expression and subsequent EMT[125]. Integrin α5β3 is similarly activated in hypoxic pancreatic cancer by increased levels of its ligand, osteopontin, and induces EMT characteristics[126]. Endoplasmic reticulum disulphide oxidase (ERO1α) promotes cancer progression in hypoxic conditions. Interestingly, ERO1α expression is linked to ITGB1 activation, and loss of ERO1α attenuates EMT-related gene expression through an ITGB1-dependent pathway[127].

5. Role of Hypoxia-regulated RNA on EMT

The regulation of EMT is not only limited to signaling pathways and transcriptional regulation, as various forms of RNA impact the process. miRNA are potent regulators of

cellular processes, including EMT, and serve as post-transcriptional repressors of mRNA activity by either guiding mRNA degradation or inhibiting translation of mRNA[36]. In the hypoxic niche, various EMT-regulating miRNA are affected, playing a role in the regulation of hypoxia-induced EMT (Fig. 1A). In hypoxia, DICER expression is repressed, leading to decreased processing and activation of EMT-suppressing miRNA species[128]. Forced expression of DICER in this context inhibits hypoxia-induced EMT, indicating a general suppressive role for miRNA in this process[129].

In an HCC model, hypoxia was found to downregulate miR-204 levels, allowing for increased VASP activity and the upregulation of various mesenchymal markers[130]. In p53-deficient CRC, miR-34A was repressed by HIF-1 occupancy in an HRE located in the miR-34A promoter[131]. Hypoxia induction of EMT required downregulation of miR-34A, and ectopic expression of miR-34A inhibited the transition process[131]. Hypoxia similarly repressed miR-1236 through a TWIST-mediated pathway, while ectopic expression of the miRNA abolished hypoxia-induced EMT[132]. Although several examples exist whereby hypoxia regulates EMT by downregulating miRNA, upregulation of miR-210 in the hypoxic niche causes suppression of E-cadherin and promotes EMT[133]. Other miRNA are proposed to influence hypoxia-induced EMT, including miR-1296, −200b, and −3194–3p[134–136]. EMT was promoted through hypoxia-induced exosomes containing miR-1273f, suggesting a potential role for extracellular processes in the complex regulation of hypoxia-induced EMT[137].

LncRNA similarly affect transcriptional regulation, though by acting as “miRNA sponges” to degrade miRNA targets[138]. Although miR-508 normally blunts TGFβ-mediated EMT, miR-508 is repressed under hypoxia by HIF-induced lncRNA AK000053, allowing for hypoxia-induced EMT[139]. The lncRNA NORAD promoted hypoxia-induced EMT in pancreatic cancer, possibly through its repression of miR-125a-5p activity[140]. HOTTIP sponged miR-101 in glioma, increasing ZEB1 expression and promoting hypoxia-induced EMT[141]. In glioblastoma, hypoxia-induced H19 binds miR-181d, promoting EMT via activation of the β-catenin pathway[142].

6. Hypoxia and Tumor Microenvironment

To this point, the focus of this review has been on how the hypoxia signaling pathway within the cancer cell is also capable of promoting the EMT of cancer cells. However, hypoxia within a tumor elicits a highly complex response including changes in the cell types of the TME. These recruited cell types are capable of profoundly influencing the biology of the cancer cells, including the induction of EMT. For example, numerous cell types accumulate within the hypoxic zone of tumors, including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and T-regulatory cells (T-regs) (Fig. 1B). These cell types can directly contribute to EMT-promoting pathways (e.g., TGFβ, NF-κB, and Notch) via a variety of mechanisms including paracrine signaling. Furthermore, cancer cells are not passively influenced by other cell types within the hypoxic TME, but rather can actively regulate and recruit other cells to this complex ecosystem. Thus, a comprehensive analysis of how hypoxia influences tumor cell biology, including EMT, requires a careful consideration of the entire hypoxic TME.

6.1 Hypoxia, the tumor microenvironment, and EMT

Hypoxia in the TME remodels the cellular landscape, which can directly and indirectly influence cancer cell EMT. EMT utilizes numerous pathways that depend on external cytokine signaling (eg. TNFα, TGFβ, interleukins, and chemokine ligands), and infiltrating immune cells in the hypoxic TME secrete several of these factors[143]. For instance, macrophages exposed to hypoxia increase secretion of EMT-inducing cytokines TNFα, CCL2, IL-1, and IL-6 (Fig. 1B)[144,145]. These hypoxia-induced changes in the activity and function of immune cells not only promotes cancer cell EMT, but may also promote a permissive immune environment with a blunted anti-tumor immune response[146]. For example, cancer cells partake in hypoxia-mediated chemokine signaling that recruits TAMs and MDSCs to the TME[147]. These hypoxic TAMs then promote an immunosuppressive environment through HIF-1 signaling to upregulate Arg1, which depletes the tumor milieu of L-arginine and suppresses T-cell activation under hypoxia (Fig. 1B)[148,149]. Similarly, hypoxic MDSCs upregulate Arg1 along with another suppressive factor, iNOS, to suppress T-cell proliferation[150]. Through a HIF-1-dependent pathway, numerous cell types (eg. TAM, MDSC, DC, and cancer cells) in the hypoxic TME upregulate PD-L1 levels, diminishing the antitumor immune response[151]. Hypoxia induces FOXP3 expression in T-cells, differentiating them to immunosuppressive regulatory T-cells (Tregs)[152]. Thus, various cell types respond in different manners to hypoxia to cooperatively promote an immunotolerant environment for cancer progression.

Similarly, there is now considerable evidence associating EMT with immune escape[153]. EMT mesenchymal markers are correlated with increased tumor Treg cell infiltration, a decrease in $CD8^+$ tumor infiltrating lymphocytes, and immunosuppressive TAM recruitment to the tumor[153,154]. Further, EMT in lung adenocarcinoma was associated with upregulated immune checkpoint molecules (i.e. PD-L1, PD-L2, PD-1, TIM-3, B7-H3, BTLA, and CTLA-4)[155]. EMT-TFs also act noncanonically in immunity, as Snail1-mediated EMT in cancer cells promotes an immunosuppressive environment through upregulated TSP1 cytokine signaling, inducing T-reg-like T-cells and impairing dendritic cell (DC) maturation[156]. Twist1 expression in cancer cells similarly regulates an immunosuppressive TME, and recruits macrophages by secreting chemoattractant CCL2[157]. Thus, both hypoxia within the TME and cancer cell EMT directly promote an immunotolerant environment. Recent research has shown that the two pathways, EMT and hypoxia, possibly synergistically remodel the TME in favor of immunosuppressive immune cells. Hypoxic cervical cancer cells upregulate ZEB1 to both promote EMT and immunotolerance[39]. Hypoxia-induced ZEB1 activates *CCL8* transcription, a cytokine that recruits immunosuppressive TAMs to the hypoxic invasive front during EMT and metastasis (Fig. 1B)[39]. In hepatomas, hypoxia-induced EMT signaling upregulated CCL20, a cytokine that induced surrounding macrophages to an immunosuppressive phenotype[154]. Thus, a paradigm is emerging whereby cancer cell EMT not only regulates the behavior of the individual cancer cell, but actively contributes to the evolution of an immunosuppressive TME.

7. Therapeutic Implications

Evading immune clearance is a hallmark of cancers, allowing malignant cells to avoid immune surveillance[158]. Immune escape occurs through a variety of mechanisms but includes TME remodeling and activation of immunosuppressive immune checkpoint blockade pathways. Understanding of this pathway has contributed to the revolutionary success of immuno-oncology (IO) in the clinic, with numerous FDA-approved therapies, including immune checkpoint inhibitors (ICIs). ICIs reinvigorate antitumor immunity by disrupting immune checkpoint blockade signaling, and are active in cancers such as melanoma, renal cell carcinoma (RCC), HCC, CRC, OEC, and numerous others[159]. As our understanding of the complex TME evolves, and as we better understand the many factors that contribute to the evasion of anti-tumor immunity, including hypoxia and tumor cell EMT, novel therapeutic strategies are emerging that seek to combine ICIs with other drugs in order to optimize the immune response.

One of the leading frontline therapies for RCC is the combination of pembrolizumab and axitinib, an anti-PD-1 monoclonal antibody paired with a VEGF receptor tyrosine kinase inhibitor (VEGFR TKI)[160]. A similar strategy is likely to be approved soon in HCC as well, given the recent phase III success of the IMBrace150 trial in which atezolizumab and bevacizumab (anti-PD-L1 and anti-VEGF monoclonal antibody, respectively) were combined[161]. Further, although still in early phases, combination of lenvatinib and pembrolizumab (VEGFR TKI and anti-PD-1 monoclonal antibody) showed promise across various solid tumor types[162]. Notably, these combinations target the VEGF pathway, which is a major component of hypoxic signaling and also potentiates EMT[163]. The clinical activity of these combinations suggests possible synergism between immune checkpoint blockade and the VEGF pathway. VEGF modulates immunity in a generally immunosuppressive manner[164]. VEGF suppresses T-cell activation through VEGF receptor-2 (VEGFR-2) signaling within the T-cell and increases PD-1 expression on $CD8^+$ T-cells, while VEGFR inhibition reversed both[165,166]. Further, sunitinib, a VEGFR tyrosine kinase inhibitor, reduces Treg cells in metastatic RCC patients, indicating that VEGF-based immunosuppression is multifold[167]. Thus, targeting both hypoxia and immune checkpoints simultaneously clearly has clinical efficacy.

While some of hypoxia-induced immunosuppression is VEGF-mediated, it is possible that more effective targets of hypoxia-induced immunotolerance exist. Current understanding of the mechanism and causes for immune evasion under hypoxia is still partially speculative, and the role for EMT is still not well understood. Given the connection between EMT and immunosuppression, it is feasible that EMT inhibition in this hypoxic context can potentiate antitumor immunity. Although harmine was recently identified as a potent inhibitor of TWIST1, other agents targeting EMT-TFs are rare (Fig. 1A)[168]. Other agents may prove useful in inhibiting other pathways that mediate EMT, such as SD-093, DHMEQ and PF-03084014, which inhibit TGFβ, NF-κB, and Notch pathways, respectively[61,169,170]. EMT inhibition appears to pair well with ICI, as inhibition of the potent EMT-inducer TGFβ synergizes well with PD-1 immune checkpoint blockade, causing durable responses in urothelial cancer mouse models[171]. Alternatively, HIF inhibition remains an attractive pairing with ICIs, and several HIF antagonists (eg. PT2977 and EZN-2208) are currently

being tested in trials, including in combination therapy with ICIs[172]. In a prostate cancer model, elimination of hypoxia with prodrug TH302 paired well with ICI and resulted in increased T-cell infiltration and vastly improved clearance of tumors[173].

8. Summary and Outlook

Hypoxia plays numerous roles in cancers, an aspect of which includes the induction of EMT-related genes. Hypoxia and metastasis are closely correlated, and EMT accounts for at least part of this relationship. HIF signaling affects the transcription of numerous genes, and directly stimulates the production of EMT-TFs and affects the activity of EMT signaling pathways. A better understanding of the most essential components for hypoxia-induced EMT is necessary, as numerous reports have contradictory results. For instance, in some models, hypoxia induces transcriptional expression of *TWIST1*, alongside other EMT-TFs[88]. Other models observe that *TWIST1* levels remain unchanged, while other EMT-TFs are induced under hypoxia[174]. It is possible that the strength and mechanism of hypoxia-mediated EMT induction is dependent on several factors, including cell type, hypoxia severity, exposure length, and microenvironment, and thus warrants further investigation.

The recent therapeutic advancements with the introduction of ICIs signal the start of a new era in oncology. Combination therapies are becoming mainstay in numerous cancers. As our understanding of immuno-oncology progresses, the significance of immune evasion by cancers is becoming clear. As both targeting hypoxia and EMT may synergize with ICIs, further investigation of the role of EMT in hypoxia-mediated immunosuppression is necessary. Improved understanding of the molecular pathways can drive informed treatment of hypoxia and/or EMT independently or in combination with emerging IO-strategies.

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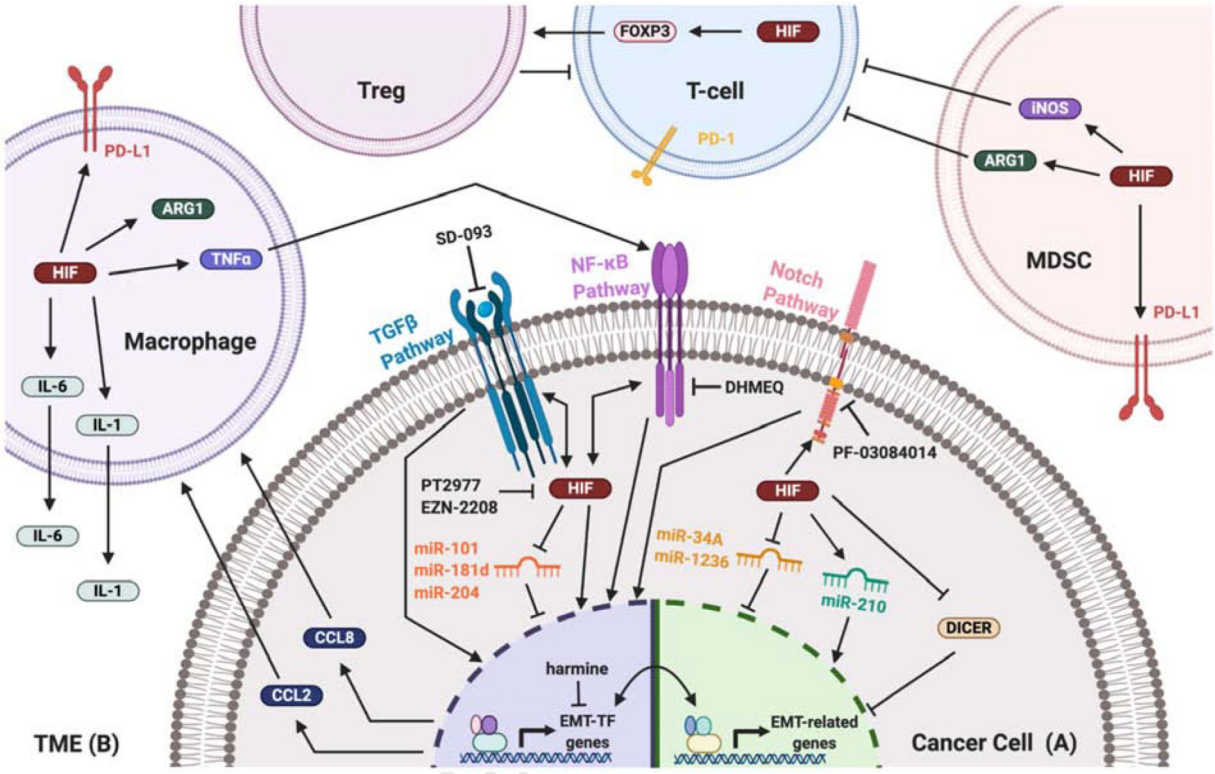

Fig. 1:

Hypoxia is a potent driver of EMT, whereby it actively promotes tumor progression and metastasis in part by promoting an immunosuppressive TME. A) Within the cancer cell, hypoxia activates EMT through various pathways. This includes through TGFbeta, NF-kappaB, and Notch signaling, along with EMT-regulating miRNA networks. Activation of these pathways increases expression of several EMT-TFs, which upregulate mesenchymal genes and downregulate epithelial genes. Numerous inhibitors have been discovered to hinder various components of these pathways, including directly blocking HIF activity. B) The hypoxic TME similarly influences EMT of cancer cells. Diverse immune cell types contribute to hypoxia-induced EMT, while also promoting an immunosuppressive environment to avoid detection of the cancer by the immune system.

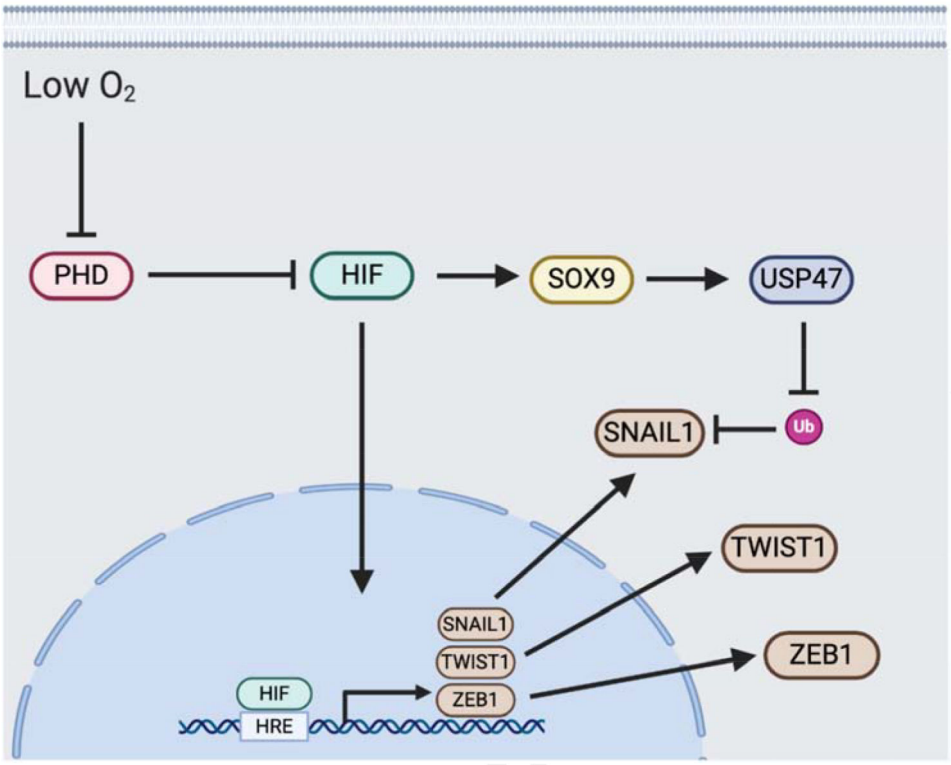

Fig. 2:

Under low oxygen levels, PHD proteins do not hydroxylate HIFalpha, allowing HIF to accumulate. Active HIF binds to HRE sequences in gene promoters to up-regulate transcription. Several EMT-TFs contain HRE sequences in their promoters, including SNAIL1, TWIST1 and ZEB1. As such, upregulation of HIF in hypoxia promotes EMT. Outside of direct EMT-TF gene activation, HIF upregulates SOX9 and subsequently USP47, which stabilizes SNAIL1 protein by reducing its ubiquitination (Ub).