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Review

Advances in Hypoxia-Inducible Factor Biology

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Hypoxia-inducible factor (HIF), a central regulator for detecting and adapting to cellular oxygen levels, transcriptionally activates genes modulating oxygen homeostasis and metabolic activation. Beyond this, HIF influences many other processes. Hypoxia, in part through HIF-dependent mechanisms, influences epigenetic factors, including DNA methylation and histone acetylation, which modulate hypoxia-responsive gene expression in cells. Hypoxia profoundly affects expression of many noncoding RNAs classes that have clinicopathological implications in cancer. HIF can regulate noncoding RNAs production, while, conversely, noncoding RNAs can modulate HIF expression. There is recent evidence for crosstalk between circadian rhythms and hypoxia-induced signaling, suggesting involvement of molecular clocks in adaptation to fluxes in nutrient and oxygen sensing. HIF induces increased production of cellular vesicles facilitating intercellular communication at a distance—for example, promoting angiogenesis in hypoxic tumors. Understanding the complex networks underlying cellular and genomic regulation in response to hypoxia via HIF may identify novel and specific therapeutic targets.

Introduction

Oxygen is essential for mammalian metabolism and physiological functions because of its use in cellular energy production and cofactor/substrate for many enzymes. The central regulator of oxygen detection and adaptation at the cellular level is hypoxia inducible factor (HIF), a heterodimeric transcription factor that consists of either HIF-1α or HIF-2α and HIF-1β/ARNT subunits. In the presence of oxygen (normoxia), HIFα interacts and binds to the von Hippel–Lindau (VHL) protein, which consequently activates the ubiquitin ligase system, leading to proteasomal degradation of HIFα. Hydroxylation of proline residues in HIFα is vital for VHL binding and depends on α-ketoglutarate-dependent dioxygenases, prolyl hydroxylases (PHD), and the asparaginyl hydroxylase, factor-inhibiting HIF (FIH). During hypoxia, PHDs are inactive, leading to HIF-α stabilization and dimerization with HIF-1β. Upon dimerization, HIF translocates to the nucleus to bind to E-box-like hypoxia response elements (HREs) within the promoter region that contain the sequence 5′-[A/G]CGTG-3′ (Kaelin and Ratcliffe, 2008). HIF activates genes that control cellular oxygen homeostasis, including genes involved in oxygen consumption, erythrocyte production, angiogenesis, and mitochondrial metabolism. Hypoxic cells counter stress by transcriptional and post-transcriptional mechanisms, mainly regulated by HIF. These molecular changes allow cells to adapt to stress by lowering oxygen consumption through a shift to glycolysis rather than oxidative metabolism and by reducing energy demand for cellular processes such as cell division (Ratcliffe, 2013). Most solid tumors have some degree of hypoxia which is associated with poor clinical outcome. Induction of HIF activity upregulates genes involved in many hallmarks of cancer, including metabolic reprogramming, cell proliferation, invasion and metastasis, apoptosis, and resistance to therapies (Rankin and Giaccia, 2016).

In contrast to these other well-studied pathways, in this review, we discuss recent advances in the biology of hypoxia and HIF regulating epigenetics, non-coding RNAs, biological clocks and cellular vesicles. These findings provide new insights on the complex networks underlying cellular and genomic regulation in response to hypoxia and may provide novel targets for future therapies.

Hypoxia, HIFs, and Epigenetics

DNA and histone methylation are two key mechanisms of epigenetic regulation of gene expression. The histone methylation is modulated via histone methyltransferases and histone demethylases. Histone acetylation is a common marker of gene activation, whereas histone deacetylation is a maker of repression. Methylation status of specific amino acids in histones lead to gene activation or repression. For example, histone 3 lysine 4 methylations (H3K4me, me2 and me3) are markers of gene activation, while histone 3 lysine 9 methylations (H3K9me2 and me3) and H3K27me3 are markers of transcription suppression (Dawson, 2017).

Several histone lysine demethylases (KDM) are induced under hypoxia upon HIF-1α stabilization (Table 1). All Jumonji-type KDMs are members of the 2-oxoglutarate-dependent dioxygenase family (2-OGDO) and thus are dependent on oxygen and a Krebs cycle intermediate "2-oxoglutarate" to catalyze their enzymatic reactions. Most KDM enzymes are structurally similar to the HIF hydroxylase Factor Inhibiting HIF-1 (FIH), suggesting that KDM enzymes may act as molecular oxygen sensors in the cell. KDMs can either enhance or suppress gene expression. For instance, KDMs can demethylate histone 3 di- or trimethylated lysine 4 (H3K4me2 and 3) and H3K36me2 and 3 (activation markers) or H3K9me1 and 2 and H3K27me2 and 3 (repression markers). Several Jumonji domain containing histone lysine

Table 1. HIF-Dependent Histone Lysine Demethylases

Histone Lysine Demethylases (KDMs)	Other Symbols	Target	Types of Cells	References
KDM3A	JMJD1A, JHDM2A	H3K9me1, H3K9me2	liver cancer, glioblastoma, clear-cell renal cell carcinoma, osteosarcoma, breast cancer and cervical carcinoma	(Krieg et al., 2010; Pollard et al., 2008; Xia et al., 2009)
KDM2B	JHDM1	H3K4me3, H3K36me1, H3K26me2	liver cancer, glioblastoma	(Xia et al., 2009)
KDM4B	JMJD2B	H3K9me2, H3K9me3, H3K36me2, H3K36me3	liver cancer, glioblastoma, clear-cell renal cell carcinoma, osteosarcoma, breast cancer and cervical carcinoma, colon cancer, epithelial cells	(Beyer et al., 2008; Fu et al., 2012; Krieg et al., 2010; Pollard et al., 2008; Xia et al., 2009)
KDM5B	JAR1D1B	H3K4me2, H3K4me3	liver cancer, glioblastoma, clear-cell renal cell carcinoma	(Krieg et al., 2010; Xia et al., 2009)
KDM6B	JMJD3	H3K27me2, H3K27me3	liver cancer, glioblastoma, adipose tissue	(Lee et al., 2014; Xia et al., 2009)
KDM4C	JMJD2C	H3K9me2, H3K9me3, H3K36me2, H3K36me3	liver cancer, glioblastoma, osteosarcoma, breast cancer and cervical carcinoma, epithelial cells	(Beyer et al., 2008; Pollard et al., 2008; Xia et al., 2009)

demethylases (KDM2-7) present different protein binding domains, allowing their interaction with other chromatin associated proteins (Estarás et al., 2013).

Pollard et al. and Beyer et al. (2008) reported KDM3A and KDM4B induction under hypoxia in a HIF-1α-dependent manner (Beyer et al., 2008; Pollard et al., 2008). Krieg et al. (2010) identified KDM3A-dependent genes, many of which are hypoxia inducible genes such as adrenomedullin (ADM), heme oxygenase 1 (HMOX1), and SERPINE1. KDM3A loss significantly reduces expression of these genes and tumor growth *in vivo* models (Krieg et al., 2010). Therefore, hypoxic regulation of KDM3A acts as a signal amplifier to facilitate hypoxic gene expression, ultimately enhancing tumor growth.

KDM4B is also induced by hypoxia in a HIF-1α-dependent manner in colorectal cancer cells, which decreases H3K9me3 level at the promoter of hypoxia-inducible genes (Salminen et al., 2016). KDM4B is involved in cell proliferation, apoptosis, and cell-cycle arrest. Hence, the expression of KDM4B in CRC correlates positively with the hypoxia marker, carbonic anhydrase 9 (CA9) expression (Salminen et al., 2016).

Genome-wide analysis of HIF-1α binding sites reported HRE sites on the promoter region of two other histone demethylases, KDM4C (JMJD2C) and KDM5B (JARID1B). Both KDMs were significantly upregulated under hypoxia (Xia et al., 2009). KDM5B catalyzes the removal of methyl groups from tri-, di-, and monomethylated lysine 4 of histone H3 (H3K4me3/2/1), while KDM4C converts specific trimethylated histone residues to dimethylated residues. At protein level, KDM4C selectively interacts with HIF-1α and that enhances HIF-1α binding to HRE to activate transcription of several genes which encode proteins for metabolic reprogramming and metastasis such as BNIP3, LDHA, LOX, PDK1, and SLC2A1 (Luo et al., 2012). KDM4C is overexpressed in several malignancies, including prostate, bladder, and lung cancers. In contrast, KDM4C is reported downregulated in melanoma and triple receptor negative breast cancer, where it inhibits cell proliferation (Klein et al., 2014).

Protein expression of KDM5B and KDM3A (JMJD1A) are significantly induced in hypoxic cells and in renal cancer cells that have lost VHL expression. However, the demethylase activity of both enzymes is reduced but remains active under low oxygen stress (Beyer et al., 2008), suggesting that HIF mediates upregulation of their expression which might provide a secondary mechanism to retain a dynamic regulation of H3K9 methylation in hypoxia. Recently, KDM3A was reported to enhance glycolysis through interaction with HIF-1α in cancer cells. KDM3A facilitate HIF1α-mediated Phosphoglycerate Kinase 1 (PGK1) transcription by reducing the levels of H3K9me2 at the HRE site on the PGK1 promoter in hypoxia (Wan et al., 2017). Mutated JMJD1A (H1120Y) failed to interact with HIF-1α and was unable to reduce the level of H3K9me2 at the HRE of PGK1 promoter, thus suggesting that the demethylase activity of KDM3A is essential for cooperation with HIF-1α and for the modulation of levels of H3K9me2 to enhance glycolysis. Generally, hypoxia globally induces levels of H3K4me2, H3K4me3, H3K79me3, H3K9me2, H3K9me3 and H3K36me3 in different cell line models. These changes indicate hypoxia inhibits or significant reduces the enzymatic activity of different histone demethylase such as KDM5A, KMD6B (Johnson et al., 2008; Prickaerts et al., 2016; Tausendschön et al., 2011; Zhou et al., 2010). There are limited data on biochemical and kinetics of KDMs activity with respect to oxygen availability (Cascella and Mirica, 2012), however, it is clear that enzymatic activity of KDMs is altered under hypoxia with potential consequences on gene regulation.

Hypoxia also influences the remodeling of the nucleosome architecture for transcriptional regulation. Johnson et al. (2008) found an increase in total histone H3 occupancy at the promoters of hypoxia-suppressed genes such as *ALB* and *AFP* and decreased occupancy at hypoxia-upregulated genes such as *EGR1* and vascular endothelial growth factor *(VEGF)*, suggesting an inverse correlation between nucleosome occupancy and transcriptional activation in response to hypoxia. Hypoxia-induced *VEGF* and *EGR1* promoters were marked with increased H3K9 acetylation and a significant decrease in H3K9me2 and H3K27me2 methylation (Johnson et al., 2008). In contrast, hypoxia-repressed *AFP* and *ALB* promoters

showed low acetylation of H3K9 and high H3K9 and H3K27 methylation.

Several chromatin-modifying complexes control hypoxia-inducible gene expression. The SWI/SNF chromatin remodeling complex is associated with HIF-1α to regulate hypoxia inducible genes (Kenneth et al., 2009). A nucleosome remodeling deacetylase complex, Metastasis-associated 1 (MTA1) is significantly induced in hypoxic breast cancer cells. MTA1 physically associates with HIF-1α to increase HIF-1α transcriptional activity and VEGF expression (Yoo et al., 2006). The imitation switch (ISWI) is another chromatin remodeling complex linked to the hypoxic response. Unlike the SWI/SNF complex, ISWI downregulation promotes HIF-1α activity without affecting its levels. Moreover, ISWI depletion alters a subset of HIF-1α target genes and, subsequently, reduces autophagy and increases cell death during hypoxia. The ISWI is vital for the regulation of gene and protein expression level of FIH by altering RNA polymerase II loading onto the FIH promoter (Melvin and Rocha, 2012). These findings suggest a dynamic remodeling of the chromatin structure under hypoxia, which influences the downstream regulation of transcription.

Pan-genomic analysis of DNase1 hypersensitivity sites and nucleosome occupancy revealed that, under hypoxia, a large number of HIF binding sites overlap with open chromatin sites defined in normoxic cells (Schödel et al., 2011; Tanimoto et al., 2010). Thus, HIF may bind at pre-existing open chromatin sites as described for glucocorticoid receptor binding at the genome-wide level (John et al., 2011). The open chromatin conformation is associated with HIF binding at the enhancer site in cells with VHL loss, but not in cells with intact VHL (Platt et al., 2016), suggesting cell type specificity in the formation of enhancers for HIF transcriptional response.

Several studies shown that hypoxia modulates chromatin remodelling and histone modifications to facilitate transcription of HIF-dependent genes. Integrated genomic analysis using massively parallel sequencing revealed that, under hypoxia, RNApol2 is already bound at the promoter of most hypoxia-inducible genes in normoxic cells. However, during hypoxia, there was a slight increase in loading of RNApol2 at the TSS with significant increase in release of pre-bound promoter-paused RNApol2 across the body of the gene. Similarly, little change in H3K4me3 signal was observed at the promoter under hypoxia, but the signal increased downstream of the TSS (Choudhry et al., 2014). These findings support the hypothesis that RNApol2 recruits histone methyl transferases that trimethylate H3K4 to facilitate transcriptional regulation during hypoxia.

Large numbers of HIF-binding sites are located at long chromosomal distances from hypoxia inducible transcripts. Therefore, it is challenging to define the specific targets of HIF binding sites and to determine how HIF affects the chromatin conformation over the distance to interact with functional elements. Recently, Platt et al. (2016) employed a high-resolution chromosome conformation method to defined specific high affinity interactions of HIF-binding regions with single or multiple promoters of hypoxia-inducible genes. They reported the presence of multiple chromosomal loops, which generate interaction between promoter-enhancer, and enhancer-enhancer during hypoxia (Platt et al., 2016). They found that promoter distant HIF-binding sites establish cis-interactions with HIF inducible genes to maintain the transcriptional repertoire, supporting the notion that hypoxia causes dynamic changes in the chromosome structure for HIF to bind at primed enhancer–promoter complexes, allowing rapid activation of its transcriptional cascade through the release of promoter paused RNA polymerase II.

Hypoxia-induced histone demethylases regulate not only gene expression, but also modulate chromatin structures such as heterochromatin and polycomb complexes. For instance, hypoxia modulates chromatin conformation to induce expression of SLC2A3 (GLUT3), through interaction between KDM3A and HIF-1α in endothelial cells (Mimura et al., 2012). KDM3A is recruited at the promoter of SLC2A3 gene in a HIF-1α-dependent manner, inducing SLC2A3 expression and subsequently promoting glycolysis.

Reduction of heterochromatin because of increase expression of specific histone demethylases (KDM3, KDM4, and KDM6) is commonly associated with oncogenesis (Slee et al., 2012; Young and Hendzel, 2013). In contrast, KDM2 and KDM5 overexpression promotes the maintenance of heterochromatin and genome stability (Li et al., 2014). Hypoxia upregulates euchromatic histone-lysine N-methyltransferase 2 (G9a) to increase the H3K9me2 level and, consequently, controls the expression of several hypoxia-regulated genes, including breast cancer 1, early onset (*BRCA1*), colon cancer, nonpolyposis type 2 (*Mlh1*) and mutL homolog 1 (Lu et al., 2011). Hypoxia also modulates the de-SUMOylation of transcriptional repressor CTCF (CCCTC binding factor) (Wang et al., 2012).

Histone deacetylases (HDACs) are other epigenetic modifications, which are altered in hypoxic conditions. Hypoxia regulates the expression and activity of several HDACs. Histone Deacetylase 1 (HDAC1) overexpression enhances angiogenesis of human endothelial cells by downregulating hypoxia-responsive tumor suppressor genes, including *p53* and *VHL* (Kim et al., 2001). Several HDACs (Class I and Class IIa) were found to promote HIF-1α stability and accumulation by regulating HIF-1α-PHD2 interaction. HDAC4, HDAC5, HDAC6 enhance HIF-1α stability and activity through modulation of acetylation level and activity of key HIF-1α cofactors such as HSP90 and p300 (Chen et al., 2015; Geng et al., 2011; Kong et al., 2006; Schoepflin et al., 2016). Inhibition of either HDAC4 or HDAC5 reduces HIF-1α protein levels and suppresses HIF-1α activity (Chen et al., 2015). Therefore, HDACs may be involved in the regulation of posttranslational processing of HIF-1α by modulating the Hsp70/Hsp90. On the other hand, HDAC inhibition (Vorinostat) was reported to increase HIF-2α accumulation, which suppresses sarcoma tumor growth in a HIF-2α-dependent manner (Nakazawa et al., 2016). These findings provide a rationale for targeting HIF with HDAC inhibitors. Hypoxia upregulates HDAC3 to regulate the expression of EMT markers in cancer cells (Wu et al., 2011). HDAC3 deacetylates the histone 3 lysine 4 (H3K4Ac) in the promoter regions of EMT marker genes and elevates the levels of H3K4me2 and H3K4me3. Hypoxia-induced EMT is abolished upon HDAC3 suppression. Under hypoxia, HDAC3 interacts with the WD repeat domain 5 (WDR5), which increases the activity of histone methyltransferases (HMT) (Wu et al., 2011). HDAC3 enhances HMT activity by increasing the stability of the HMT complex or through conformational remodeling. However, the molecular mechanisms remain to be explored.

Histone modifications in collaboration with DNA methylation play a vital role in controlling gene expression and modulating chromatin structure. The HIF-1α promoter contains an HRE, which harbors a CpG island. In colon cancer, this site is aberrantly demethylated, allowing binding of HIF-1α to its own promoter (Koslowski et al., 2011). This leads to auto-transactivation of HIF-1α expression and transactivation of HIF-1α target genes. Treating tumor cells with DNMT inhibitor, 5-aza-deoxycitidine (5-aza-dC) elevates the expression of hypoxia-induced genes. DNA methylation can also affect HIF-1α stability. For example, *VHL* hypermethylation results in HIF-1α constitutive activation. Epigenetic silencing of *VHL* has been associated with increased nuclear translocation of HIF-1α and upregulation of HIF-1α target genes such as CA9 and GLUT1 (Schmitt et al., 2009). *VHL* hypermethylation has been observed in many solid epithelial tumors and cancer cell lines (Sánchez-Vega et al., 2013; Stewart et al., 2016). In gastric cancer, CA9 expression is associated with tumor progression and metastasis. *CA9* overexpression has been linked with promoter DNA hypomethylation (Nakamura et al., 2011). In addition, studies reported *PHD3* silencing because of DNA methylation in multiple myeloma, prostate cancer, B cell lymphoma, and breast cancer cell lines (Hatzimichael et al., 2010; Place et al., 2011). However, epigenetic silencing *of PHD3* showed no significant effect on HIF-1α or HIF-2α protein levels. The above studies reported that PHD3 and VHL, two vital enzymes involved in HIF-1α protein destabilization and regulators of the HIF pathway, are commonly hypermethylated under hypoxia.

HRE methylation status can have a profound impact on HIF transactivation of its target genes. HRE hypermethylation blocks the HIF binding at erythropoietin (EPO) enhancer and represses its expression (Wenger et al., 1998). Mammalian stanniocalcin-2 (STC2) is a secreted glycoprotein, which is overexpressed in cancer and involved in EMT, drug resistance, and cell proliferation (Chen et al., 2016). HRE hypermethylation at *STC2* promoter has been reported in different cancer cell lines. Treating cancer cells with 5-aza-2′-deoxycytidine (5-aza-CdR) under hypoxia significantly increased STC2 expression (Law et al., 2008). Another example is BCL2/Adenovirus E1B 19kDa Interacting Protein 3 (BNIP3) is induced by hypoxia in a HIF-dependent manner. BNIP3 is a mitochondrial protein that functions as a pro-apoptotic factor (Feng et al., 2016; Vasagiri and Kutala, 2014). In contrast to many other cancers, some colorectal and pancreatic cancer cell lines showed little or no hypoxic induction of BNIP3 despite an intact HIF signaling pathway (Bacon et al., 2007; Okami et al., 2004). Analysis revealed that *BNIP3* promoter is located within a CpG island and is hypermethylated under hypoxia, thus blocking *BNIP3* induction. Hypermethylation silencing of BNIP3 is detected in 66% of primary colorectal and 49% of primary gastric cancers and associated with worse clinical outcome (Murai et al., 2005).

The ten-eleven translocation (TET) family proteins promote key epigenetic changes and regulate crucial cancer development processes. In mammals, TET enzymes catalyze DNA demethylation by hydroxylating 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC). 5hmC is further oxidized to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) and subsequently substituted with an unmodified cytosine by base-excision repair (BER) to complete demethylation (Ito et al., 2011; Tahiliani et al., 2009). Similar to PHDs, TET enzymes are dependent on Fe2+- and are α-ketoglutarate dioxygenases. Decrease in 5mC oxidation due to reduce TET activity causes an increase in DNA methylation levels. Shahrzad et al. reported global DNA hypomethylation in hypoxic colorectal and melanoma cancers measured by the amount of 5mC. They found an inverse correlation between the magnitude of tumor hypoxia and the incidence of methylation both in cells and in xenograft models (Shahrzad et al., 2007). In addition, prolong hypoxic stress causes hypomethylation of retrotransposable Alu or short interspersed nuclear elements (SINEs) and reverses transcriptase coding long interspersed nuclear element (LINE) transcripts in glial tumor and osteosarcoma (Pal et al., 2010). These repetitive elements play a vital role in increasing genomic instability during hypoxia. In hepatocellular carcinoma, hypoxia induces global DNA demethylation by decreasing S-adenosylmethionine (SAM) levels both *in vitro* and *in vivo*. Methionine adenosyltransferase 2A (MAT2A) catalyzes the production of SAM. Hypoxia induces MAT2A expression in a HIF-1α-dependent manner and recruits p300 and HDAC1 (Liu et al., 2011b). This suggests that hypoxia promotes DNA demethylation via HIF-1α activation and transcriptional upregulation of MAT2A.

In contrary to these observations, other studies reported that hypoxia causes DNA hypermethylation. Watson et al. (2009) found an increase in global DNA methylation and H3K9 histone acetylation in hypoxia-adapted PwR-1E benign prostate epithelial cells. They found upregulation of DNA methyltransferase DMNT3b and gene-specific changes in DNA methylation (Watson et al., 2009). In another study, prolonged hypoxia exposure of human cardiac fibroblast cells caused a pro-fibrotic phenotype. The hypoxia-induced pro-fibrotic phenotype was associated with global DNA hypermethylation and increased levels of DNMT1 and DNMT3B (Watson et al., 2014).

Recently, Thienpont et al (2016) reported that hypoxia promotes hypermethylation through 5hmC loss in a number of human cancer and murine cell lines. Hypoxia-induced hypermethylation is due to reduced activity of TETs, but not their expression. The hypoxic reduction of TET activity was independent of TET expression, metabolism, HIF, and reactive oxygen species. Using DNA-immunoprecipitation sequencing (DIP-seq), they found global loss of 5hmC in hypoxic conditions and primarily at promoter region of genes associated with gain of 5mC. The Cancer Genome Atlas (TCGA) data revealed an inverse association between TET2 and TET3 expression and DNA hypermethylation, while a positive association with TET1 and TET3 mutations and hypermethylation (Thienpont et al., 2016), indicating that reduced TET activity limits 5hmC generation and promotes DNA hypermethylation. Interestingly, hypoxia-induced DNA hypermethylation in breast tumors occurred at the promoter region of tumor suppressor genes, but oncogenes were not affected (Thienpont et al., 2016). These findings reveal that hypoxia reduces TET activity, leading to downregulation of tumor suppressor genes, and establishes a link between hypoxia and DNA methylation. In contrast, other studies reported a positive regulation and activity of the TET proteins and induction of global DNA hypomethylation during hypoxia. Wu et al. (2015b) reported that HIF-1α-dependent regulation of TET1 and TET3 promotes global DNA hydroxymethylation during hypoxia. Hypoxia-induced overexpression of TET1/TET3 proteins activates the

TNFα- p38-MAPK pathway to enhance breast cancer stemness. Expression of 5hmC, TET1, and TET3 was significantly correlated with tumor hypoxia, tumor progression, and poor clinical outcome in breast cancer (Wu et al., 2015b). Moreover, HIF-independent TET1 overexpression, leading to global DNA hypomethylation, was also reported in scleroderma fibroblasts (Hattori et al., 2015). Tsai et al. (2014) demonstrated that hypoxia regulates the expression of TET1 that interacts with HIF-1α and HIF-2α to enhance their transactivation activity and promote hypoxia-induced EMT. Furthermore, several groups reported that TET proteins are linked with glucose and lipid metabolism (Chen et al., 2013; Tsai et al., 2014). Accumulation of fumarate and succinate metabolites can increase HIF-1α levels and expression of HIF target genes in part by inhibiting the PHD enzymes in cancer cells (Isaacs et al., 2005; Selak et al., 2005). Fumarate and succinate also inhibit TET1 and TET2 enzymes, resulting in DNA hypermethylation and downregulation of HIF-dependent genes (Laukka et al., 2016). There are several contradictory data in the literature on the regulation of TETs and their impact on DNA methylation in hypoxic conditions. Further investigations are needed to understand the mechanism underlying TET protein function and its up/downstream regulators in hypoxia.

Many studies demonstrated that hypoxia provokes epigenomic alterations in the chromatin and DNA methylation landscape, which consequently modulates the transcriptional output of tissues. However, hypoxic epigenetic change is a complex mechanism, which is variable in response because of various factors, including level of oxygen, exposure time to hypoxia, type of hypoxic treatments, tissue- and cell-line-specific responses, and hypoxia-dependent and -independent protein synthesis. These factors could explain inconclusive results from many global histone and DNA methylation studies on hypoxia. For example, KDM3A and KDM4B activity does not change at 1% O_2 tension, whereas the reduction of O_2 to 0.2% significantly abrogates histone demethylase activity (Beyer et al., 2008).

Overall, it is clear that different epigenetic factors including transcriptional co-regulators, DNA methylation, histone and chromatin modifications mediate regulation of hypoxia-responsive gene expression through HIF-dependent and non-dependent mechanisms in cancer. Further epigenetic mechanisms to control hypoxia response will be the major focus of upcoming research endeavors.

Hypoxia, HIFs, and Non-coding RNAs

Recent large-scale genomic sequencing projects revealed that less than 2% of human transcriptional output encodes for proteins, while the remaining genome encrypts different classes of non-coding RNAs. Emerging evidence has been revealed that hypoxia regulates expression of different non-coding RNAs classes and they in turn influence on HIF expression and stability. These hypoxia/HIF associated non-coding RNAs modulate range physiological and pathological pathways including cellular growth, metabolism, and angiogenesis.

HIF and MicroRNA

MicroRNAs (miRNAs) are a class of small RNAs (~22 nucleotide duplexes) that regulate RNA stability and mRNA translation. The extensive literature on the regulation of individual and genome-wide miRNA expression, biogenesis miRNA pathway, and the regulation of miRNA target genes in hypoxia has been recently reviewed (Choudhry et al., 2016). Hypoxia has a profound impact on miRNAs expression, which is controlled by a complex network of gene regulation. For instance, hypoxia directly regulates miRNA expression through HIF or indirectly by other hypoxia-regulated factors such as Oct-4. miRNA also regulates expression or stabilization of HIF-1α and/or HIF-2α by direct binding to their mRNAs or through controlling the expression of a regulatory unit of the HIFs such as VHL or a PHD. In addition, miRNA biogenesis machinery is tightly regulated by hypoxia.

Hypoxic miRNA expression signatures have been develop from primary tumors and cancer cell lines, including brain, breast, colorectal, and bladder cancers (Agrawal et al., 2014; Blick et al., 2015; Choudhry et al., 2016). Most miRNAs identified in the hypoxia signature such as miR −23, miR-24, miR-26, miR-27, miR-103, miR-107, miR-181, miR-210, and miR-213 are commonly overexpressed in different tumor types.

Several differentially expressed miRNAs were identified in human endothelial cells grown under hypoxia (1% O_2 for 24 hr), including miR-210, which is overexpressed in most hypoxic tumors, and miR-150, which is downregulated in hypoxic tumor studies (Voellenkle et al., 2012). Similarly, RNA-seq analysis of the breast cancer cell line (MCF-7) grown under hypoxia indicated the upregulation of 41 miRNAs and downregulation of 28 miRNA by hypoxia (Camps et al., 2014). Analysis of hypoxic responses at different time points (16, 32, and 48 hr) indicated an increase in the number of differentially expressed miRNAs with time. Several hypoxia-regulated miRNAs are located within intronic regions of protein coding genes. However, there was no significant association between the miRNA and host gene expression during hypoxia (Camps et al., 2014). Some of the upregulated hypoxia-induced miRNAs (miR-210-3p, miR-27a-3p, and miR-24-3p) were associated with a hypoxic signature in breast cancer.

Various miRNAs upregulated by hypoxia are direct targets of HIF-1α and/or HIF-2α. HIF binds to their promoter region to induce their expression and target both upstream and downstream signaling molecules that function as oncogenes and/or tumor suppressors. Changes in hypoxia-regulated miRNAs have been associated with clinico-pathological features and clinical outcome in various cancer types (Favaro et al., 2011; Rupaimoole et al., 2016a). miR-34 expression is decrease in hypoxic conditions to modulate the tumor microenvironment and EMT by targeting *IL6*, *NOTCH1*, and *JAG1* (Rokavec et al., 2014). Another study reported that miR-34 targets *CD44*, hence influencing cancer stem cell signaling (Liu et al., 2011a). miR-15 and miR-16 function as tumor suppressor by downregulating anti-apoptotic oncogenes. miR-155 is upregulated in hypoxia and has an HRE in its promoter in colorectal cancer cell lines (Bruning et al., 2011). Hypoxic downregulation of miRNAs, Let-7a, miR-135a, miR-146a, and miR-30, causes the upregulation of pro-metastatic genes, including *RHOB1*, *TAGLN*, *SRTAD1*, *TXNIP*, *JAG1*, *CTGF*, and *JUN*.

miR-210 is a well-established target of HIF-1α and is strongly induced in most cancer types in response to hypoxia. miR-210 reduces the level of glycerol-3-phosphate dehydrogenase 1-like (GPD1L) to stabilize HIF-1α protein by downregulating HIF-1α hyperhydroxylation, suggesting a positive feedback

loop of HIF-1α-dependent regulation via miR-210 (Kelly et al., 2011). In addition, miR-210 feedback loop functions through targeting HIF-1α inhibitor such as Succinate Dehydrogenase Complex Subunit D (SDHD). Thus, miR-210 downregulates SDHD functions to promote HIF-1α stabilization (Gorospe et al., 2011).

Many miR-210 targets regulate several key cellular processes, including cell cycle, cell morphology, polarization, differentiation, apoptosis, metabolism, tumor migration, and metastasis (Qin et al., 2014). The mitochondrial iron sulfur scaffold protein (ISCU) is among the critical targets of miR-210 (Chan et al., 2009). ISCU is a vital component of iron sulfur clusters, which are cofactors for many enzymes, including those that modulate metabolism, iron homeostasis, and oxidative stress. In addition, ISCU is a key part of TCA cycle components, including succinate dehydrogenase and mitochondrial complex components. miR-210 reduces the ISCU expression, which results in decreased tricarboxylic acid "TCA" cycle and mitochondria electron transport chain function (Favaro et al., 2010). In breast cancer, miR-210 and ISCU levels were inversely correlated and low ISCU expression was associated with poor recurrence-free survival. miR-210 enhances angiogenesis and metastasis by promoting glucose transporters such as GLUT-1. Induction of GLUT-1 generates an extracellular microenvironment that supports angiogenesis through upregulation of VEGF and Platelet-Derived Growth Factor (PDGF)(Bailey et al., 2012). In addition, miR-210 can regulate VEGF cellular expression by regulating levels of EFNA3 and PTP1B, which are adverse regulators of VEGF. Downregulation of *EFNA3* or *PTP1B* by miR-210 causes increased VEGF production and leads to angiogenesis (Fasanaro et al., 2008; Kim et al., 2013). miR-210 is also involved in controlling apoptosis by negatively regulating the expression of key molecules of apoptosis-related cell signaling pathways, including apoptosis-Inducing Factor Mitochondrion-associated 3 (AIFM3) (Yang et al., 2012), CASP8AP2 (Kim et al., 2009), and SIN3A. miR-210 promotes metastasis by downregulating the vacuole membrane protein 1 (VMP1), which inhibits cell migration and invasion. Increased level of miR-210 results in a decrease in VMP1 gene and protein expression in various cancer types, thus promoting cell migration and invasion (Ying et al., 2011).

In addition to HIF, several other factors play a role in modulating miRNA expression in hypoxia. For example, hypoxia activates the AKT signaling, resulting in an increase of miR-21 expression in an NF-κB- and CREB-dependent manner (Polytarchou et al., 2011). HIFs control the expression of several transcription factors. The promoter region of miR-210 contains several conserved transcription factor sites, including Oct-4, which is regulated by hypoxia (Ivan et al., 2008). HIFs also control the expression of the transcription factor, TWIST1, which regulates oncogenic miR-10b that mediates metastasis (Haque et al., 2011). In endothelial cells, C/EBP-α /RUNX-1 transcription factor induces the expression of miR-424 during hypoxia to modulate vascular remodelling (Ghosh et al., 2010). These findings indicate the role of HIF-independent regulation of miRNA expression under hypoxia.

Studies reported that many miRNAs modulate the expression of HIFs and/or regulatory units of the HIF pathway. These miRNAs are commonly downregulated in hypoxia, resulting in increased *HIF* gene and protein expression. miR-18a is suppressed by hypoxia in different cancer types and directly targets the 3′-UTR of HIF-1α to inhibit metastasis (Wu et al., 2015a). Moreover, hypoxia reduces the expression of miR-199a, which targets 3′-UTR of HIF-1α, and HIF-2α. Changes in miR-199a affect HIF levels and the expression of genes that control cell migration and metastasis, including the matrix-remodeling enzyme, lysyl oxidase (LOX) (Joshi et al., 2014). miR-138 directly targeted *SOX4* and *HIF-1α* in ovarian cancer, modulating tumor migration and invasion phenotypes (Yeh et al., 2013). miR338-3p also binds the 3′-UTR of HIF-1α, resulting in decrease expression of HIF-1α and its regulated genes such as *VEGF* and *GLUT-1* (Xu et al., 2014).

Recent studies uncovered a novel oncogenic role of hypoxia in regulating the miRNA biogenesis pathway (Bandara et al., 2017). Hypoxia activates EGFR signaling to enhance cell growth and tumorigenesis. This activation increases the phosphorylated form of AGO2 at Tyr 393, hence obstructing the interaction between DICER1 and AGO2 and blocking miRNA accumulation and maturation. Hypoxia-induced EGFR-dependent AGO2-Tyr 393 phosphorylation is vital for cellular adaptation under hypoxia and is associated with poor clinical survival outcome of patients with breast cancer (Shen et al., 2013). Global miRNA downregulation in the hypoxic tumor microenvironment results from alteration and suppression of key members of the miRNA biogenesis pathway. Hypoxia downregulates Dicer and Drosha in an ETS1/ELK1-dependent manner. Moreover, deep RNA sequencing revealed aberrant miRNA maturation under hypoxia that was linked with increased ovarian cancer progression. Similarly, in breast cancer, enzymes involved in microRNA biogenesis (Dicer, Drosha, TARPB2, and DCGR8) were significantly repressed under hypoxic conditions (Bandara et al., 2014). Recently, Rupaimoole et al. (2016b) demonstrated that Dicer downregulation during hypoxia results from hypoxia-induced miR-630, which targets the 3′-UTR of Dicer. They reported that mice treated with a combination of anti-miR-630 and anti-VEGF therapy presented smaller tumors with less metastatic nodules compared with mice treated with anti-VEGF therapy alone (Rupaimoole et al., 2016b). These findings not only provide novel insights on miRNA biogenesis downregulation detected under hypoxia, but also identify potential therapeutic targets that are deregulated in cancer. In another study, DICER suppression during hypoxia was due to epigenetic alteration. This involves inhibition of oxygen-dependent H3K27me3 demethylases, KDM6A/B, which consequently hypermethylate the *DICER* promoter, leading to DICER downregulation of in hypoxic breast cancer cells (van den Beucken et al., 2014).

HIF and lncRNAs

Several long noncoding RNAs (lncRNAs) are also aberrantly expressed in hypoxic tumor microenvironments. LncRNAs are a heterogenous class of non-coding RNAs, which are more than 200 nucleotides in length. They include antisense RNAs, transcribed ultraconserved regions (T-UCR), intergenic RNAs, and pseudogenes. Growing evidence has established that lncRNAs play vital roles in regulating genome at several levels, including genomic imprinting, transcription activation or inactivation, RNA splicing, translation control and RNA interference.

Recent studies demonstrated the regulation of lncRNAs in response to hypoxia modulate the HIF pathway, metabolism, tumor growth, and metastasis (Choudhry et al., 2016). However,

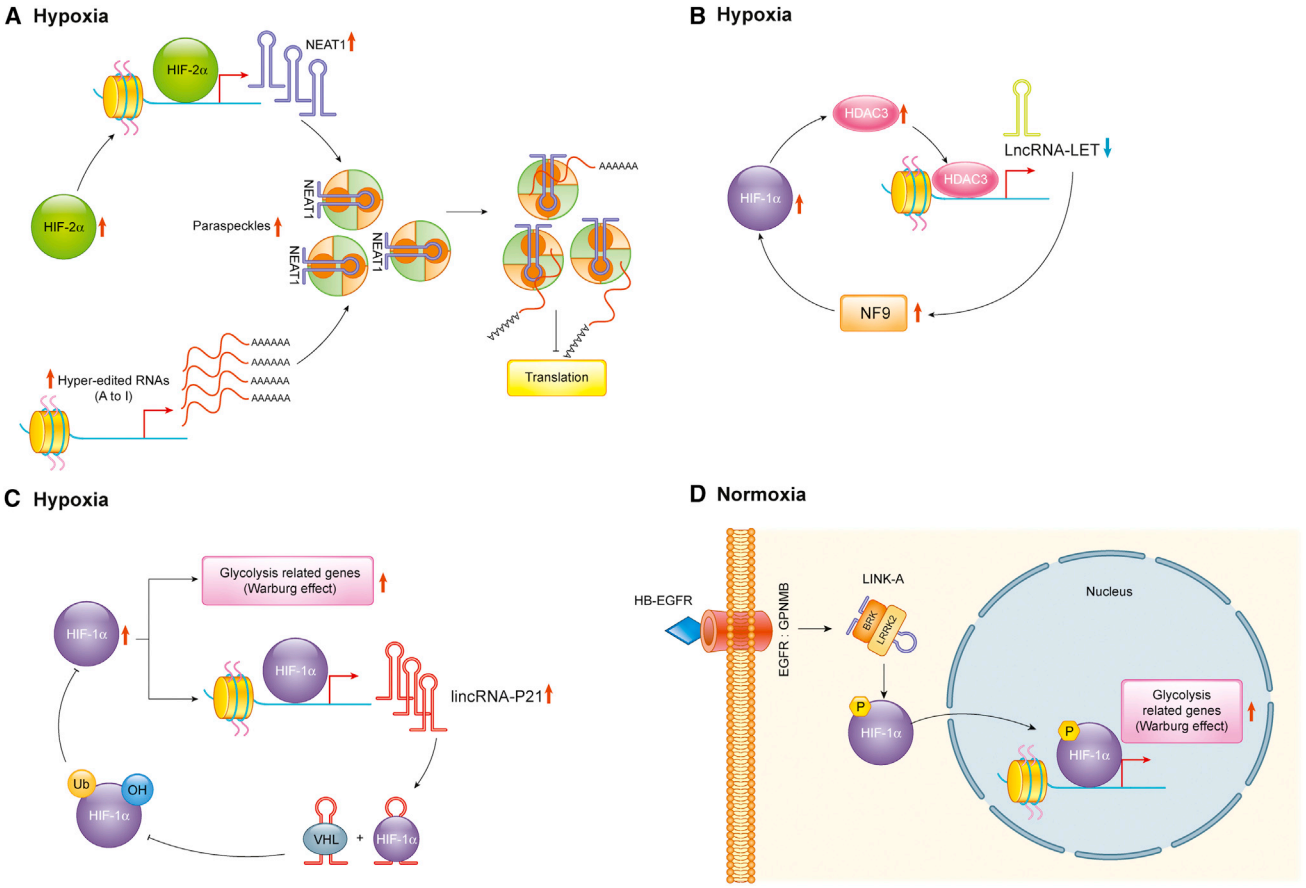

Figure 1. Examples of Regulatory Mechanisms between lncRNAs and HIFs

(A) HIF-2α binds HRE at the promoter region of NEAT1 to induce its expression under hypoxia. Upregulated NEAT1 increases the formation of paraspeckle bodies. On the other hand, upon hypoxia the editing of RNA is also increased. Hyper-edited RNA molecules (in particular A to I editing) bind to paraspeckle bodies and retained in the nucleus, thus inhibiting their translation. NB, only detected in one cell type (Chen and Carmichael, 2009).

(B) Hypoxia downregulates lncRNA-LET expression through hypoxia-induced HDAC3, a HIF-1α-dependent gene. Hypoxia-induced HDAC3 reduces the histone H3 and H4 acetylation-mediated modulation at the promoter region of LncRNA-LET, which consequently suppresses its expression. Decreased lncRNA-LET expression increases the abundance of NF90 protein and hence upregulates the HIF-1α level.

(C) Hypoxia induces lincRNA-P21 expression in a HIF-1α-dependent manner. Hypoxia- induced lincRNA-P21 binds to VHL and HIF-1α that causes disassociation of VHL and HIF-1α, therefore inhibiting proteasome-dependent degradation of HIF-1α under hypoxia. LincRNA-p21 modulates the Warburg effect through regulating expression of a number of glycolysis-related genes.

(D) Signal from Heparin-binding EGF (HB-EGF) triggers "EGFR:GPNMB" heterodimerization. This leads to the recruitment of LINK-A, which interacts with both BRK and LRRK2 to facilitate phosphorylation of HIF1α and promotes glycolysis reprogramming in TNBC.

the exact mechanisms underlying the interaction of lncRNAs with the hypoxic tumor microenvironment require further elucidation. Current findings indicate two mechanisms of interaction of lncRNAs and hypoxia in cancer (Figure 1). First, hypoxia regulates hypoxia-responsive lncRNA expression via HIF. Additionally, lncRNAs modulate HIF expression and pathways (Table 2).

HIF directly regulates lncRNAs transcription in hypoxia. In silico and experimental analyses identified the presence of HREs at the promoter region of most hypoxia-responsive lncRNAs. HIF ChIP-seq analysis identified that HIF-2α bound slightly more at lncRNA promoters than HIF-1α in hypoxic MCF-7 breast cancer cells. NEAT1 was identified among the most highly upregulated lncRNAs during hypoxia and is dependent on HIF-2α (Figure 1A) (Choudhry et al., 2015). On the other hand, UCA1(Xue et al., 2014), EFNA3 (Gómez-Maldonado et al., 2015), H19 (Matouk et al., 2016), MALAT1 (Choudhry et al., 2014; Michalik et al., 2014), and HOTAIR (Bhan et al., 2017; Zhou et al., 2015), FALEC (Zhao et al., 2017), HAS2-AS1 (Zhu et al., 2017) are example of HIF-1α dependent lncRNAs that contains HREs on their promoters. These studies provide evidence that the hypoxia-responsive lncRNAs can be directly regulated by HIF in different types of cancer.

Through different mechanisms, some lncRNAs can also be indirectly influenced by HIF. For instance, HIF upregulates the expression of WT1 lncRNA in a TET2- and TET3 (DNA demethylating enzymes)-dependent manner in leukemia cells (McCarty and Loeb, 2015). Moreover, HIF-1α-dependent HDAC3 reduces lncRNA-LET expression by decreasing acetylation levels in the lncRNA-LET promoter region, suggesting that lncRNA-LET is indirectly regulated by HIF-1α (Figure 1B) (Yang et al., 2013). These examples indicate that HIF indirectly regulates lncRNA expression via epigenetic modulation.

LncRNAs have the ability to control gene expression through diverse mechanisms as a guide, scaffold, decoy, or sponge.

Table 2. LncRNAs Regulate HIF Pathways in Cancer

lncRNA	Regulation in Hypoxia	HIF Dependence	Cancer Types	Impact on HIF Pathway	References
lncRNA-LET	Downregulated		Gallbladder cancer, squamous-cell lung cancer, hepatocellular carcinoma and colorectal cancers	Regulates HIF1α level	(Yang et al., 2013)
HIF2PUT			Osteosarcoma	Upregulates HIF2α	(Li et al., 2016b)
aHIF-1α	Upregulated	HIF-1α	Multiple cancer types	Downregulates HIF1α	(Uchida et al., 2004)
Linc-ROR	Upregulated		Hepatocellular carcinoma	Upregulates HIF1α	(Takahashi et al., 2014)
lincRNA-p21	Upregulated	HIF-1α	Cervical cancer, breast cancer	Upregulates HIF1α and enhances glycolysis	(Yang et al., 2014)
RERT			Hepatocellular carcinoma	Downregulates HIF	(Sun et al., 2014)
ENST00000480739			Pancreatic cancer	Downregulates HIF-1α	(Sun et al., 2014)
PVT1			Gastric cancer	Downregulate HIF-1α	(Huang et al., 2017)
MEG3			Lung cancer	Upregulate HIF-1α protein translation	(Zhou et al., 2017)
UCA1	Upregulated	HIF-1α	Breast cancer	Upregulate HIF-1α	(Li et al., 2016c)
LncRNA-SARCC	Downregulated in RCC VHL wild-type	HIF-2α	Renal cell carcinoma	Upregulate HIF-2α	(Zhai et al., 2016)
CASC9			Nasopharyngeal carcinoma	Upregulate HIF-1α	(Su et al., 2017)
LncHIFCAR	Upregulated		Oral carcinoma	Upregulate HIF-1α	(Shih et al., 2017)
LINK-A			Triple-negative breast cancer	Upregulate HIF-1α	(Lin et al., 2016)

Recent studies demonstrated the role of lncRNAs in the direct and indirect regulation of HIF expression and pathway. An antisense lncRNA named HIF-2α promoter upstream transcript (HIF2PUT) is a cis-regulatory lncRNA, which co-regulates *HIF-2α* mRNA in osteosarcoma (Wang et al., 2015). Similarly, the HIF-1α locus contains two antisense transcripts, one transcribed from the 3′-UTR "3′aHIF-1α" and the other from the 5′-promoter region "5′aHIF-1α" of the sense *HIF-1α* mRNA (Bertozzi et al., 2011). These aHIF-1α lncRNAs negatively regulate *HIF-1α* mRNA level *in cis* by modulating chromatin or mRNA stability (Uchida et al., 2004) and associated with clinical outcome (Tasharrofi et al., 2016). In mesenchymal glioblastoma stem-like cells (GSCs),*aHIF-1α* interacts with proteins including insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) and ATP-dependent RNA helicase A (DHX9) to regulate expression of high mobility group AT-hook 1 (HMGA1) and HIF-2α in hypoxic stress (Mineo et al., 2016). The above studies indicate a new role of lncRNAs directly regulating HIF levels.

Other lncRNAs indirectly regulate HIF levels. For instance, in pancreatic ductal adenocarcinoma (PDAC), low expression of lncRNA ENST00000480739 inhibits HIF-1α expression by upregulating osteosarcoma amplified-9 (OS-9) (Sun et al., 2014). OS-9 induces an interaction between HIF-1α and proline hydroxylase domain (PHD2/3) protein, leading to HIF-1α degradation (Baek et al., 2005). OS-9 inhibition in hypoxia abrogates ENST00000480739-induced downregulation of HIF-1α. In addition, ENST00000480739 upregulation significantly reduces the expression of HIF-1α-dependent genes, including *MXI-1*, *PDGFC* and *MMP28* (Sun et al., 2014), indicating that ENST00000480739 may negatively control HIF-1α activity by inducing OS-9 expression. Similarly, RERT-lncRNA transcriptionally upregulates PHD1 (EGLN2) expression and consequently suppress HIF-1α activity (Zhu et al., 2012). Long intergenic non-coding RNA, regulator of reprogramming "Linc-RoR," is also induced under hypoxia and modulates HIF-1α expression. Suppression of hypoxia-induced linc-RoR reduces the expression of HIF-1α and pyruvate dehydrogenase kinase isozyme 1 (PDK1), indicating that linc-RoR promotes hypoxia responses by controlling HIF-1α levels and its target genes (Takahashi et al., 2014). Studies indicated that linc-RoR might function as a miRNA sponge under hypoxia to modulate and control the expression of miRNAs such as miR-145 that regulates the expression of HIF-1α and HIF-dependent genes (Takahashi et al., 2014; Zhou et al., 2014). Similar, PVT1 and UCA1 act as sponges for miR-186 and miR-18a, respectively, hence regulate HIF-1α expression (Huang et al., 2017; Li et al., 2016c). Low expression of Maternally expressed gene 3 (MEG3) lncRNA has been reported in multiple cancer types. Recently, downregulation of MEG3 promoter due to hypermethylation leads to c-Jun inhibition of PHLPP1 transcription, which enhance protein translation of HIF-1α and activation of the Akt/p70S6K/S6 axis (Zhou et al., 2017). The lncRNA-SARCC (Suppressing Androgen Receptor in Renal Cell Carcinoma) found differentially respond to hypoxia in a VHL-dependent manner in renal cancer. LncRNA-SARCC physically interacts with androgen receptor (AR) to suppress the AR/HIF-2α/C-MYC axis (Zhai et al., 2016). HIF-2α suppress LncRNA-SARCC expression via binding to its hypoxia-responsive elements in the LncRNA promoter, suggesting a negative feedback loop between LncRNA-SARCC and HIF-2α that modulates tumorigenesis for RCC in hypoxia.

Under hypoxia, HIF-1α epigenetically decreases lncRNA-LET expression, while lncRNA-LET destabilizes *HIF-1α* mRNA level via degrading nuclear factor 90 (NF90). Low lncRNA-LET expression promotes HIF-1α accumulation (Yang et al., 2013). On the

other hand, HIF-1α directly binds at the promoter region for the transcriptional activation of lincRNA-p21, while lincRNA-p21 enhances HIF-1α accumulation by disrupting the HIF-1α-VHL interaction during hypoxia (Figure 1C) (Yang et al., 2014). Both lincRNA-p21 and lncRNA-LET form feedback loops that reciprocally regulate HIF levels under hypoxia.

LncRNAs can also modulate HIF-1α accumulation and activation in normoxia. Recently, a ~1.5 kb long intergenic non-coding RNA for kinase activation (LINK-A) was found to be important for the growth factor-induced normoxic HIF-1α signaling in triple receptor-negative breast cancer (TNBC) (Lin et al., 2016). LINK-A is essential for the recruitment and enzymatic activation of Tyrosine protein kinase 6, also known as breast tumor kinase (BRK). This activation is triggered by Heparin-binding EGF-like growth factor (HB-EGF),which mediates epidermal growth factor receptor (EGFR) and transmembrane glycoprotein NMB (GPNMB) heterodimerization 'EGFR:GPNMB'. LINK-A recruits activated BRK along with leucine-rich repeat kinase 2 (LRRK2) which leads to HIF-1α phosphorylation at Tyr 565 and Ser 797, respectively. The phosphorylation at Tyr 565 supresses hydroxylation at the Pro 564, which averts HIF1α protosomal degradation in normoxia. Whereas, the Ser 797 phosphorylation enhances HIF1α–p300 interaction resulting in HIF-1α target genes activation in the presence of HB-EGF (Figure 1D) (Lin et al., 2016). Interestingly, LINK-A expression and LINK-A induced normoxic HIF1α signaling activation were associated with TNBC and induced glycolysis reprogramming in breast cancer. Another example of a lncRNA regulating HIF-1α activity is lncRNA cancer susceptibility candidate 9 (CASC9) which is found highly expressed in nasopharyngeal carcinoma (NPC) (Su et al., 2017). CASC9 binds HIF-1α and promotes the stabilization and activation of HIF-1α, thus inducing glycolysis metabolism and tumorigenesis. Both LINK-A and CASC9 need to be further investigated for their expression and function in hypoxia.

The host gene of microRNA-31 (MIR31HG), also known as a long noncoding HIF-1α co-activating RNA (LncHIFCAR), was reported to activate the pseudohypoxia signature required for hypoxia-induced metabolic reprogramming (Shih et al., 2017). Suppression of LncHIFCAR but not mir-31 significantly downregulated hypoxia-induced glucose uptake and lactate production. Mechanistically, lncHIFCAR physically interacts with HIF-1α and binds to HIF-1 target genes. Consequently, this results in the recruitment of co-activator p300 which enabled the activation of HIF-1 transcriptional network (Shih et al., 2017). Moreover, hypoxia-responsive lncRNA uc.475 regulates polypeptide glycosylation (Ferdin et al., 2013). These are examples of lncRNAs that have an effect on the regulation or stabilization of HIF, hence they potentially modulate tumor metabolism.

Increasing evidence suggests that hypoxia-responsive lncRNAs play important roles in regulating all the hallmarks of cancer. Several hypoxia-responsive lncRNAs are involved in regulating apoptosis via different pathways. Suppression of HIF-1α-dependent UCA1 during hypoxia induces apoptosis in bladder cancer cells through upregulation of Bax and cell-cycle arrest at G1 phase and downregulation of Bcl-2 (Zhen et al., 2017). Hypoxic exosomal lncRNA-UCA1 was reported to stimulate tumor growth and progression via EMT (Xue et al., 2017). H19 is overexpressed in various types of tumors with anti-apoptotic function and dependent on the tumor suppressor p53 (Matouk et al., 2016). NEAT1, HIF2PUT, MALAT1, and H19 regulate the proliferation of cancer cells during hypoxia. Hypoxia-induced NEAT1 is essential for the formation of nuclear structures called paraspeckles during hypoxia. NEAT1 knockdown remarkably inhibits cell proliferation and survival in both normoxia and hypoxia. However, the inhibition was more significant in hypoxic conditions (Choudhry et al., 2015). Similar regulation of cell proliferation was observed for UCA1 and hypoxia-induced noncoding ultraconserved transcripts (HINCUTs) (Ferdin et al., 2013; Xue et al., 2014). aHIF-1α shown to promote mesenchymal glioblastoma stem-like cells (GSCs) growth, self-renewal, and hypoxia-dependent molecular reprogramming (Mineo et al., 2016). Recently, histone methyl-transferase MLL1 modulation with HIF-1α and p300 found to control induction of HOTAIR under hypoxia hence promote tumorigenesis (Bhan et al., 2017).

The hypoxic microenvironment promotes angiogenesis and EMT via a series of signaling pathways, including HIF pathways. Examples of lncRNAs that probably regulate cancer angiogenesis include linc-ROR, which regulates HIF-1 activity (Takahashi et al., 2014) and hypoxia-induced MALAT1 that promotes vascular growth *in vivo* (Michalik et al., 2014). HIF-1α-dependent induction of HAS2-AS1 promotes hypoxia-regulated EMT and invasiveness via stabilizing HAS2 (Zhu et al., 2017).

In addition to miRNAs and lncRNAs, in-depth investigation of hypoxic non-coding transcriptome identified other classes of hypoxia-responsive non-coding RNAs such as snRNAs, piwiRNAs, tRNAs, and circular RNAs (Boeckel et al., 2015; Choudhry et al., 2016). However, their functional implication in hypoxia biology and metabolism remains to be determined.

Hypoxia, HIFs, and the Circadian Clock

In living organisms, the circadian clock characterizes the 24-h oscillations that control daily rhythmicity of molecular, physiological, and behavioral processes. A master clock modulating circadian rhythms is located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Takahashi, 2017). The SCN is a central oscillator induced by environmental signals, thus coordinating the SCN-driven output rhythms. A set of genes coordinate the biological rhythms including clock genes, CLOCK/NPAS2, BMAL1/2(ARNTL/2), ARNT3, Period (PER1, PER2, and PER3), cryptochrome (CRY1 and CRY2), and MOP3. In mammals, the molecular clock is composed of activators (CLOCK/BMAL) that promote the transcription of repressors (PER/CRY) that, in turn, suppress the forward limb in a cycle, which repeats itself every 24 hr, with an additional supporting loop involving the nuclear receptor REV-ERB and the retinoic acid receptor-related orphan receptor (ROR) transcription factors (Takahashi, 2017). A growing number of studies demonstrated that alteration of the circadian clock is linked with the initiation and progression of several types of cancers, including HCC, colorectal, breast, blood, and lung cancers (Fu and Kettner, 2013).

Recent studies reported interrelationships between hypoxic response pathways and circadian pathways. The fundamental components of circadian clockwork and oxygen homeostasis are the PAS protein family members (PER and CLOCK) and HIF-1α. Numerous genes are involved in the circadian clock circuitry, and response to hypoxia is deregulated in diseases and stress conditions, hence influencing the physiological process as well as disease progression and outcome.

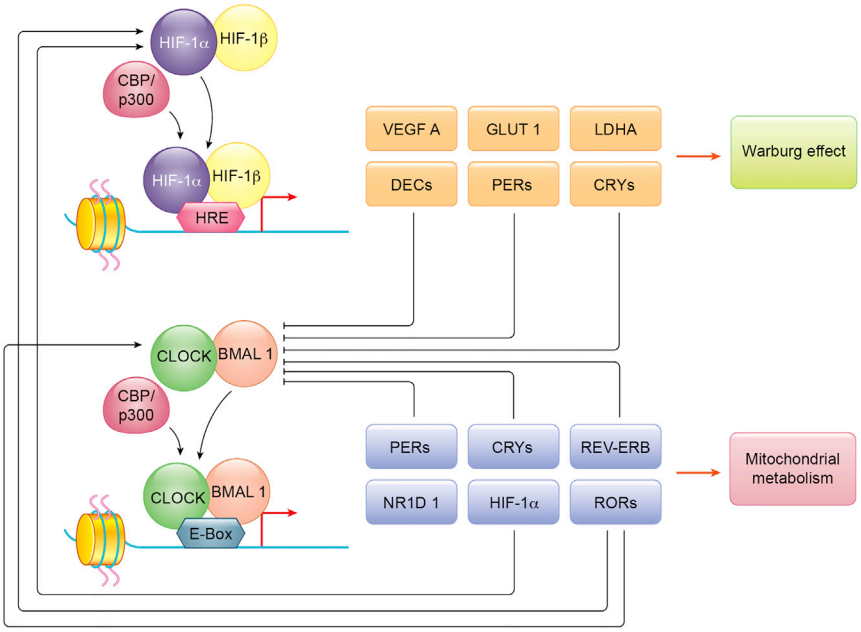

Figure 2. Bidirectional Interactions between Circadian Clock and HIF Pathways

Under hypoxia, HIF-1α heterodimerizes with HIF-1β in nucleus and binds to HREs in the promoters of hypoxia-induced genes. Upon recruitment of CBP/P300 (co-activator), the HIF-1α:HIF-1β complex drives the transcription of target genes such as glycolysis-related genes and some circadian clock genes such as PERs, CRYs, and DECs. On the other hand, BMAL1 heterodimerizes with CLOCK to form a BMAL1:CLOCK complex which binds at E-box-containing motifs and transactivates the clock-controlled genes such as PERs, CRYs, REV-ERB, and RORs, including HIF-1α. CBP/P300 acts as co-activator to induce the activation. There are a number of interconnected feedback loops between HIF and circadian clock pathways that regulate the circadian transcription. The key feedback is a native loop of PER and CRY (transcriptionally activated by HIF and by BMAL1:CLOCK) that leads to the repression of CLOCK:BMAL1-mediated transcription. The other feedback loop is by ROR, which activates BMAL1:CLOCK by binding the ROR-elements (RORE). In addition, ROR physically interacts with HIF-1α, hence inducing the stabilization and transcriptional activation of HIF-1α. REV-ERB acts as a repressor for BMAL1 transcription by competing at the same ROR sequence. HIF-1α-dependent DECs also negatively feedback by suppressing BMAL1:CLOCK transactivation. These interactions and feedback loops provide strong evidence that HIF plays an important role in modulating the circadian rhythm.

The underlying mechanism could involve the transcriptional control of circadian gene expression by HIF or though HIF protein–protein interactions, leading to decreased proteolytic degradation of circadian proteins. *In vivo* experiments revealed that hypoxia upregulates levels of circadian proteins, PER1 and CLOCK, possibly through protein interaction between PER1 and HIF-1α (Chilov et al., 2001). In addition, HIF-1α interacts with BMAL1/MOP3 and CLOCK to regulate gene expression (Ghorbel et al., 2003; Hogenesch et al., 1998), suggesting that HIF-1α may regulate the circadian clockwork, and the crosstalk between hypoxia and circadian pathways modulates the expression of target genes. Hypoxia-induced HCC with CoCl2 revealed an increase in of the expression of Clock, BMAL1, and CRY2, and decreased levels of PER1, PER2, PER3, CRY1, and CKIε in hypoxia. Both HIF-1α and HIF-2α are involved in regulating the expression of circadian genes in HCC. However, they transcriptionally regulate different set of circadian genes (Yu et al., 2015).

The post-translational modifications of core clock proteins significantly contribute in the circadian system flux. These modifications control the timing between the activation and the repression of circadian transcription to regulate distinct functions. For example, BMAL1, a clock protein, is subject to various post-translational modifications, including phosphorylation though casein kinase (CK) 1 δ/ε and CK 2 (Agostino et al., 2009; Sahar et al., 2010). Under hypoxia, CK1δ plays a vital role, phosphorylating the N-terminal heterodimerization (PAS) domain of HIF-1α. This obstructs the association with ARNT, thereby controlling the activity of HIF-1α during hypoxia (Kalousi et al., 2010).

The circadian organization of the molecular clockwork affects VEGF levels in hypoxic cells. For instance, PER2 and CRY1 inhibit hypoxia-induced VEGF promoter activity, indicating a negative feedback loop, which periodically suppresses the transcriptional upregulation of *VEGF* during hypoxia, resulting in the circadian fluctuation of its gene expression (Koyanagi et al., 2003). Moreover, the basic helix-loop-helix (bHLH) transcription factors, differentiated embryonic chondrocyte-expressed gene 1 (DEC1) and DEC2, are part of an important crosstalk between hypoxia responses and circadian pathways (Sato et al., 2016).

Recently, a number of studies have showed the crosstalk and feedback loops between circadian clock and oxygen sensing pathways (Figure 2). Peek et al. (2017) reported a bidirectional crosstalk between circadian and HIF pathways that modulates the metabolic adaptation in a tissue-specific manner. Genetic disruption of the core clock component, BMAL1, in mouse skeletal muscle reduces anaerobic glycolysis, HIF-1α activity, and the expression of its target genes, including *PHD3, VEGFA, MCT4, PK-M,* and *LDHA*. HIF-1α binds directly on the promoters of several core clock genes. In response to strenuous exercise, expression level of CLOCK and HIF-1α target genes varied depending on the time of day in mice. They concluded that circadian clock cooprate with HIF-1α to mediate anaerobic glycolysis in Muscle (Peek et al., 2017). Another study showed that the hypoxia response is gated by the circadian clock through HIF-1α, that acts as a regulatory node that connects both pathways (Wu et al., 2017). Genome-wide analysis of HIF-1α and BMAL1 binding revealed hypoxia-clock reciprocal regulation at the genome level. An *in vivo* heart attack model described that the circadian clock protects the heart from hypoxia-induced cell death (Wu et al., 2017), suggesting that the circadian clock can be utilized therapeutically to reduce the severity of hypoxia-associated diseases. Adamovich et al. (2017) measured continuous oxygen levels in the blood and tissue of rodents and identified daily rhythms in tissue oxygenation. Interestingly, the physiological oxygen rhythms synchronize clocks in cultured cells in a

HIF-1α-dependent manner. Moreover, modulation of oxygen levels hasten the recovery of wild-type mice from a jet lag protocol, but not that of HIF-1α-deficient mice (Adamovich et al., 2017). These recent studies provide strong evidence of important crosstalk between circadian and hypoxia signaling pathways in a HIF-1α-dependent fashion (Adamovich et al., 2017; Peek et al., 2017; Wu et al., 2017) (Figure 2).

Currently, circadian rhythm and hypoxia-signaling are active areas of research aiming at identifying the molecular mechanisms and regulators of these pathways in cells. The absence of models in which these pathways can be investigated under controlled conditions delayed our progress in understanding the crosstalk between hypoxia and the circadian clock in physiological and pathological states. Interestingly, circadian clocks are capable of not only mediating changes in the external light cycle, but also regulate adaptation to flux in nutrient and oxygen sensing.

Hypoxia, HIFs, and Cellular Vesicles

The discovery of cellular vesicles including exosomes and microvesicles led to a better understanding of cell-cell interaction and communication. Exosomes originate from endocytic multivesicular bodies that follow the endosomal pathway and end up with exocytosis. Exosomes range from 30–100 nm in size. Recent studies suggest that cancer-associated exosomes, through their content, induce metastasis and create a pre-metastatic niche. For instance, low cellular pH is a hallmark of tumor malignancy. In cancer cells, the acidic microenvironment leads to increased exosomal release and uptake by recipient cells (Parolini et al., 2009). Riches et al. measured the release of exosomes from normal human mammary and breast cancer cells. They reported a significant increase in release of exosomes from cancer cells compared to that from normal cells within 24 hr (Riches et al., 2014). Recent findings clearly suggest that cellular vesicles serve as a significant mediator of cell-to-cell communication within the tumor microenvironment to facilitate tumorigenesis and modulate metabolism. For example, breast cancer cells can suppress glucose uptake of stromal cells in the pre-metastatic niche, by releasing cellular vesicles that contain high levels of the miR-122 which downregulate the glycolytic enzyme pyruvate kinase (Fong et al., 2015). *In vivo* suppression of miR-122 restores glucose uptake in distant organs and significantly reduce metastasis. These data suggest breast cancer cells derived vesicles can reprogram energy metabolism and create a niche with high glucose availability for their own consumption. Proteomic analysis of exosomes released from HCC revealed enrichment of glucose metabolism regulatory proteins (Zhang et al., 2017). Exosomal miR-126 is an emerging novel regulator of different aspects of cell metabolism including glucose homeostasis, mitochondrial respiration, and regulation of genes involved in gluconeogenesis and oxidative stress (Tao et al., 2016; Tomasetti et al., 2014). Recently, cancer-associated fibroblast exosomes were shown to promote metabolic reprogramming in cancer cells through supressing mitochondrial function and inducing glucose metabolism of other cancer cells (Zhao et al., 2016).

Increasing evidence suggests that hypoxia-secreted cellular vesicles in a tumor microenvironment are involved in a number of functions, such as prompting intratumoral heterogeneity, responding to immunological reactions, inducing cancer-associated fibroblasts, metabolic reprogramming, and promoting angiogenesis and metastasis.

HIF and Exosomes

Many studies reported that tumor hypoxia increases the release of exosomes from malignant cells. HIF regulates the expression of many plasma membrane receptors, including glucose transporter (GLUT-1), transferrin receptor, and Epidermal Growth Factor Receptor (EGFR), and it is thought that increased expression of receptors causes their activation and internalization, which consequently induces endocytosis and promotes exosome release. Hypoxia-induced exosomes content varies depending on cell origin including signal transducers, transcription factors, enzyme, lipids, mRNAs, and non-coding RNAs (Table 3). Aberrant exosomal secretion is associated with the adaptation to a different microenvironment that promotes cancer survival. King et al. (2012) found that exosome secretion increased as which contained high levels of HIF-regulated miR-210 (King et al., 2012).

Several studies indicated that hypoxia-induced exosomes contribute to tumor angiogenesis and metastasis. Aga et al. (2014) detected HIF-1α in exosomes secreted from invasive Epstein–Barr virus (EBV) malignancy, nasopharyngeal carcinoma (NPC). The oncoprotein, latent membrane protein 1 (LMP1), upregulates HIF-1α expression in exosomes. Interestingly, transcriptionally active *HIF-1α* was detected in recipient cells upon exosome uptake. In addition, HIF-1α regulates exosome-mediated pro-metastatic effects through epithelial–mesenchymal transition (EMT) changes in E- and N-cadherin expression in the recipient cells (Aga et al., 2014). Exosomes secreted from prostate cancer under hypoxia enhance stemness, invasiveness, and EMT by modulating the cancer-associated fibroblast phenotype in prostate stromal cells (Ramteke et al., 2015). Hypoxic prostate cancer exosomes are unique and express high levels of proteins such as heat shock proteins (HSP90 and HSP70), matrix metalloproteinases, AKT, annexin II, IL6, TGFβ2, β-catenin, TNF1α, CD63, and CD81 compared to those observed in normoxic secreted exosomes (Ramteke et al., 2015). Similarly, Rong et al. (2016) showed that hypoxia induces the secretion of exosomes that express immunosuppressive cytokines such as TGF-β and IL-10 from breast cancer cells (Rong et al., 2016).

Co-culturing of K562 leukemic cells with human umbilical vein endothelial cells (HUVECs) significantly promoted tube formation by HUVECs during hypoxia (Tadokoro et al., 2013). Exosomes released during hypoxia were similar in size as those secreted during normoxia. Interestingly, exosomal miR-210 released from leukemic cells during hypoxia downregulates the expression of the anti-angiogenic factor, Ephrin-A3 (EFNA3), in HUVECs, indicating the interaction between cancer and endothelial cells via exosomes to modulate angiogenesis during hypoxia (Tadokoro et al., 2013). Similarly, Umezu et al. (2014) developed an *in vitro* chronic hypoxia model by continuous growth of multiple myeloma (MM) cell lines (more than 6 months) under hypoxic conditions, named hypoxia-resistant MM cells. This model mimics the *in vivo* microenvironment of bone marrow myeloma cells. The number of exosomes secreted from hypoxia-resistant MM cells is twice that secreted by parental cells grown in normoxia or hypoxia (Umezu et al., 2014). Exosomes released from hypoxia-resistant MM cells promote tube

Table 3. Secreted Molecules in Exosomes under Hypoxia

Molecules	Type	Cancer	HIF Dependent	References
HIF-1α	Transcription Factor	Nasopharyngeal carcinoma		(Aga et al., 2014)
miR-210	Non-coding RNA	Breast cancer, leukemia		(Jung et al., 2017; King et al., 2012)
miR-486	Non-coding RNA	Erythroleukemia, endothelial cells		(Shi et al., 2017; Viñas et al., 2016)
miR-24-3p	Non-coding RNA	Nasopharyngeal carcinoma.		(Ye et al., 2016)
miR-135b	Non-coding RNA	Multiple myeloma		(Umezu et al., 2014)
miR-21	Non-coding RNA	Oral squamous cell carcinoma	HIF-1α and HIF-2α	(Li et al., 2016a)
Myristic, Palmitic, Palmitoleic, Stearic, Oleic, Linoleic, Arachidonic	Fatty acid	Prostate cancer		(Schlaepfer et al., 2015)
TGF-β, IL10		Breast cancer		(Rong et al., 2016)
Wnt4	mRNA and Protein	Colorectal cancer	HIF-1 α	(Huang and Feng, 2016)
Proteins: MMP9, PTX3, IL8, PDGF-AB/AA, CD26, PAI1,CAV1; mRNAs: IGFBP3, NDRG1, LOX, ADM, IGFPB3, BNIP3, ID2, NDRG1, PLOD2, PAI1	mRNA and Proteins	Glioblastoma		(Kucharzewska et al., 2013)
Tetraspanins (CD81 and CD63), HSP70, HSP90, MMP-2, MMP-9, TGF-β2, TNF1α, IL6	Protein, cytokines, growth factors	Prostate cancer		(Ramteke et al., 2015)

formation of HUVECs during normoxia, but to a greater degree under hypoxia. Interestingly, secreted miR-135b by hypoxia-resistant MM cells induces the endothelial tube formation in hypoxia and enhances HIF-1 transcriptional activity by inhibiting factor-inhibiting hypoxia-inducible factor 1 (FIH-1) (Umezu et al., 2014). Further studies reported that exosomes secreted from pericytes upon HIF activation promote the angiogenic activity of endothelial cells (Mayo and Bearden, 2015). Moreover, exosomes derived from hypoxic endothelial cells remodel the extracellular matrix via exosome-associated lysyl oxidase-like 2 (LOXL2) for fibrosis and wound healing (de Jong et al., 2016).

Recently, Ling et al. demonstrated that hypoxia increases oral squamous cell carcinoma (OSCC)-derived exosomes, which promotes cell migration and invasion in a HIF-1α- and HIF-2α-dependent manner(Li et al., 2016a). miR-21 was the most significantly upregulated miRNA in exosomes released from hypoxic OCSS cells. miR-21 suppression in hypoxic OSCC cells reduced miR-21 expression in exosomes and significantly impaired cancer cell migration and invasion. Exosomal miR-21 promotes the expression of snail and vimentin, while decreasing E-cadherin expression. Moreover, exosomal miR-21 levels and HIF-1α/HIF-2α expression were associated with lymph node metastasis in patients with OSCC (Li et al., 2016a). Moreover, miR-24-3p is found enriched in hypoxic cells and exosomes from neural progenitor cells (NPC) cells and serum. miR-24-3p regulates T cell proliferation and differentiation and may be a prognostic marker for NPC (Ye et al., 2016).

Both *in vitro* and clinical studies using specimens from patients with glioblastoma multiforme (GBM) showed enrichment of hypoxia-regulated mRNAs and proteins such as platelet-derived growth factors (PDGF), matrix metalloproteinases, IL-8, caveolin 1, and lysyl oxidase in exosomes (Kucharzewska et al., 2013). Many of these molecules modulate angiogenesis and are associated with poor clinical outcome in patients with glioma. In GBM, hypoxia-induced exosomes stimulate endothelial cells through several growth factors and cytokines, leading to the activation of PI3K/AKT signaling and migration. Hypoxia-induced GBM exosomes significantly increase cell proliferation, tumor vascularization, and pericyte vessel coverage (Kucharzewska et al., 2013). This study indicates that exosomal protein and RNA content recapitulates the oxygenation status of exosome releasing cells and patient tumors.

Hypoxic regions are also detected in adipose tissues because of adipocyte hypertrophy. Hypoxia induces release of exosomes from differentiated adipocytes. Hypoxia-derived exosomes are enriched in proteins responsible for de novo conversion of acetyl-CoA to fatty acids, including fatty acid synthase, acetyl-CoA carboxylase, and glucose-6-phosphate dehydrogenase, suggesting a role of hypoxia-induced release of exosomes by adipocytes in regulating lipogenesis. Given that lipid metabolism is one of the hallmarks of hypoxic cancer cells, increased accumulation of lipids during hypoxia may stimulate and induce the biogenesis and secretion of extracellular vesicles. Hypoxic prostate cancer exosomes are significantly enriched in triglycerides, owing to the activation of lipogenic enzymes and signaling molecules, which play important roles in prostate cancer invasiveness (Schlaepfer et al., 2015). Moreover, fatostatin and silibinin (lipogenesis inhibitors) reduce the concentration of extracellular vesicles and VEGF level in exosomes, suggesting the important role of lipid metabolism in hypoxic prostate cancer exosomes supporting cancer invasiveness and metastasis.

HIF and Microvesicles

HIF also regulates other extracellular vesicles such as microvesicles. These vesicles are budded directly from the membranes

and shed from almost all cell types. Microvesicles have a wide range of sizes from 100 nm to 1 μm and play an important role in intercellular communication. Wang et al. (2014) reported that HIF mediates microvesicle production by breast cancer cells during hypoxia. HIF increases the activity of a member of the Rab family of small GTPases, RAB22A, which co-localizes with budding microvesicles at the cell surface. RAB22A is HIF-dependent and essential for the formation of vesicle, trafficking, and membrane fusion. Thus, microvesicle biogenesis depends on HIF-1α during hypoxia. RAB22A is required to promote invasion and metastasis of recipient breast cancer cells (Wang et al., 2014). Similarly, Berchem et al. (2015) reported that hypoxia-derived microvesicles from GR-Heu and K562 tumor cells suppress natural killer (NK) cell function and decrease cytotoxicity compared to macrovesicles released during normoxia. Impaired cytotoxicity of NK cells by hypoxia-derived microvesicles results from decreased expression of NKG2D in a tumor growth factor (TGF-β1)-dependent manner. In addition, miR-23a is significantly overexpressed during hypoxia when compared to that in normoxic tumor microvesicles. miR-23a directly regulates the expression of Lysosomal-associated membrane protein 1 (LAMP-1)/CD107a in NK cells (Berchem et al., 2015), suggesting that suppressive signals of immune cells such as TGF-β1 and miR23a in the hypoxia-derived microvesicles impair the anti-tumor immune response during hypoxia.

The above studies suggest that hypoxia/HIF affects the synthesis of extracellular vesicles and their biological effects in the tumor microenvironment, contributing to the major hallmarks of cancer and supplementing many of the pathways induced directly in cells by hypoxia e.g., metabolism, angiogenesis and EMT. It is also reasonable to think that cellular vesicles are heterogeneous and this may contribute to tumor heterogeneity adding new layer of complexity in our understanding of cancer.

Hypoxia/HIF regulation on exosome and microvesicles function is a new and exciting area of research, however, it is in early stages. The direct mechanism of extracellular vesicles induction by HIF and impact of HIF in modulating processes including cellular vesicles formation, content selection, loading, trafficking, and release remains to be determined. How these processes are orchestrated during hypoxia should be further investigated.

Future Perspectives

Decades of research on hypoxia and HIF biology significantly improved our understanding of oxygen homeostasis in health and diseases. However, advancement in analytical tools and genomic technologies opened new important areas for investigation. Recently, pan-genomic analysis shows several cancer risk polymorphisms overlap with HIF-binding sites, hence may modulate HIF signaling and cancer development (Grampp et al., 2016; Grampp et al., 2017).

The role of HIF in hypoxia responses has been the topic of many investigations. Some of these studies provide inconsistent findings because of the experimental tools used and design biases. For instance, researchers utilized either cell-based *in vitro* models or animal models maintained under hypoxia to infer their conclusions. However, hypoxia responses vary between cell lines from the same cancer type and between models and within subpopulations of the same cell line (Ledaki et al., 2015). The other major barrier to investigating the effects of hypoxia on tumor cells *in vitro* is that cells can only grow for a few days under hypoxic conditions. In most studies, cells are commonly exposed to hypoxia for 24–72 hr. In such cases, tumor cells might respond to acute hypoxic stress, which could be different from long-term intratumoral hypoxia.

The new mechanisms described above point to many ways of individualising responses in each cell, influencing neighboring cells and those at a great distance, diversifying the response well beyond the recognized core metabolism genes. This provides the possibility of substantial advances in biomarkers of hypoxia in specific tissues, but also far more specific modulation of the hypoxia response than previously recognized e.g., use of JQ1 a BRD4 modulator that specifically inhibited induction of a subset of genes in hypoxia (da Motta et al., 2017).

Deciphering the role of epigenetics, non-coding RNAs, circadian rhythms and extracellular vesicles in hypoxia will advance our understanding of cellular modulation under low oxygen stress, and should lead to the development of more specific therapeutic agents.

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