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The strict regulation of HIF-1α by non-coding RNAs: new insight towards proliferation, metastasis, and therapeutic resistance strategies

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Abstract
The hypoxic environment is prominently witnessed in most solid tumors and is associated with the promotion of cell proliferation, epithelial-mesenchymal transition (EMT), angiogenesis, metabolic reprogramming, therapeutic resistance, and metastasis of tumor cells. All the effects are mediated by the expression of a transcription factor hypoxia-inducible factor-1α (HIF-1α). HIF-1α transcriptionally modulates the expression of genes responsible for all the aforementioned functions. The stability of HIF-1α is regulated by many proteins and non-coding RNAs (ncRNAs). In this article, we have critically discussed the crucial role of ncRNAs [such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), Piwi-interacting RNAs (piRNAs), and transfer RNA (tRNA)-derived small RNAs (tsRNAs)] in the regulation of stability and expression of HIF-1α. We have comprehensively discussed the molecular mechanisms and relationship of HIF-1α with each type of ncRNA in either promotion or repression of human cancers and therapeutic resistance. We have also elaborated on ncRNAs that are in clinical examination for the treatment of cancers. Overall, the majority of aspects concerning the relationship between HIF-1α and ncRNAs have been discussed in this article.

Keywords MicroRNA · Long non-coding RNA · Circular RNA · Piwi-interacting RNA · tRNA-derived small RNA · HIF-1α · Angiogenesis

1 Introduction

A condition in which a supply of oxygen is limited to any particular tissue is termed a hypoxic condition. Hypoxia is a commonly observed feature in tumors. The severity of hypoxia varies among tumors and depends on a wide range of factors [1]. In the uncontrollably dividing cells of the tumor, the oxygen demand is elevated more than the supply which leads to the hypoxic condition. Also, an insufficient amount of blood is supplied to tumor tissues due

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to critical structural and functional abnormalities including non-uniform vasculature, an incomplete endothelial lining, an absence of flow regulation, and intermittent stasis [2]. Additionally, the increased distance between tumor cells and existing blood vessels (> 70 μm) further interferes with the diffusion of oxygen and pushes the tissue towards a hypoxic condition referred to as diffusion-limited hypoxia [3–5]. Hypoxia can either induce death in cancer cells or promote their survival depending on the length of exposure to reduced oxygen levels. It has been well-established that tumor hypoxia greatly promotes angiogenesis, antiapoptosis, epithelial-mesenchymal transition (EMT), cancer cell invasion, metastasis, and resistance against radiation therapy and chemotherapy. Hypoxic condition diminishes therapeutic efficacy and accelerates tumor progression [6, 7].

Hypoxia imparts its effect on tumor cells through a transcription factor named hypoxia-inducible factor (HIF). HIF transcription factors are present in the form of heterodimers consisting of HIF-α and HIF-β subunits. HIF-α is a cytoplasmic resident whereas HIF-β is constitutively expressed and housed in the nucleus. In humans, HIF-α has three paralogs, namely, HIF-1α, HIF-2α/EPAS, and HIF-3α whereas HIF-β has two paralogs, namely, ARNT and ARNT2 [8]. In normoxic conditions, oxygen-sensitive prolyl hydroxylases (PHDs) hydroxylate proline in a C-terminal and an N-terminal oxygen-dependent degradation domain of HIF-α [9]. The proline hydroxylation is recognized by Von Hippel-Landau (VHL) E3 ligase protein and subsequently delivers the HIF-α to proteasome and promotes its degradation thereby making it unavailable to interact with its binding partner, HIF-β (Fig. 1) [10]. An additional layer to the regulation is provided by FIH (factor-inhibiting HIF), an oxygen-sensitive asparaginyl hydroxylase. FIH also catalyzes the hydroxylation of HIF-α and prevents its association with transcriptional coactivators (such as p300/CBP) [11–13]. In hypoxic conditions, the reduced oxygen levels decrease the catalytic activity of PHDs as they need oxygen as a cofactor for hydroxylation reactions. In the absence of hydroxylation, HIF-α translocates into the nucleus and complexes with HIF-β and p300/CBP. The complex interacts with hypoxia-responsive elements (HREs) to drive the transcription of target genes [14]. The HIF transcription factors are known to drive the transcription of over 150 genes. Some of the target genes of HIFs are erythropoietin, heme oxygenase-1, transferrin, transferrin receptors, adrenomedullin, epidermal growth factor, vascular endothelial growth

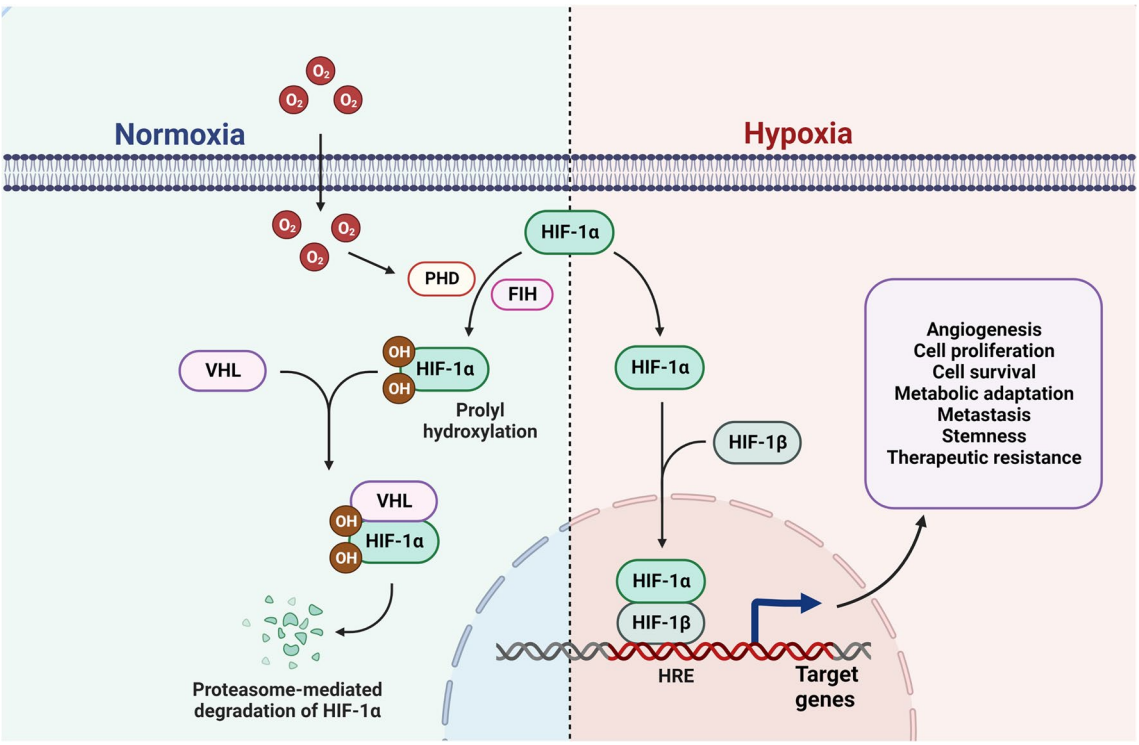

Fig. 1 Mechanism of HIF-1α signaling in normoxia and hypoxia. In normoxia, oxygen-sensitive PHDs hydroxylate proline residues on HIF-1α which leads to the subsequent VHL-mediated degradation of HIF-1α. In hypoxia, HIF-1α couples with HIF-1β to transcribe the target genes that are responsible for angiogenesis, cell proliferation, survival, metabolic adaptations, metastasis, stemness, and therapeutic resistance

factor, transforming growth factor-β, platelet-derived growth factor-B, glucose transporter-1, and insulin-like growth factor-2 [15]. In tumor hypoxia, increased expression of these proteins is witnessed indicating the overactivation of HIF signaling which contributes to the disease progression and aggressive of tumors.

The function of HIF-1α in cancer has been of great interest in recent years as the inhibition of HIF-1α has demonstrated good suppression of cancer cell proliferation [16, 17]. Overexpression of HIF-1α promoted bladder cancer progression, while SRT1720 (a pharmacological activator of SIRT1) suppressed hypoxia signaling by activating SIRT1 (a deacetylase) and deacetylating HIF-1α to impart antitumor effect [18]. USP25 (ubiquitin-specific protease 25) is a deubiquitinating enzyme which was found to prevent the ubiquitination of HIF-1α and accelerate pathological HIF-1-driven metabolic reprogramming of pancreatic cancer [19]. Curcumol induced the degradation of HIF-1α to suppress EMT and metastasis of colorectal cancer [20]. Similarly, many reports have emphasized the significance of targeting the HIF-1α pathway in cancers.

About 2% of genes present in the human genome code for functional polypeptides and the other 98% were considered to be junk. Of lately, the discovery of an abundant amount of non-coding RNAs (ncRNAs) in cells of human origin has spread light on the importance of the 98% non-coding region of the genome. The advancement in high-throughput technologies and research in the last two decades have revealed that a major portion of the non-protein-coding region of DNA (98%) codes for ncRNAs that are crucially involved in the maintenance of all cellular functions. microRNA (miRNA), long non-coding RNA (lncRNA), circular RNA (circRNA), Piwi-interacting RNA (piRNA), and transfer RNA (tRNA)-derived small RNAs (tsRNAs) are some of the ncRNAs that have been discovered so far. The mode of action of all the types of ncRNAs is different, and they can behave as either tumor promoters or tumor suppressors. Some ncRNAs can also modulate the expression and activity of HIF-1α to promote or retard tumor progression. The biogenesis and functions of miRNA, lncRNA, and circRNA are provided in Fig. 2. In the following section, we have emphasized the role of individual types of ncRNAs and their role in the regulation of HIF-1α in human cancers.

2 Non-coding RNAs in cancer

2.1 miRNA

Basic research on microRNAs (miRNAs) has garnered much attention because miRNAs have proven to be cardinal factors in regulatory gene circuits [21]. miRNAs are single-stranded small ncRNA molecules with an average length of 22 nucleotides, and they often modulate the gene expression by interacting with the complementary sequences present at the 3′-UTR of target mRNA [22]. The interaction between miRNA and mRNA leads to the decapping, deadenylation, and translation suppression of the target mRNA. miRNAs can also repress translation by binding to the 5′-UTR or other regions of mRNA [23]. Additionally, few studies have demonstrated that some miRNAs possess the function of interacting with gene promoters to elevate the expression of target genes [24, 25]. miRNA is transcribed by RNA polymerase II. miRNA is produced as primary-miRNA (pri-miRNA) which is subsequently acted upon by a ribonuclease named DROSHA in the presence of DGCR8 to generate a precursor miRNA (pre-miRNA). The pre-miRNA is transported with the aid of exportin-5 from the nucleus to the cytoplasm where Dicer, an RNase III-like enzyme, cleaves the pre-miRNA to produce a mature miRNA, which is subsequently loaded to argonaute proteins and some auxiliary proteins to form RNA-induced silencing complex (RISC) (Fig. 2A) [26–29]. The RISC machinery is involved in the modulation of target mRNA expression [30]. miRNAs have been demonstrated to be involved in the regulation of metabolism, metastasis, proliferation, drug resistance, and remodeling of tumor microenvironment in cancers [31–36]. For example, ATAD2 (ATPase family AAA domain containing 2) is an oncoprotein which is overexpressed in various types of malignancies and positively correlated with tumor progression. miR-217 was found to target 3′-UTR of ATAD2 to downregulate the proliferation of prostate cancer cells [37]. In another study, miR-423-3p was reported to activate Beclin-1-dependent autophagy and encourage gastric cancer progression by decreasing the expression of Bim [38]. miRNAs also modulate the HIF-1α signaling, and the specific role of miRNAs in regulation of the HIF-1α is provided in the subsequent sections.

2.2 LncRNA

LncRNAs are transcribed similarly to mRNAs, but they lack protein-coding ability. The length of lncRNA is more than 200 nucleotides [39, 40]. LncRNAs can be found in the nucleus as well as in cytoplasm but predominantly in the nucleus. Depending on the origin of lncRNA, they are categorized into intergenic, intronic, bidirectional, sense, and antisense lncRNAs. Unlike miRNAs, lncRNAs can modulate gene expression by various mechanisms. LncRNAs can function as a signal, decoy, guide, scaffold, and RNA sponge to regulate the biological behavior of cells (Fig. 2B) [41]. LncRNAs are implicated in the regulation of cellular

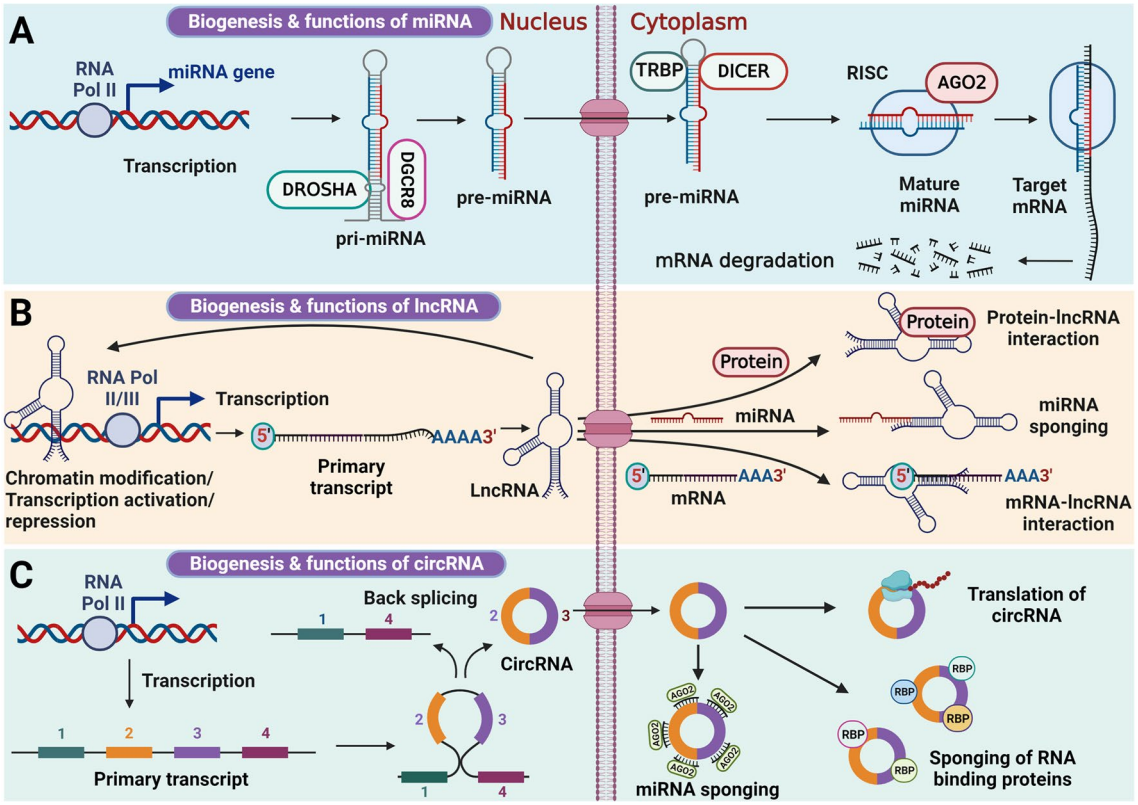

Fig. 2 Biogenesis and functions of miRNA, lncRNA, and circRNA. **A** miRNA-coding gene is transcribed by RNA polymerase-II to form pri-miRNA which is processed by DROSHA and DGCR8 to form pre-miRNA, and subsequently, pre-miRNA is transported to cytoplasm. Further, pre-miRNA undergoes DICER-TRBP-mediated endonucleolytic cleavage and is loaded with AGO2 proteins to form mature miRNA. Functionally, miRNA interacts with and degrades the target mRNA. **B** LncRNA-coding genes are transcribed by RNA polymerase-II/III to produce primary transcripts which are eventually modified (capping/polyadenylation) and functionally controls the gene expression by chromatin modifications and transcription activation/repression. Also, lncRNAs are transported to the cytoplasm where they can interact with target proteins, miRNA, and mRNA to modulate their activity. **C** CircRNA-coding genes are transcribed by RNA polymerase-II in which the primary transcript undergoes back splicing to produce a circRNA. CircRNA is transported to the cytoplasm where it can sponge miRNAs, sequester RNA binding proteins, and can undergo translation

mechanisms and are also involved in disease pathogenesis [42, 43]. Altered expression of lncRNAs is commonly observed in many types of human malignancies. LncRNAs can have paradoxical functions. Some lncRNAs can serve as oncogenic, and some can be onco-suppressors. Variation in the expression of oncogenic and onco-suppressor lncRNAs is commonly observed in the majority of human malignancies. For instance, lncRNA miR155HG promoted the expression of TYRP1 (tyrosinase-related protein 1) by sponging miR-155-5p and thereby increased the progression of ovarian cancer [44]. Besides, overexpression of LINC01793 mediated an unfavorable clinical outcome in hepatocellular carcinoma [45]. LncRNAs are also involved in drug resistance. Silencing lncRNA DDX11-AS1 increased miR-497 expression to elevate paclitaxel sensitivity in breast cancer [46]. Overexpression of lncRNA LHFPL3-AS1 promoted HOXA6 expression by suppressing miR-143-5p to mediate radio-resistance in nasopharyngeal cancer [47].

2.3 CircRNA

CircRNAs are endogenous ncRNA molecules with a closed continuous loop structure which confers higher stability to them compared to linear counterparts [48, 49]. The first circRNA was identified in an RNA virus in 1976 and subsequently identified using electron microscopy in the cytoplasm of monkey renal CV-1 cells [50, 51]. In the initial days, it was believed that circRNAs are the product of erroneous RNA splicing. Advancements in RNA sequencing technologies revealed the presence of an abundant amount of circRNAs demonstrating that circRNAs are one of the major players in the maintenance of cellular homeostasis. CirRNAs are formed as a result of specialized splicing named "back splicing" in which the 5′ terminus of an upstream exon is non-collinearly joined with the 3′ terminus of a downstream exon (Fig. 2C). Circularization of exons results in the absence of 5′ capping and 3′ polyadenylation. Recent studies have demonstrated

that circRNAs can be formed either between two exons, two introns, or one intron and one intron which are termed exonic, intronic, and exon-intronic circRNAs, respectively. Like lncRNAs, circRNAs also participate in the sponging of miRNAs and RNA-binding proteins, scaffolding, and mediating the assembly of protein machinery. Of lately, the role of circRNAs in oncogenesis and disease progression is well demonstrated. Elevated levels of circRNA-100876 were witnessed in tumor tissues derived from colorectal cancer patients, and its expression was directly linked to lymph node metastasis [52]. CircRNAs can sponge miRNAs to modulate the expression/activity of various proteins. CircRNA C190 was found to sponge miR-142-5p to facilitate the EGFR-MAPK-ERK axis and thereby increase lung cancer progression [53].

2.4 piRNA

piRNAs are one of the least explored ncRNAs. The length of piRNAs varies between 26 and 31 nucleotides, and they interact with PIWI (P-element induced wimpy testis) proteins [54]. The expression of piRNAs was initially discovered in germline cells, and later, their expression was also found in somatic cells. piRNAs are transcribed by RNA polymerase-II, and they take part in epigenetic and retrotransposon post-transcriptional gene silencing by interacting with PIWI proteins [55, 56]. Deregulation of the expression of piRNAs can either promote or suppress oncogenesis and tumor progression *via* DNA methylation, mRNA turnover, and translational regulation. For instance, piR-36712 is an onco-suppressor piRNA that was found to be downregulated in tumor tissues of breast cancer patients [57]. Mechanistically, piR-36712 competed with miR-7 and miR-324 to interact with SEPW1P mRNA and inhibit SEPW1 protein expression. In the case of low expression of piR-36712, increased expression of SEPW1 was observed which led to the suppression of p53 and elevation of Slug and subsequent malignant progression [57]. In contrast, piR-651 was overexpressed in gastric cancer tissues in comparison with non-cancerous tissues, and inhibition of piR-651 resulted in growth suppression of gastric cancer cells [58]. These reports indicated that piRNAs can serve either as tumor promoters or tumor suppressors.

2.5 tsRNA

RNA polymerase-III transcribes the gene coding for tRNA to produce pre-tRNA which further undergoes nucleolytic cleavage at 5′ and 3′ ends by RNase P and RNase Z, respectively, followed by the addition of CCA nucleotides at the 3′ terminus to form a mature tRNA. Some tRNAs are also processed for the removal of a stretch of nucleotides present between the anticodon and variable arm [59]. tRNAs are the parent molecules of tsRNAs. tRNAs undergo cleavage to produce tsRNAs with the length varying between 13 and 48 nucleotides. tsRNAs can be classified into tRNA halves (30–40 nucleotides) and tRNA-related small RNA fragments (tRFs) (18–30 nucleotides) [60]. tRNA halves are generally called tRNA-derived stress-induced RNAs (tiRNAs) as they are largely produced under stress conditions such as oxidative stress, hypoxia, and inadequate nutrition [61]. Angiogenin is a stress-dependent RNase that breaks tRNA at anticodon loops to give tiRNAs.

tsRNAs can induce their biological effect in multiple ways including the regulation of translation, functioning like miRNAs, serving like piRNAs, and inhibition of apoptosis. 5′-tiRNA mitigated translation by disengaging eIF4G/eIF4A and eIF4F (eukaryotic translation initiation factors) from mRNA [62]. It is important to note that tsRNAs can be associated with AGO proteins (like miRNA) and make complementation with target mRNA to promote their degradation [63]. Some tsRNAs were found to interact with an oncogenic RNA-binding protein (Y-box binding protein 1) and thereby destabilizing the oncogenic transcripts [64]. tiRNAs were found to interact with cytochrome c to form ribonucleoprotein complexes and thereby suppressed the oligomerization of Apaf-1 to protect mouse embryonic fibroblasts from undergoing apoptosis [65]. tsRNAs can form a complex with PIWI protein and can act as piRNA [61]. The deregulated expression of tsRNAs has been found in various types of human cancers. tRF-Leu-CAG was reported to be highly elevated in tumor tissues and serum of NSCLC and positively associated with tumor stage [66]. In another report, tRF-20-M0NK5Y93 was identified to suppress the EMT process by targeting Claudin-1 in colorectal cancer cells [67]. In the following section, we have elaborated on the role of ncRNAs that are involved in the modulation of the HIF-1α pathway to impart their oncogenic or onco-suppressor functions in different cancers.

3 miRNAs and HIF-1α

3.1 Oncogenic miRNAs

Some miRNAs can modulate the HIF-1α signaling pathway or themselves can be under the transcriptional control of HIF-1α to promote tumorigenesis (Fig. 3). For instance, the expression of miR-224 was reported to be upregulated during hypoxia and it was found to be transcriptionally controlled by HIF-1α [68]. 3′-UTR of RASSF8 mRNA was found to be the direct target of miR-224. Depletion of RASSF8 elevated the activity of NF-κB while the overexpression of RASSF8 displayed reverse effects [68]. In another study, the expression of miR-224 was shown to

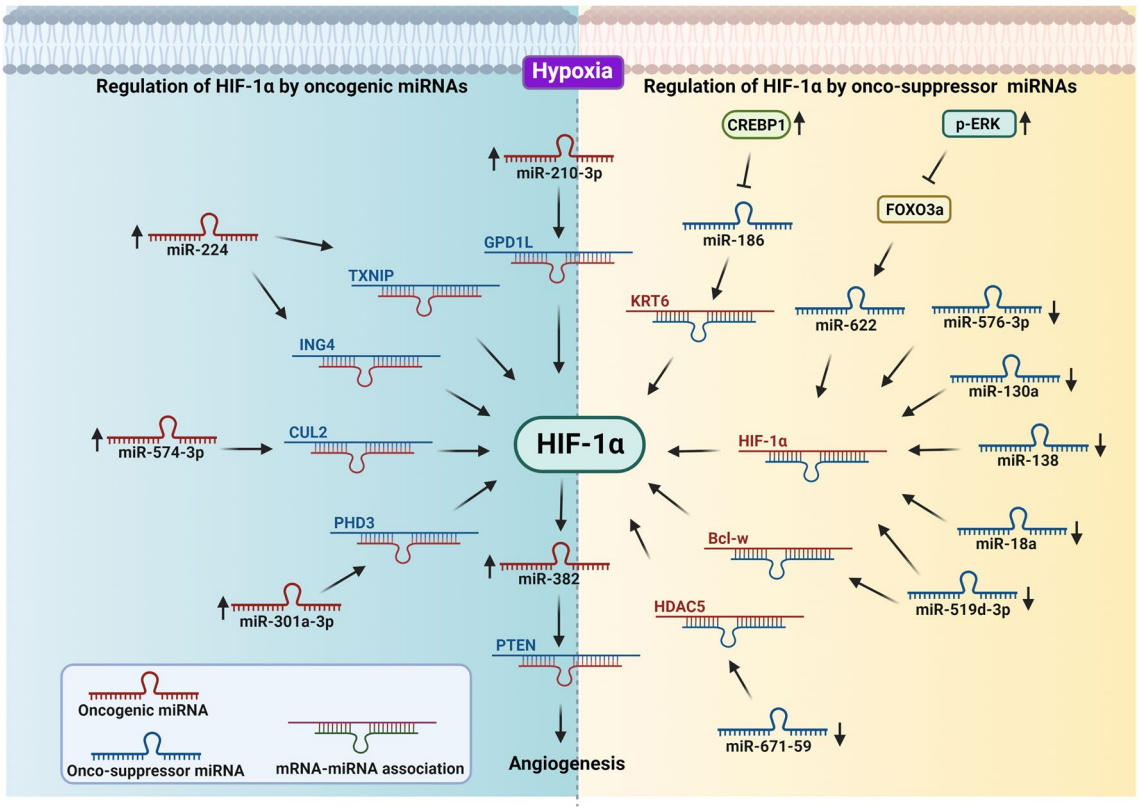

Fig. 3 HIF-1α is regulated by oncogenic as well as onco-suppressor miRNAs. miRNAs are well-known to impart their biological action by interacting with their target mRNAs and promoting their degradation. The mRNAs that code for tumor-suppressor proteins are targeted by oncogenic miRNAs, and mRNAs that code for oncogenic proteins are targeted by tumor-suppressor miRNAs. In tumors, the expression of oncogenic miRNAs is frequently upregulated whereas the onco-suppressor miRNAs are often downregulated leading to the deregulated expression of oncogenic proteins such as HIF-1α

be upregulated in pancreatic cancer tissues, and the overexpression was positively correlated with proliferation, migration, and metastasis in pancreatic cancer cells [69]. miR-224 targeted 3′-UTR of TXNIP (thioredoxin-interacting protein) which led to the activation of HIF-1α [69]. This suggests that the HIF-1α pathway is activated when the expression of its negative regulator is suppressed by miRNAs. miR-224 targets different mRNAs in different cancers. It was reported to target PAK4 to accelerate gastric cancer [70]. The downregulation of miR-224 led to a reduction in the expression of mTOR to induce apoptosis in gastric tumors [71]. As mentioned earlier, VEGF is a transcriptional target of HIF-1α. miR-214 was found to target ING4 (inhibitor of growth 4) in lung cancer cells and reduction of ING4 increased HIF-1α, thereby subsequent upregulation of VEGF [72].

Networking between miRNAs and HIF-1α through different mediators can significantly contribute to tumor progression by driving the EMT process. Ji and colleagues demonstrated that expression of miR-574-3p is elevated in gastric cancer tissues. The forced expression of miR-574-3p resulted in the acceleration of cell proliferation, motility, and EMT of gastric cancer cells [73]. The observed inhibitory effect of miR-574-3p was found to be mediated through targeting cullin 2 (CUL2), a scaffold protein that has been known to suppress HIF-1α expression. miR-574-3p promoted the expression of HIF-1α by decreasing CUL2 to stimulate EMT and metastasis [73]. HIF-1α and miRNA can form a positive feedback loop to modulate the expression of each other. In an interesting study, Xia and colleagues demonstrated that HIF-1α facilitated the release of miR-301a-3p-containing exosomes in gastric cancer cells and tissues under hypoxic conditions. In turn, miR-301a-3p suppressed the HIF-1α degradation by targeting PHD3 [74]. As learnt in the previous section, PHD3 can promote the degradation of HIF-1α by hydroxylating and marking it for ubiquitin-proteasome-mediated degradation. In another report, hypoxia-induced expression of miR-210 was found to downregulate the levels of GPD1L (glycerol-3-phosphate dehydrogenase 1-like) by directly targeting the mRNA of GPD1L and thereby stabilized HIF-1α to increase the expression of HIF-1α-driven genes to form a positive feedback loop [75]. miRNAs generally target and degrade the mRNAs of tumor-suppressor proteins to promote tumor growth. For example, miR-210-3p modulated aerobic

glycolysis and contributed to the Warburg effect in triple-negative breast cancer (TNBC) by directly targeting tumor suppressors such as GPD1L and CYGB (cytoglobin) [76]. Aerobic glycolysis [Warburg effect (in tumor cells)] metabolizes glucose into lactate. Although the efficacy of glycolysis in ATP production is not optimal, it is vital for biosynthesis, apoptosis, and production of signaling metabolites for promoting survival in cancer cells [77–83]. Angiogenesis is a crucial event in the progression of tumors, and many miRNAs are positively correlated with angiogenesis. miR-574-5p and HIF-1α were elevated in gastric cancer cells under hypoxic conditions, and this was found to be mediated through directly targeting PTPN3 (protein tyrosine phosphatase non-receptor type 3) [84]. PTPN3 negatively modulates angiogenesis by targeting the MAPK pathway. HIF-1α-induced miR-382 promoted angiogenesis by targeting PTEN (phosphatase and tensin homolog) in gastric cancer cells [85]. All these reports suggest that the association between miRNAs and the HIF-1α pathway can significantly contribute to cancer progression.

3.2 Onco-suppressor miRNAs

Apart from oncogenic functions, some miRNAs can also impart tumor suppressor functions by negatively modulating the HIF-1α pathway in cancer cells. In general, miRNAs impart an onco-suppressor effect by binding and degrading the mRNAs that code for oncogenic proteins. Notably, the expression of onco-suppressor miRNAs is downregulated with a parallel increase in the expression of oncogenic miRNAs. The expression of miR-138 and HIF-1α was found to be decreased and increased, respectively, in tumor tissues derived from melanoma patients. Interestingly, miR-138 was found to directly target HIF-1α in *in vitro* setup, and overexpression of miR-138 substantially alleviated the tumor expansion and metastasis in the xenograft melanoma model [86]. The expression of miR-18a was reported to be downregulated in gastric cancer cells under hypoxia whereas the forced expression of miR-18a induced apoptosis. The results of bioinformatic analysis and luciferase assay demonstrated that miR-18a targets HIF-1α to impart anticancer function in gastric cancer cells [87]. HIF-1α targeting miRNAs often alters glucose metabolism as HIF-1α plays a crucial role in the Warburg effect and expression of glucose-metabolizing enzymes. miR-18a-5p and miR-130a were found to target HIF-1α to regulate the Warburg effect in chronic myelogenous leukemia and non-small cell lung carcinoma (NSCLC), respectively, in hypoxic conditions [88].

Bcl-w is an antiapoptotic protein that is overexpressed in various types of tumors including NSCLC. miR-519d-3p targeted Bcl-w and HIF-1α to decrease tumorigenicity and metastasis of NSCLC. The existence of a positive feedback loop between Bcl-w and HIF-1α was observed [89]. Some miRNAs target HIF-1α to impart antiangiogenic activity and counteract tumor growth. For instance, miR-576-3p inhibits angiogenesis in glioma and impairs the progression of cancer cells by downregulating HIF-1α expression under hypoxic conditions [90]. Abrogation of HIF-1α is also one of the good strategies to suppress the EMT process. It was reported that miR-622 directly targets 3′-UTR of HIF-1α to downmodulate EMT in lung cancer cells [91]. Mechanistically, miR-622 was found to be under the transcriptional control of FOXO3a. FOXO3a is a transcription factor whose activity is regulated by EGF/ERK signaling axis. Phosphorylation of ERK results in ubiquitin-proteasome-mediated degradation of FOXO proteins, and inhibition of ERK allows the operation of FOXO proteins. Inhibition of ERK by U0126 resulted in upregulation of FOXO3a and miR-622. miR-622-driven suppression of HIF-1α correlated with reduced expression of mesenchymal markers such as Snail, β-catenin, and vimentin [91]. Snail, Zeb, and Twist are the transcription factors which are involved in the regulation of the expression of EMT-related genes [92].

miR-186 imparted tumor-suppressor functions by targeting mRNA of KRT6 (keratin 8), which is a positive modulator of expression of HIF-1α. miR-186 was found to be transcriptionally suppressed by CREBP1 (cAMP response element-binding protein 1), and elevated expression of CREBP1 was observed in gastric cancer cells indicating that CREBP1 suppresses the expression of miR-186 to promote proliferation, invasion, and EMT by enabling the operation of KRT6/HIF-1α axis [93]. Some miRNAs modulate epigenetic modifiers to serve the functions of onco-suppressors. miR-671-5p was found to be downregulated in ovarian cancer tissues. An inverse relationship was observed between miR-671-5p and HDAC5/HIF-1α in ovarian cancer cells [94]. Similarly, lung cancer tissues and cells exhibited elevated expression of KDM3A (lysine demethylase 3A) and HIF-1α and lowered expression of miR-449a. KDM3A was reported to interact with HIF-1α and miR-449a. miR-449a refrained lung cancer development by suppressing KDM3/HIF-1α axis [95]. The antitumor effects of miR-449a have also been documented in gastric cancer, cervical cancer, breast cancer, and endometrial cancer [96–99]. All these reports have comprehensively demonstrated the onco-suppressor functions of HIF-1α-targeting miRNAs in human cancers.

3.3 Association of miRNAs with therapy response

Exosomes are extracellular vesicles with a particle size ranging from 20 to 100 nm and are primarily enriched in the tumor microenvironment [100, 101]. The secretion and release of exosomes are increased under hypoxia [102] which enhances the shedding of pro-angiogenic

micro-vesicles [103]. Exosomes serve as vehicles for the transportation of ncRNAs and proteins. Exosomes can modulate the drug sensitivity of cancer cells [104]. For instance, epithelial ovarian cancer cells transformed macrophages into tumor-associated macrophage (TAM)-like phenotype under hypoxia [105]. The exosomes released by these macrophages carried miR-223, and exosomal miR-223 contributed to the acceleration of drug resistance in epithelial ovarian cancer cells [105]. HIF-1α can repress certain miRNAs to elicit drug resistance. Xu and colleagues demonstrated that HIF-1α repressed miR-338-5p to impart drug resistance in colorectal cancer cells [106]. miR-338-5p was found to target IL-6 which is essential for the activation of oncogenic proteins namely STAT3 and Bcl-2 [106]. The role of STAT3 and Bcl-2 in oncogenesis and chemotherapeutic resistance has been well documented [107–110]. Elevated expression of miR-338-5p or use of PX-478 (inhibitor of HIF-1α) increased the sensitivity of colorectal cancer cells to oxaliplatin by impeding the HIF-1α/miR-338-5p/IL-6 axis [106]. In another study, HIF-1α was found to upregulate TGF-β through the elevation of miR-210-3p. Subsequently, miR-210-3p promoted EMT and induced resistance to temozolomide in glioma cells [111]. Cobalt chloride and dimethyloxalylglycine are the agents used to induce hypoxia in *in vitro* cancer cell cultures. The expression levels of HIF-1α increase in the cancer cells upon treatment with these agents independently. HIF-1α expression was found to be stabilized by cobalt chloride and dimethyloxalylglycine, and increased levels of HIF-1α triggered resistance to cisplatin in gastric cancer cells [112]. It was found that HIF-1α transcriptionally induces the expression of miR-421 and subsequently miR-421 targets E-cadherin and caspase-3 to promote metastasis and cisplatin resistance in gastric cancer [112]. In addition to chemotherapy, miRNAs can also determine the response of cancer cells to radiation therapy. miR-200c decreased the expression of phospho-EGFR, phospho-AKT, VEGF, HIF-1α, and MMP2 and escalated the radiosensitivity of cancer cells [113]. Figure 3 and Table 1 provide a summary of miRNAs modulating HIF-1α signaling in various cancers.

4 LncRNAs and HIF-1α

4.1 Oncogenic lncRNAs

LncRNAs regulate HIF-1α by various mechanisms to elicit oncogenic effects. Some lncRNAs serve as scaffolds and thereby mediate the interaction between two different proteins. For example, the levels of lncRNA HABON (hypoxia-activated BNIP3 overlapping non-coding RNA) were significantly increased under hypoxia in hepatocellular carcinoma cells to promote their proliferation. Mechanistic investigation revealed that HABON is under the transcriptional control of HIF-1α. Unconventionally, HABON was found to

Table 1 The regulation of HIF-1α by miRNAs in cancer

Cancer type	Molecular axis	Mechanism and observed effects	Ref.
Lung cancer	miR-200c/HIF-1α	HIF-1α downregulation by miR-200c to impair the migration of tumor cells	[114]
Colorectal cancer	HIF-1α/miR-338-5p/IL-6	HIF-1α represses the expression of miR-338-5p to elicit chemoresistance. IL-6 is the downstream target of miR-338-5p	[106]
Colorectal cancer	CCL19/miR-206/HIF-1α/VEGF-A	CCL19 promotes the expression level of miR-206 and suppresses HIF-1α/VEGF-A axis to impair angiogenesis	[115]
Breast cancer	HIF-1α/MALAT1/miR-141	HIF-1α promotes MALAT1 expression to downregulate miR-141 and autophagy induction to increase the growth and metastasis of tumor cells	[116]
Breast cancer	HIF-1α/miR-210	HIF-1α accelerates the growth of breast cancer cells by regulating miR-210	[117]
Gallbladder cancer	miR-143-5p/HIF-1α/EMT	Loss of miR-143-5p leads to induction of HIF-1α/EMT axis to increase invasion of tumor cells	[118]
Gastric cancer	PRL-3/NF-κB/HIF-1α/miR-210	PRL-3 induces the NF-κB/HIF-1α axis to increase miR-210 expression in facilitating the tumorigenesis	[119]
Renal cell cancer	HIF-1α/miR-320a/HECTD2	HIF-1α reduces miR-320a expression to upregulate HECTD2 to promote tumor progression	[120]
Pancreatic cancer	miR-421/SIRT3/HIF-1α	Cancer-associated fibroblasts secrete miR-421 which increases HIF-1α expression via SIRT3 downregulation to accelerate tumorigenesis	[121]
Pancreatic cancer	miR-142/HIF-1α	Loss of miR-142 during hypoxia results in HIF-1α upregulation and carcinogenesis	[122]
Breast cancer	miR-182/FBXW7/HIF-1α/VEGFA	miR-182 reduces FBXW7 expression to induce HIF-1α/VEGF-A axis in promoting tumor progression	[123]
Colorectal cancer	HIF-1α/miR-23a~27a~24	Upregulation of miR-23a~27a~24 cluster by HIF-1α results in an increase in cancer progression and mediating metabolic reprogramming	[124]

promote the degradation of HIF-1α protein by facilitating the interaction of VHL and PHD2 with HIF-1α [125]. In an interesting study, lncRNA-packed in an extracellular vesicle was found to function as a messenger between immune cells and tumor cells in the tumor microenvironment. Chen and colleagues demonstrated that a lncRNA named HISLA (HIF-1α-stabilizing long non-coding RNA) is transmitted through extracellular vesicles to breast cancer cells from tumor-associated macrophages [126]. In breast cancer cells, HISLA interacted with PHD2 and prevented the interaction between PHD2 and HIF-1α which led to suppression of hydroxylation and degradation of HIF-1α and acceleration of aerobic glycolysis to produce lactate (Warburg effect). In turn, lactate produced by breast cancer cells elevated the levels of HISLA in tumor-associated macrophages forming a feed-forward loop between tumor-associated macrophages and breast cancer cells [126]. Clinical findings suggested that the expression of HISLA was correlated with reduced chemotherapeutic response and poor survival of patients with breast cancer [126]. Some lncRNAs regulate the activity of proteins associated with glucose metabolism to encourage the growth of cancer cells. LncRNA AC020978 was elevated in clinical samples of NSCLC and positively correlated with disease progression and poor clinical outcomes. Mechanistically, AC020978 physically interacted with pyruvate kinase isozyme M2 (PKM2) and increased the stability of PKM2. Additionally, AC020978 promoted the nuclear translocation of PKM2 and modulated PKM2-driven HIF-1α transcription activity [127].

Epigenetic modifications in the regulatory region of the lncRNA gene can modulate its expression. The hypomethylation of the promoter of lncRNA SNHG11 (small nucleolar RNA host gene 11) activated the expression of SNHG11 and contributed to dismal prognosis in colorectal cancer patients [128]. SNHG11 physically interacts with VHL recognition sites on HIF-1α and thereby impedes the interaction of VHL with HIF-1α. As discussed earlier, recognition of HIF-1α by VHL is essential for the proteasome-mediated degradation of HIF-1α. Altogether, SNHG11 prevented the degradation of HIF-1α and facilitated tumor metastasis of colorectal cancer cells [128]. Similarly, lncRNA MIR210HG was upregulated in ovarian cancer cells under hypoxic conditions and MIR210HG promoted EMT and angiogenesis by preventing the VHL-dependent degradation of HIF-1α [129]. LncRNAs can also be involved in facilitating the maintenance of mesenchymal stem-like cells in hypoxia. Mineo and colleagues showed that lncRNA HIF1A-AS2 is elevated in mesenchymal glioblastoma stem-like cells under hypoxic conditions. IGF2BP2 and DHX9 were identified as the binding partners of HIF1A-AS2. Depletion of HIF1A-AS2 resulted in reduced growth of mesenchymal glioblastoma stem-like cell tumors [130]. HIF-1α can directly promote the transcription of some lncRNA genes which are known to trigger tumorigenesis. HIF-1α elevated the levels of lncRNA DARS-AS1 which was reported to accelerate growth and antiapoptosis of myeloma cells. DARS-AS1 interacted with and prevented the ubiquitin-mediated degradation of RBM39 (RNA-binding motif protein 39) whose expression is positively correlated with dismal prognosis [131].

LncRNAs can modulate the activity of HIF-1α to regulate EMT, invasion, and metastasis of cancer cells. Inhibition of EMT-related transcription factors (such as Snail, Twist, and Zeb) has been widely demonstrated as an ideal strategy to combat EMT and subsequent metastasis of tumor cells [132]. Upregulation of Zeb1 expression was reported in the clinical samples of patients with invasive ductal breast cancer [133]. Deng and colleagues have shown that lncRNA-BX111887 (also termed BX111) was induced by HIF-1α under hypoxia, and overexpression of BX111 substantially elevated the proliferation and invasion of pancreatic cancer cells. The mechanistic approach revealed that BX111 directs the Y-box protein (YB1, a protein involved in a broad range of DNA/RNA-dependent events), to the promoter of the Zeb1 gene to activate its transcription [134]. Similarly, lncRNA PCGEM1 was induced by hypoxia which resulted in the expression of Snail to stimulate the invasion and metastasis of gastric tumor cells [135]. LncRNA HIF-1A-AS2 was demonstrated to competitively interact with miR-153-3p to allow the translation of HIF-1α to promote angiogenesis in HUVECs in hypoxia [136]. Taken together, these reports suggest that there is a complicated relationship that exists between oncogenic lncRNAs and hypoxia to promote tumor progression [137].

4.2 Onco-suppressor lncRNAs

Some lncRNAs can act as onco-suppressors. Tumor cells generally adapt different mechanisms to reduce the expression of onco-suppressor lncRNAs. Several studies have shown that forced expression of onco-suppressor lncRNAs results in the suppression of tumor progression. Pancreatic cancer is a lethal malignancy with no druggable targets and accounts for a 5-year survival rate of about 9% [138]. Due to the unavailability of effective drugs, many efforts are being made to discover new therapeutic agents for the treatment of pancreatic cancer. Hypoxia can trigger the formation of a feedback loop between the expression of HIF-1α and lncRNAs in pancreatic cancer. For example, lncRNA-CF129 is markedly reduced in pancreatic cancer tissues compared to the normal counterpart, and reduced expression of CF129 contributed to the poor overall survival of pancreatic cancer patients [139]. In normoxia, CF129 interacts with p53 and MKRN1 (an E3 ubiquitin ligase) and promotes the degradation of p53. Under hypoxic conditions, HIF-1α in association with HDAC1 represses the expression

of CF129 which enables p53 to transcribe the FOXC2 gene. FOXC2 is a transcription factor that drives the expression of HIF-1α and further ensures the suppression of CF129 expression to promote tumor progression [139].

LncRNAs can serve as decoys to regulate the expression of mRNA at the translation level. For example, lncRNA HITT (HIF-1α inhibitor at translation level) is reduced in many types of cancer cells. It was found that increased expression of HITT led to the inhibition of angiogenesis and tumor growth. Mechanistically, HITT was found to act as a decoy for YB-1, preventing the interaction of YB-1 with 5′-UTR of HIF-1α mRNA, and subsequently, the translation of HIF-1α mRNA is hampered [140]. YB-1 protein is involved in the regulation of many cellular processes such as DNA repair, transcription, post-transcriptional processing of transcripts, and translation. During the unavailability of YB-1, HIF-1α mRNA is not translated leading to tumor suppression. Unfortunately, HIF-1α induces the expression of miR-205 in tumor cells, and subsequently miR-205 directly targets and promotes the degradation of HITT for an autoregulatory loop [140]. In a follow-up study by the same group, the role of HITT and epigenetic machinery in silencing HIF-1α was studied. HITT was found to form an RNA–DNA triplex with the promoter of HIF-1α and thereby guided EZH2 (enhancer of zeste homolog 2) to the promoter leading to the suppression of HIF-1α transcription. EZH2 is a functional subunit of Polycomb repressive complex 2 (PRC2), a complex that is involved in the methylation of lysine 27 of histone H3 to repress the transcription of target genes [141].

Reducing the expression of HIF-1α by lncRNAs can greatly suppress the disease progression. The lncRNA ENST00000480739 is lowly expressed in pancreatic cancer cells, and its ectopic expression resulted in overexpression of OS-9 (osteosarcoma amplified-9) to downregulate HIF-1α thereby preventing the metastasis of tumor cells [142]. Some lncRNAs can modulate EMT and autophagy in a HIF-1α-dependent manner. LncRNA CPS1-IT1 (CPS1 intronic transcript 1) was found to inhibit metastasis and EMT by suppressing hypoxia-induced autophagy through the inactivation of HIF-1α in colorectal cancer [143]. LncRNA MT1JP (metallothionein 1 J, pseudogene) was reported to be reduced in tumor tissues of TNBC patients, and its overexpression resulted in the elevation of miR-138 and reduction of HIF-1α in TNBC cells [144]. The crucial role of hypoxia on the expression of lncRNAs and tumor angiogenesis was demonstrated in the study by Li and colleagues. In normoxic conditions, the expression of lncRNA ZNFTR was high which sequestered the transcription factor ATF3 (activating transcription factor 3) and thereby blocked transcriptional activity of ATF3. Also, this enabled the expression of the ZNF24 protein which further served the role of transcription repressor of the VEGFA gene [145]. In hypoxic conditions, HIF-1α/HDAC1-driven deacetylation repressed the expression of ZNFTR which allowed ATF3 to repress the expression of ZNF24. The reduction in the expression of ZNF24 resulted in the elevated expression of VEGFA and subsequent tumor angiogenesis in pancreatic cancer [145]. These studies have demonstrated the different mechanisms by which lncRNAs behave as onco-suppressors in various cancers.

4.3 Association of lncRNAs with therapy response

Therapeutic resistance is a major concern in many disease conditions including cancer. In this section, we have discussed how the relationship between HIF-1α and lncRNAs impacts the therapeutic response of cancer cells. LncRNA PVT1 (plasmacytoma variant translocation 1) is overexpressed in tumor tissues of pancreatic cancer patients, and it was found to be associated with poor clinical outcomes. HIF-1α was reported to interact with the promoter of the PVT1 gene to express it as well as to stabilize PVT1 transcripts. Interestingly, PVT1 was also found to transcriptionally regulate the expression of the HIF-1α gene as well as stabilize the HIF-1α protein forming a feedback regulatory loop in pancreatic cancer cells [146]. In another report, PVT1 was found to sponge miR-143 to modulate the expression of HIF-1α. Depletion of PVT1 and overexpression of miR-143 potentiated the sensitivity of pancreatic cancer cells to gemcitabine indicating that HIF-1α modulating lncRNAs can regulate therapeutic response [147]. LncRNA NORAD (non-coding RNA activated by DNA damage) was demonstrated to be elevated in colorectal cancer tissues, and it promoted the expression of HIF-1α by sponging miR-495-3p [148]. Under hypoxia, colorectal cancer cells presented resistance to 5-fluorouracil and a stronger ability to form vasculogenic mimicry, whereas depletion of NORAD resulted in the sensitization of colorectal cancer cells to 5-fluorouracil [148].

Cisplatin is the first-line anticancer drug administered to treat advanced gastric cancer patients, and unfortunately, cisplatin resistance is not uncommon in gastric cancer patients [149]. LncRNA HMGA1P4 promoted cisplatin-resistance in gastric cancer cells by modulating the expression of genes that are associated with multidrug-resistance such as MDR1, MRP1, mTOR, and HIF-1α [150]. Another lncRNA that participates in cisplatin resistance in gastric cancer is DANCR. Overexpression of DANCR prevented apoptosis and promoted the proliferation of tumor cells. DANCR increased the expression of MDR1 and MRP1 in gastric cancer cells while having no effect on the levels of HIF-1α and mTOR [151]. Similarly, the expression of PVT1 was elevated in tumor tissues derived from cisplatin-resistant gastric cancer patients. Increased expression of PVT1 elevated the expression of MDR1, MRP, mTOR, and HIF-1α [152]. These reports suggest that targeting lncRNAs could be a good strategy for

counteracting therapeutic resistance in cancers. Figure 4 and Table 2 provide a summary of lncRNAs modulating HIF-1α signaling during cancer progression.

5 CircRNAs and HIF-1α

The majority of the circRNAs studied in connection with HIF-1α so far were found to impart their activity through the sponging of miRNAs. For instance, the levels of circ-MAT2B were reported to be significantly high in tumor tissues of gastric cancer patients in comparison with adjacent normal counterparts [186]. Circ-MAT2B served as a competitive endogenous RNA to sponge miR-515-5p whereas the direct molecular target of miR-515-5p was found to be HIF-1α [186]. Interestingly, the promoter of circ-MAT2B was found to have two HIF-1α binding sites, and results of the ChIP-PCR assay demonstrated that HIF-1α transcriptionally regulates the expression of circ-MAT2B forming a regulatory loop. The knockdown of circ-MAT2B abrogated tumor growth in xenograft model and suppressed glucose uptake and lactate production in cell-based studies [186]. Similarly, circ-MAT2B was demonstrated to sponge tumor suppressor miRNAs such as miR-610 and miR-431 in colorectal cancer and NSCLC, respectively, to promote tumor progression (Fig. 5) [187, 188].

Liu and colleagues reported the elevation of circ-03955 in pancreatic cancer tissues as well as in cells, and it was found to sponge miR-3662 to allow the stabilization and translation of HIF-1α transcripts [189]. miR-200c-3p was sponged by circ-001783 to increase breast tumor proliferation and invasion [190]. Circ-0007331 was predicted to act as a molecular sponge to sequester miR-200c-3p whose downstream target is HIF-1α in endometriosis [191]. Exosomal miR-200c-3p suppressed the migration and invasion of lipopolysaccharide-treated colorectal cancer cells by targeting Zeb1 mRNA [192]. High expression of miR-200c-3p decreased the levels of PD-L1, c-Myc, and β-catenin and sensitized ovarian cancer cells to olaparib and irradiation [193]. As discussed earlier, HIF-1α plays a crucial role in aerobic glycolysis and the regulation of glycolytic pathways. A recent study demonstrated that HIF-1α transcriptionally upregulates the

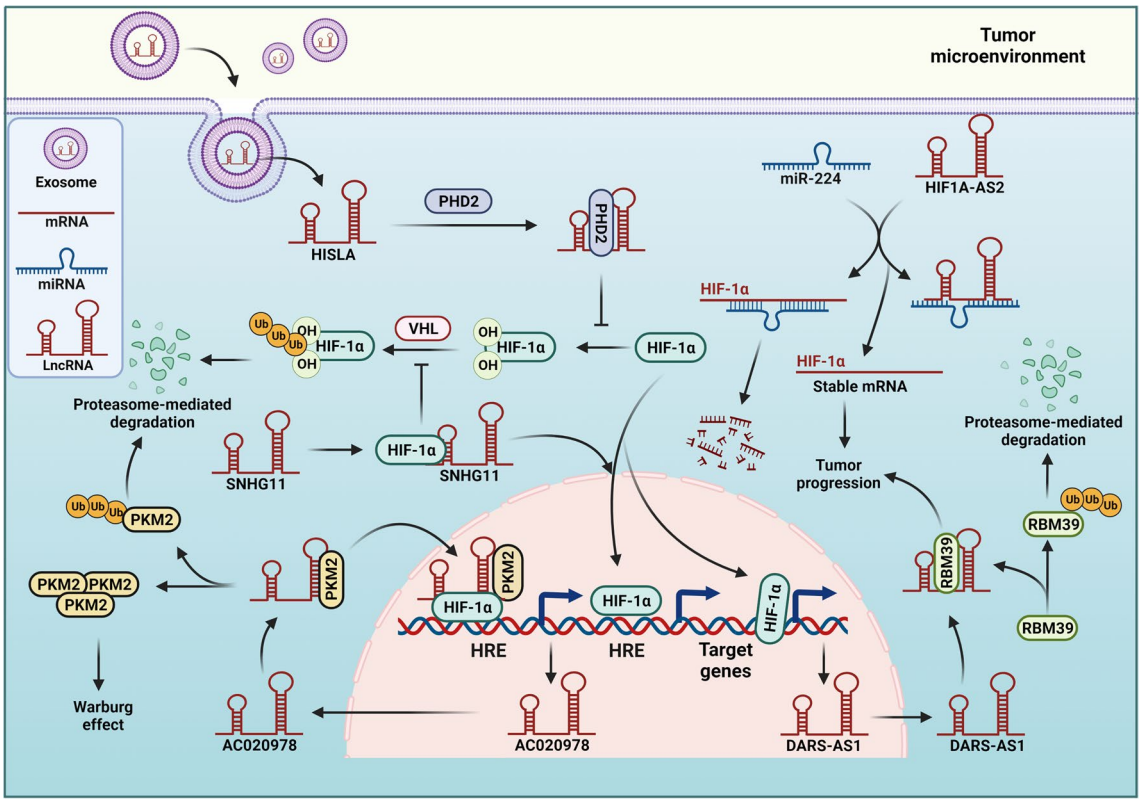

Fig. 4 The activity and expression of HIF-1α is regulated by lncRNAs. LncRNAs (HISLA) can be transmitted between different cells in the tumor microenvironment through exosomes. HISLA can interact with PHDs to prevent the prolyl hydroxylation of HIF-1α. LncRNA SNHG11 can interact with HIF-1α and prevent the recognition of HIF-1α by VHL. LncRNA AC020978 can interact with and stabilize PKM2 to increase HIF-1α-mediated transcription of AC020978 and also other target genes. The stabilized PKM2 can also promote the Warburg effect. HIF-1α transcriptionally activates the expression of DARS-AS1 which eventually interacts with and prevents RBM39 from degradation. LncRNA HIF1A-AS2 sponges miR-224 and prevents the degradation of HIF-1α transcripts

Table 2 Role of lncRNAs regulating HIF-1α signaling in tumorigenesis

LncRNA	Molecular axis	Cancer type	Mechanism and observed effects	Ref
COL4A2-AS1	miR-20b-5p/HIF-1α	Colorectal cancer	Induction of glycolysis, antiapoptosis, and acceleration of proliferation. COL4A2-AS1 increases HIF-1α expression via sponging miR-20b-5p	[153]
LINK-A	HIF-1α	Ovarian cancer	Enhanced metastasis of tumor cells via HIF-1α overexpression	[154]
GHET1	HIF-1α	Ovarian cancer	GEHT1 interacts with the VHL and blocks the degradation of HIF1α	[155]
AWPPH	HIF-1α	Glioma	Promoted cell motility by upregulating HIF-1α	[156]
PMAN	HIF-1α/PMAN	Gastric cancer	HIF-1α increases PMAN expression to promote peritoneal metastasis of gastric cancer	[157]
PVT1	KAT2A/HIF-1α	Nasopharyngeal cancer	PVT1 functions as a scaffold for KAT2A to recruit TIF1β for increasing HIF-1α stability and promoting tumor progression	[158]
ZEB1-AS1	HIF-1α	Pancreatic cancer	A positive feedback loop between ZEB1-AS1 and HIF-1α increases carcinogenesis and invasion	[159]
ZEB2-AS1	miR-143-5p/HIF-1α	Gastric cancer	ZEB2-AS1 promotes HIF-1α expression via sponging miR-143-5p thereby enhancing growth and invasion	[160]
OIP5-AS1	miR-124-5p/IDH2/HIF-1α	Cervical cancer	OIP5-AS1 suppresses miR-124-5p expression to increase IDH2 expression thereby triggering HIF-1α signaling	[161]
LINC00649	NF90/NF45/HIF-1α	Breast cancer	LINC00649 enhances stability and expression of HIF-1α via interacting with NF90/NF45	[162]
DLX6-AS1	miR-199a-5p/HIF-1α	Nasopharyngeal cancer	DLX6-AS1 sponges miR-199a-5p to increase HIF-1α expression thereby enhancing the malignant phenotype of tumor cells	[163]
TMPO-AS1	miR-199a-5p/HIF-1α	Retinoblastoma	TMP-AS1 sponges miR-199a-5p to increase HIF-1α expression thereby promoting cancer malignancy	[164]
MTA2TR	MTA2TR/ATF3/MTA2/HIF-1α	Pancreatic cancer	MTA2TR increases HIF-1α expression in a deacetylation manner	[165]
LINC00511	HIF-1α/LINC00511/miR-153-5p	Colorectal cancer	HIF-1α promotes LINC00511 expression which sponges miR-153-5p. HIF-1α is a direct target of miR-153-5p	[166]
DSCR8	miR-98-5p/STAT3/HIF-1α	Ovarian cancer	DSCR8 sponges miR-98-5p and promotes STAT3 expression to induce HIF-1α signaling for cancer progression	[167]
GHET1	HIF-1α/Notch	Prostate cancer	Silencing GHET1 impairs HIF-1α/Notch axis thereby suppressing cancer growth	[168]
NUTF2P3-001	miR-3923/KRAS	Pancreatic cancer	Hypoxia increases KRAS expression via sponging miR-3923	[169]
FAM83A-AS1	HIF-1α/glycolysis	Lung cancer	FAM83A-AS1 prevents the degradation of HIF-1α by interacting with the VHL recognition site on HIF-1α.	[170]
MEG3	DNMT3b/MEG3/HIF-1α	-	MEG3 inhibition by DNMT3B leads to HIF-1α overexpression to mediate the malignant transformation of epithelial cells	[171]
NEAT1	HIF-1α	-	NEAT1 sponges 582-5p. HIF-1α is the speculated target of miR-582-5p	[172]
PVT1	miR-199a-5p/HIF-1α	Lung cancer	PVT1 sponges miR-199a-5p to increase HIF-1α expression	[173]
LINC00525	miR-338-3p/UBE2Q1/β-catenin/HIF-1α	Colorectal cancer	LINC00525 increases UBE2Q1 expression by interacting with miR-338-3p to induce the activation of HIF-1α	[174]
CRPAT4	AVL9	Renal cancer	Hypoxia increases CRPAT4 expression to regulate AVL9 thereby increasing cancer progression	[175]

Table 2 (continued)

LncRNA	Molecular axis	Cancer type	Mechanism and observed effects	Ref
HYPAL	HIF-1α/HYPAL/miR-431-5p/CDK14	Gastric cancer	Hypoxia can increase HYPAL expression and HYPAL promotes CDK14 expression via miR-431-5p sponging	[176]
STEAP3-AS1	Wnt/β-catenin	Colorectal cancer	HIF-1α promotes STEAP3-AS1 expression to induce Wnt signaling for cancer progression	[177]
DAC3-AS1	HDAC2/FOXA3	Hepatocellular carcinoma	HIF-1α promotes DAC3-AS1 expression to increase the interaction of HDAC2 and FOXA3 thereby increasing PKM2 expression and promoting cancer metastasis	[178]
CASC9	HIF-1α/CASC9	Lung cancer	CASC9 and HIF-1α form a positive feedback loop thereby increasing cancer progression	[179]
DLEU1	HIF-1α/CKAP2	Breast cancer	DLEU1 acts as a coactivator for HIF-1α and activated the transcription of CKAP2 to facilitate malignancy.	[180]
SOS1-IT1	HIF-1α/SOS1-IT1	Endometrial cancer	HIF-1α promotes SOS1-IT1 expression thereby accelerating tumor progression	[181]
PCED1B-AS1	PCED1B-AS1/miR-411-3p/HIF-1α	Pancreatic cancer	PCED1B-AS1 promotes HIF-1α expression via targeting miR-411-3p thereby facilitating tumor progression	[182]
HOXA-AS2	HOXA-AS2/miR-519/HIF-1α	Nasopharyngeal cancer	HOXA-AS2 sponges miR-519 to increase HIF-1α expression for cancer progression acceleration	[183]
FALEC	HIF-1α/FALEC	Prostate cancer	HIF-1α-mediated FALEC expression accelerates the malignant progression	[184]
GAPLINC	HIF-1α/GAPLINC	Gastric cancer	Hypoxia increases HIF-1α expression to mediate GAPLINC expression thereby increasing cancer progression	[185]

expression of hexokinase-2 (HK2) to stimulate aerobic glycolysis and enhance breast cancer progression. However, miR-487a was found to target HIF-1α and thereby suppress HIF-1α/HK2 axis. CircRNF20 (circ_0087784) was found to sponge miR-487a to enable the stabilization and translation of HIF-1α and its downstream target HK2 to boost the progression of breast tumors [194]. Similarly, circ-0046600, circ-0004543, circPIP5K1A, and circ-HIPK3 allowed the expression of HIF-1α by sequestering miR-640, miR-217, miR-600, and miR-338-3p in the liver, cervical, lung, and cervical cancer cells, respectively, to promote the advancement of disease [195–198]. CircRNAs can also promote the growth of cancer cells by modulating the cap-independent translation of HIF-1α translation. Circ-ERBIN was shown to be overexpressed in colorectal cancer cells which encouraged the growth of colorectal cancer. The interactome analysis revealed miR-125a-5p and miR-138-5p as binding partners of circ-ERBIN [199]. Further mechanistic analysis demonstrated that both miR-125a-5p and miR-138-5p target 4EBP-1 [199]. 4EBP-1 is involved in the cap-independent translation of HIF-1α under hypoxia. Therefore, sequestration of miR-125a-5p and miR-138-5p by circ-ERBIN resulted in efficient cap-independent translation of HIF-1α and subsequent acceleration of tumor angiogenesis [199].

5.1 Association of circRNAs with therapy response

A very limited number of studies have demonstrated the role of the circRNA/HIF-1α axis in offering chemoresistance in cancer cells. Elevated expression of circNRIP1, MDR-1, P-glycoprotein, and HIF-1α and low responsiveness to 5-fluorouracil were noted in gastric cancer cells under hypoxic conditions whereas the depletion of circNRIP1 sensitized gastric cancer cells to 5-fluorouracil. Mechanistically, circNRIP1 was reported to target miR-138-5p, which is an upstream modulator of HIF-1α [200]. High expression of circZNF91 was noted in tumor specimens derived from pancreatic cancer patients, and its expression was positively correlated with elevated expression of glucose-metabolizing enzymes and reduced overall survival time [201]. It was also noted that the exosomes released from pancreatic cancer cells acted as carriers of circZNF91 which were transferred into normoxic pancreatic cancer cells to transmit gemcitabine resistance [201]. In normoxic pancreatic cancer cells, hypoxia-induced exosomal circZNF91 was found to competitively interact with miR-23b-3p and thereby enable the expression of Sirtuin1 (a protein deacetylase). Elevated Sirtuin1 subsequently deacetylated and stabilized HIF-1α to promote gemcitabine resistance in normoxic pancreatic

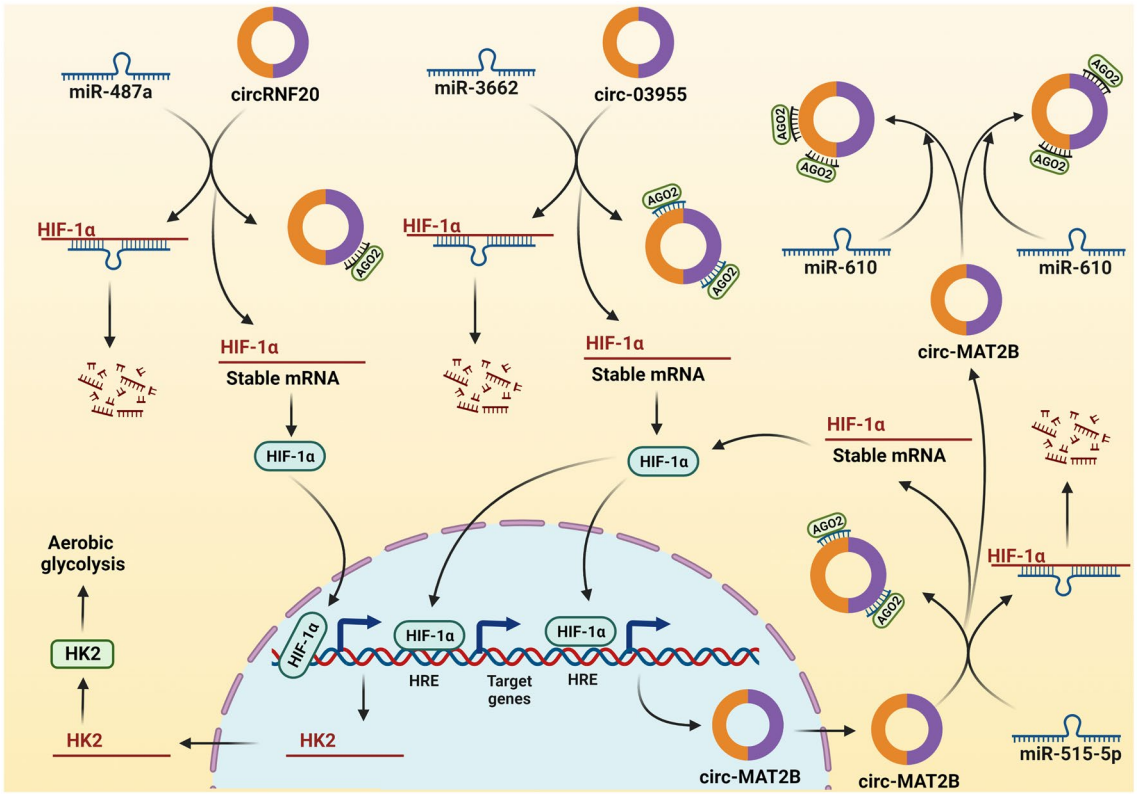

Fig. 5 The activity and expression of HIF-1α is regulated by lncRNAs. The majority of known circRNAs promote HIF-1α signaling by sponging the onco-suppressor miRNAs. CirRNAs (circRNF20, circ-03955, circ-MAT2B) sponge miRNAs (miR-487a, miR-3662, miR-515-5p, respectively) to stabilize and prevent the degradation of HIF-1α transcripts

cancer cells indicating that circZNF91 plays a key role in imparting therapeutic resistance in the tumor microenvironment. Joo and coworkers have previously demonstrated that Sirtuin1 is involved in the stabilization of HIF-1α through its deacetylation [202]. Additionally, the transcription of circZNF91 was found to be controlled by HIF-1α under hypoxic conditions [201]. In sum, it can be concluded that the interaction between miRNAs and HIF-1α is generally disrupted by circRNAs to promote tumorigenesis and drug resistance. Therefore, targeting the circRNA/HIF-1α axis can help to regulate glycolysis, proliferation, and metastasis of cancer cells. Figure 5 and Table 3 depict the relationship between circRNAs and HIF-1α in human cancers [200].

6 Other types of ncRNAs and HIF-1α

We used the keywords "piRNA and HIF-1α" and "tsRNA and HIF-1α" to search publications related to the "HIF-1α-regulating piRNAs" and "HIF-1α-regulating tsRNAs," respectively, in PubMed. In both cases, only one study was listed in the search (accessed on 19 June 2023). piRNA-823 was reported to be upregulated in colorectal cancer tumor samples [205]. Mechanistic dissection revealed that piRNA-823 mitigates the ubiquitination and subsequent degradation of HIF-1α by elevating the levels of expression of glucose-6-phosphate dehydrogenase, increasing glucose utilization, and reducing intracellular reactive oxygen species [205]. This study also proposed the use of piRNA-823 as a prognostic biomarker in CRC patients.

Tao and colleagues demonstrated that 5′tiRNA-His-GTG is overexpressed in colorectal cancer tissues compared to the normal counterpart. The mechanistic approach revealed that angiogenin is transcribed by the HIF-1α under hypoxic conditions in colorectal tumor cells. Angiogenin cleaved the tRNA into 5′tiRNA-His-GTG [206]. Subsequently, 5′tiRNA-His-GTG was loaded onto AGO1/3 proteins and targeted 3′-UTR of LATS2 (Large tumor suppressor 2) to promote the degradation of LATS2 transcript [206]. If LATS2 is not targeted, LATS phosphorylates YAP and TAZ which leads to either sequestration of these proteins or ubiquitin-facilitated protein degradation resulting in turning off of the Hippo pathway. Therefore, it was concluded that 5′tiRNA-His-GTG responded to hypoxic stress by activating HIF1α/angiogenin axis and promoting the Hippo pathway.

Table 3 The regulation of HIF-1α signaling by circRNAs for cancer therapy

CircRNA	Molecular axis	Cancer type	Mechanism and observed effects	Ref.
Circ-0004543	Circ-0004543/miR-217/HIF-1α	Cervical cancer	Circ-0004543 increases HIF-1α expression via miR-217 sponging to promote tumorigenesis	[196]
Circ-MAT2B	miR-515-5p/HIF-1α	Gastric cancer	Circ-MAT2B promotes proliferation, glucose uptake, and lactate production via miR-515-5p sponging and subsequent overexpression of HIF-1α	[186]
Circ-03955	Circ-03955/miR-3662/HIF-1α	Pancreatic cancer	Circ-03955 increases HIF-1α expression via miR-3662 inhibition for glycolysis induction	[189]
Circ-RNF20	Circ-RNF20/miR-487a/HIF-1α/HK2	Breast cancer	Circ-RNF20 promotes HIF-1α expression via miR-487a inhibition to upregulate HK2	[194]
Circ-0046600	Circ-0046600/miR-640/HIF-1α	Liver cancer	Circ-0046600 promotes HIF-1α expression via miR-640 inhibition thereby contributing to increased cell proliferation and EMT induction	[195]
CircPIP5K1A	CircPIP5K1A/miR-600/HIF-1α	Lung cancer	CircpIP5K1A sponges miR-600 which enabled the upregulation of HIF-1α	[197]
Circ-HIPK3	Circ-HIPK3/miR-338-3p/HIF-1α	Cervical cancer	HIPK3 sponges miR-338-3p to increase HIF-1α and to mediate the EMT mechanism	[198]
Circ-NRIP1	Circ-NRIP1/miR-138-5p/HIF-1α	Gastric cancer	Circ-NRIP1 sponges miR-138-5p to overexpress HIF-1α to mediate drug resistance	[200]
Circ-SLC25A16	Circ-SLC25A16 /miR-488-3p/HIF-1α/LDHA	Lung cancer	Circ-SLC25A16 promotes HIF-1α expression via miR-488-3p sponging and subsequent upregulation of LDHA	[203]
Circ-100859	Circ-100859/miR-217/HIF-1α	Colon cancer	Circ-100859 elevates HIF-1α expression via miR-217 sponging thereby accelerating colon cancer progression	[204]

7 Clinical examination of ncRNAs as therapeutic agents

Since the discovery of ncRNAs, a significant number of efforts have been made to use them as therapeutic agents against human cancers. The major hurdles in the development of ncRNA-based therapeutics are the route of administration, dosage optimization, off-target effects, and drug delivery system. Despite successful implementation in the preclinical studies, ncRNA-based therapeutics have failed to enter clinics to date. Among ncRNAs, miRNA-targeting approaches have reached clinical trials for the treatment of cancers. Upregulation of the expression of oncogenic miRNAs and downregulation of the expression of onco-suppressor miRNAs are the common trends observed in the majority of the studies performed using patient-derived tumor tissues. As learnt earlier, miRNAs interact with their target mRNA to promote mRNA degradation or suppress their translation. Considering these facts, efforts have been made to administer synthetic miRNAs (anti-miRNAs) that can make complementation with oncogenic miRNAs to allow the expression of target mRNAs. Another approach is the administration of synthetic miRNAs (miRNA mimics) that mimics the role of onco-suppressor miRNAs. miR-34 is one of the potent onco-suppressor miRNAs with inhibitory activity against tumorigenic functions facilitated by CDK4/6, SIRT1, and SOX2. Delivery of either anti-miRNAs or miRNA-mimics to target sites is a daunting task. A liposomal nanoparticle loaded with a synthetic mimic of the miR-34a (named MRX34) was examined in patients with advanced solid tumors [207]. Administration of MRX34 with dexamethasone premedication displayed a manageable toxicity profile in most patients and some clinical activity [207]. Although the study was terminated early due to serious immune-mediated adverse effects that led to the death of four patients, dose-dependent modulation of relevant target genes provided proof of concept for miRNA-based cancer therapy (NCT01829971). In another study, cobomarsen (an oligonucleotide inhibitor of miR-155) displayed a reduction in the growth of diffuse large B-cell lymphoma without any toxicity concerns in the patient (NCT02580552) [208]. A clinical investigation is being carried out to determine the effect of TargomiRs (miR-16-mimics loaded into engeneic delivery vehicles) as a second-/third-line treatment for patients with malignant pleural mesothelioma and NSCLC (NCT02369198). miR-16 is a potent onco-suppressor that was demonstrated to be downregulated in malignant pleural mesothelioma tumors/cells, and its administration provided promising anticancer effects [209].

8 Conclusion and remarks

Hypoxia is one of the hallmark features observed in the microenvironment of most solid malignancies which contributes to the oncogenic features such as metabolic reprogramming, metastasis, and drug resistance. HIF-1α regulates the expression of genes responsible for the oncogenic behavior of the cell. HIF-1α is one of the most widely studied transcription factors in relevance to cancer progression, and numerous preclinical studies have proposed that inhibition of HIF-1α could be a good therapeutic approach to counteract the proliferation of cancer cells. On the other hand, there are a few limitations associated with targeting HIF-1α in human cancers. In a phase II clinical trial, 17-(allylamino)-17-demethoxygeldanamycin failed to achieve an objective response in the treatment of renal cell carcinoma patients. 17-(Allylamino)-17-demethoxygeldanamycin is a potent inhibitor of HSP90 that elevated the degradation of HIF-1α [210]. Also, differential expression of HIF-1α may contribute to the limited efficacy of therapeutic agent that targets HIF-1α [211]. The expression, activity, and stability of HIF-1α are modulated by oxygen-sensitive enzymes which make oxygen a key player in determining the aggressiveness of the tumor cells. In addition, various ncRNAs including miRNA, lncRNA, circRNA, piRNA, and tsRNA were also reported to either promote or impede the HIF-1α pathway in cancers. Although most of the discoveries related to these ncRNAs in relevance to oncogenesis have been deciphered in the last two decades, it is important to note that these ncRNAs have a wide and critical role in the progression of cancer, and it is much more complicated than the present-day understanding. Considering the importance of ncRNAs, miRNAs are being examined as therapeutic agents in different phases of clinical trials. Some of the clinical trials were discontinued halfway through due to various problems suggesting that there are multiple challenges to be crossed before the successful clinical application of ncRNA-based drugs. For instance, although MRX34 showed some clinical activity, the study was halted due to immune-related adverse effects which resulted in the death of a few patients. Determining the route of administration, use of carriers, dosage optimization, and off-target effects are still considered a matter of concern in RNAi-based therapies. Overall, an enormous amount of research is essential to uncover and understand the role of ncRNAs in disease progression and their relationship with oncogenic/tumor suppressor proteins.

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Declarations

Conflict of interest The authors declare no competing interests.

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