Interactional role of microRNAs and bHLH-PAS proteins in cancer (Review)

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Abstract. MicroRNAs (miRNAs) are recognized as an emerging class of master regulators that regulate human gene expression at the post-transcriptional level and are involved in many normal and pathological cellular processes. Mammalian basic HLH (helix-loop-helix)-PER-ARNT-SIM (bHLH-PAS) proteins are heterodimeric transcriptional regulators that sense and respond to environmental signals (such as chemical pollutants) or to physiological signals (for instance hypoxia). In the normal state, bHLH-PAS proteins are responsible for multiple critical aspects of physiology to ensure the cell accurate homeostasis, but dysregulation of these proteins has been shown to contribute to carcinogenic events such as tumor initiation, promotion, and progression. Increasing epidemiological and experimental studies have shown that bHLH-PAS proteins regulate a panel of miRNAs, whereas some miRNAs also target bHLH-PAS proteins. The interaction between miRNAs and certain bHLH-PAS proteins [hypoxia-inducible factor (HIF) and aryl hydrocarbon receptor (AHR)] is relevant to many vital events associated with tumorigenesis. This review will summarize recent findings on the interesting and complicated underlying mechanisms that miRNAs interact with HIFs or AHR in tumors, hopefully to benefit the discovery of novel drug-interfering targets for cancer therapy.

Contents

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1. Introduction

miRNAs are small (18-25 nucleotides) non-coding RNAs that degrade target mRNA or suppress its translation by specifically binding to the 3' untranslated region (3'UTR), thus playing a role of gene silencing (1,2). To date, >1,400 different miRNAs have been found in humans and regulate >30% of mammalian gene expression (3,4). At baseline, miRNAs ensure accurate physiological functions, such as growth, development, differentiation and stress. While, abnormal expression induced by a variety of internal and external factors also plays a pivotal role in tumor origin, proliferation, migration and other pathological processes (5,6).

The bHLH-PAS proteins are heterodimeric transcription factors that form a subgroup of the bHLH superfamily. The bHLH-PAS proteins generally consist of two PAS domains that can sense and respond to environmental signals; for example benzo[*a*]pyrene (B[a]P), 2,3,7,8-tetrachlorodibenzo-r-dioxin (TCDD) or to physiological signals (such as hypoxia) (7). The bHLH-PAS superfamily includes some very important transcription factors such as AHR, the AHR nuclear translocator (ARNT; also known as HIF1β), the AHR repressor (AHRR) and different HIFs. Members of the bHLH-PAS family play a broad range role in physiological and pathological processes and take part in multiple cellular signal pathways (8-10). Recent studies have discovered several selective agonists and antagonists that directly target this multifunctional family, presenting a huge potential as an antitumor drug target (11,12).

In recent years, many studies have shown that AHR and HIF can play pro-tumor or antitumor roles. Moreover, the role of miRNAs in tumor origin and development are also focus of attention. Thus, this review focuses on the complicated interactional mechanisms between miRNAs and certain bHLH-PAS proteins (the HIF and AHR) in many vital events relevant to multiple forms of tumors.

2. miRNAs and bHLH-PAS proteins

Epidemiological and experimental research provides substantial support for the association between bHLH-PAS proteins and miRNAs in cancer (13) (Fig. 1, Tables I and II). miR-210

is a very important HIF associated miRNA that can be found consistently dysregulated in multiple forms of tumors and is involved in many HIFs associated cellular signal pathways (14-16). Similarly to the transcriptional mechanism of protein encoding genes, the transcription of miRNAs from miRNA genes is regulated by transcription factors, including HIFs and AHR. In breast cancer cells, miRNA sequencing data analysis identified 41 miRNAs significantly upregulated and 28 downregulated under hypoxia. Moreover, study on the transcriptional regulation of miRNA expression by HIFs further illustrated that significantly upregulated miR-210-3p contained a HIF-binding site at its promoter region (17). The promoter regions of miR-155 and miR-373 genes were also found containing HIF-binding site by which hypoxia could promote the transcription of related miRNAs (18). In addition, several transcripts involved in miRNA expressional processes were found to be regulated by hypoxia. For instance, HIF1 regulated the expression of two miRNA transcripts: DICER and AGO4 (17). On the other hand, some miRNAs target HIFs and AHR are involved in the regulation of members in HIFs and AHR signal pathways. Hypoxia regulates the expression of miR-20b, miR-199, miR-210 and miR-424 which can directly target HIFs or control its expression (19-23).

In regards to AHR, Gordon *et al* reported that the environmental carcinogen B[a]P and TCDD, the xenobiotic AHR ligands, upregulated the expression of a variety of miRNAs in multiple myeloma cells. Importantly, the miR-25 promoter was activated by both B[a]P and TCDD, and this response was mediated by AhR (24).

3. The potential mechanisms

Proliferation and cell cycle. miR-210 and miR-21 are upregulated by HIF1α in a variety of tumors and take part in regulating tumor growth, proliferation and the cell cycle (25). For example, the overexpression of miR-210 induced by HIF1α could be found in melanoma and lung cancer cells, upregulated miR-210 inhibited proliferation of lung cancer (26). While Li *et al* reported that upregulated miR-210 facilitated tumor proliferation in epithelial ovarian cancer via targeting protein tyrosine phosphatase, non-receptor type 1 (PTPN1) (27). In addition, inhibition of miR-210 caused cell cycle arrest prior to G2/M in melanoma (28). miR-21 promoted proliferation and overrode hypoxia-induced cell cycle arrest at the G1/S transition (29). *In vitro*, *in vivo* and pathological study showed that HIF1α was a direct target of miR-199 family, downregulated miR-199a was essential for hypoxia induced proliferation by derepressing the expression of HIF1α and influencing HIF1α mediated the glycolytic pathway in non-small cell lung cancer (NSCLC) (30). While the overexpression of miR-199a and miR-199b, by using virus vectors, significantly downregulated HIF1α and suppressed cell proliferation in hepatocellular carcinoma (HCC) (31) and prostate cancer (32), respectively. Zhang *et al* demonstrated that miR-135b promoted tumor proliferation and colony formation through targeting factor inhibiting HIF (FIH) and activating HIF1α in head and neck squamous cell carcinoma (HNSCC) (33). In addition, Taguchi *et al* showed that overexpression of miR-17-92 induced by c-myc directly targeted HIF1α and played a role in cancer cell proliferation (34).

Regarding AHR, Trivellin *et al* reported that miR-107 was overexpressed in pituitary adenoma samples, and the overexpression of miR-107 inhibited cell proliferation through directly targeting the AHR-interacting protein (AIP) (35). When exposed to B[a]P, the expression levels of miR-320 and miR-494 were upregulated and repressed the expression of cyclin-dependent kinase 6 (CDK6), which regulates cell cycle progression by impacting G1/S transition (36). Yuan *et al* identified ARNT as a novel target of miR-221, and found that delivery of the miR-221 mimics into primary hepatocytes and overexpression of miR-221 mediated by adeno-associated virus in the mouse liver could significantly promote proliferation by targeting ARNT, and suppressed the cell cycle regulator p27 (37).

Angiogenesis. Angiogenesis plays a key role in tumor growth and metastasis (38). bHLH-PAS proteins regulate several angiogenic growth factors through transcriptional modulation, such as the well-known angiogenesis inducer, the vascular endothelial growth factor (VEGF) (39-41). On one hand, bHLH-PAS proteins contribute to vascular homeostasis under adverse environment including toxins and hypoxia, on the other, bHLH-PAS proteins promote angiogenesis in various types of tumors.

He *et al* found that miR-199a-5p expression levels were significantly downregulated in arsenic transformed cells, and demonstrated that arsenic promoted tumor growth and angiogenesis due to low expression of miR-199a-5p caused loss of control on its direct targets HIF1α and its downstream target COX-2 *in vitro* and *in vivo* (19). In low-oxygen conditions, miR-320 was downregulated by HIF1α in human umbilical vein endothelial cells (HUVECs) and attenuated the inhibitory effect on its target Neuropilin 1, an important regulator of angiogenesis, thus promoting angiogenesis (42). The interaction between HIF and VEGF regulates tumor angiogenesis and enables tumor cells to adapt to different oxygen concentrations (43). Recent studies illustrate miRNAs are also involved in the HIF/VEGF network (20,44,45). For instance, miR-199a and miR-125b were downregulated in ovarian cancer tissues and cell lines and negatively correlated with tumor angiogenesis via HIF1α/VEGF pathway (46). Overexpression of miR-22 inhibited HIF1α expression, repressing VEGF production during hypoxia. Conversely, knockdown of endogenous miR-22 enhanced hypoxia-induced expression of HIF1α and VEGF (47). In addition to the inhibitory effects of miR-503 on angiogenesis through directly targeting two most potent angiogenic factors: fibroblast growth factor-2 (FGF2) and VEGFA (48), miR-128 and miR-145 were demonstrated to attenuate tumor angiogenesis by targeting p70S6K1 and suppressing the downstream signaling molecules HIF1 and VEGF (49,50). When induced by hypoxia, miR-519c resulted in a significant decrease of HIF1α protein levels and reduced the tube formation of HUVECs. Similarly, inhibition of miR-519c by antagonist increased the level of HIF1α protein and enhanced angiogenic activity (51). Moreover, increased HIF2α in hypoxia induced the repression of miR-15-16 and promoted angiogenesis in colorectal carcinoma cell lines (52).

Invasion and metastasis. Zhang *et al* found that AHR modulator TCDD and the 6-methyl-1,3,-trichlorodibenzofuran

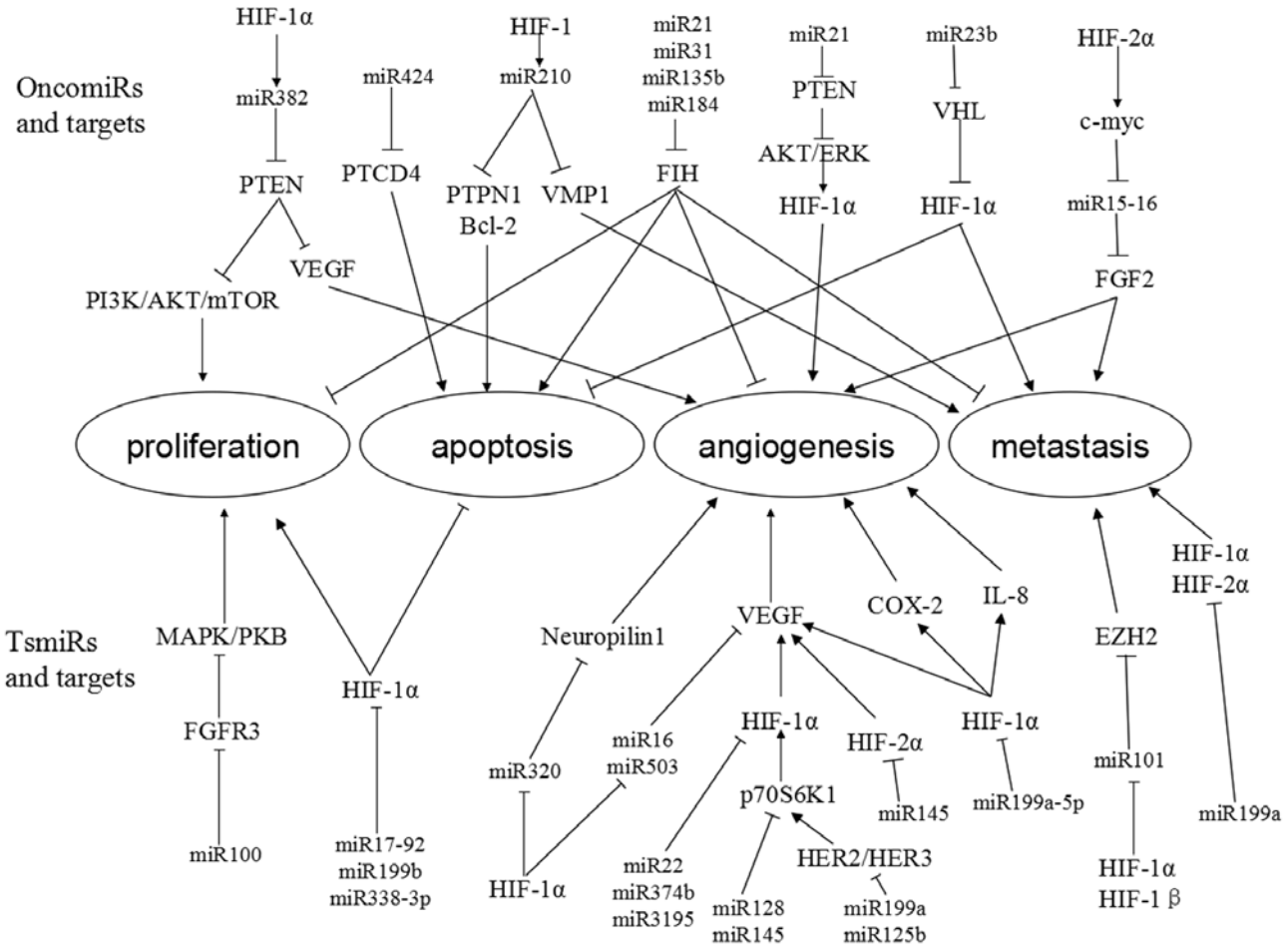

Figure 1. miRNAs involved in HIF-associated carcinogenic processes. Oncogenic miRNAs (oncomiRs) are normally upregulated and directly target or inhibit tumor suppressors, promoting proliferation, angiogenesis, migration and suppressing apoposis. By contrast, tumor suppressor miRNAs (tsmiRs) are often expressed at low level and attenuate the inhibitory effect on oncogenes.

(MCDF) inhibited breast cancer cell invasion by inducing the high expression of miR-335 and repressing a target gene of miR-335: SRY-related high mobility group box 4 (SOX4). Knocking down the AHR inhibited the effects of TCDD and MCDF on miR-335 and SOX4 expression, thus confirming AHR-miR-335 interact to inhibit breast cancer cell metastasis (53). Interestingly, SOX4 was also a target gene of miR-138, the expression of miR-138 inhibited ovarian cancer metastasis via suppressing SOX4 and HIF1α, and overexpression of SOX4 and HIF1α effectively reversed the miR-138 mediated suppression of cell metastasis (54). In low-oxygen conditions, decreased miR-199a facilitated the metastasis of ovarian cancer cells due to attenuating the inhibitory effect on HIF1α and HIF2α (55). Zhang *et al* reported that downregulated miR-145 inversely correlated with HIF2α expression in all 20 neuroblastoma samples. While overexpression of miR-145 suppressed tumor invasion and metastasis *in vitro* and *in vivo* by directly targeting HIF2α and promoting the expression of cyclin D1, VEGF and matrix metalloproteinase-14 (MMP-14) (56). miR-23b was demonstrated to induce tumor metastasis by targeting von Hippel-Lindau (VHL) and activating the HIF1α/VEGF and β-catenin/Tcf-4 signaling pathways (57). In addition, downregulation of miR-101 by HIF1α/HIF1β enhanced invasion and migration of prostate cancer cells, which may be attributed to the reduced inhibition of enhancer of zeste homolog 2 (Ezh2) by miR-101 (58).

Apoptosis. As a signature miRNA of hypoxia, miR-210 promoted neuroblastoma cell apoptosis via specifically decreasing anti-apoptotic Bcl-2 (59). The upregulation of miR-21 avoided cell apoptosis in pancreatic cancer cells and ovarian cancer cells (27,29). While lentiviral-mediated downregulation of miR-210 expression in hypoxic HCC cells significantly induced apoptosis through directly targeting apoptosis-inducing factor, mitochondrion-associated 3 (AIFM3) (60). In addition, Shang *et al* showed that miR-199b negatively regulated HIF1α by targeting its 3'UTR and promoted apoptosis (32).

Triggering the AhR by agonists such as TCDD and B[a] P decreased expression levels of miR-196a depending on AhR response element (AhRE) binding. While suppressing AHR expression induced miR-196a was able to promote cell apoptosis (61).

Metabolism. In low-oxygen conditions, Louis Pasteur identified a metabolic shift from mitochondrial oxidative phosphorylation to glycolysis that result from repression of the tricarboxylic acid (TCA) cycle, mitochondrial electron

Table I. miRNAs involved in HIF-associated carcinogenic processes.

miRNAs	Regulation	Type	Targets	Action	Refs.
miR-15-16	Down	Colorectal carcinoma	FGF2	Promotes angiogenesis and metastasis	(52)
miR-16	Down	Multiple tumors	VEGF	Promotes proliferation and angiogenesis	(90)
miR-17	Down	Tumor-associated macrophages	HIF2α	Promotes angiogenesis	(74,75)
miR-17	Down	Myeloid leukemic	p21 and STAT3	Promotes differentiation	(91)
miR-17-5p	Up	Cervical and renal cancer	VHL and HIF1α	ND	(92, 93)
miR-17-5p	Down	Breast cancer stem cell	PPARα	Regulates inflammation	(80)
miR-17-92	Up	Lung cancer	HIF1α	ND	(34)
miR-20a	Down	Tumor-associated macrophages	HIF2α	Promotes angiogenesis	(74,75)
miR-20a	Down	Myeloid leukemic	p21 and STAT3	Promotes differentiation	(91)
miR-21	Up	HNSCC	FIH	Promotes proliferation and migration	(94)
miR-21	Up	Pancreatic cancer	ND	Regulates proliferation and apoptosis	(29)
miR-21	Up	Prostate cancer	PTEN	Promotes angiogenesis	(44)
miR-22	Down	Colon cancer	HIF1α	Regulates growth and invasion	(47)
miR-23b	Up	Gliomas	VHL	Promotes proliferation and invasion	(57)
miR-30a-3p	Down	Renal cancer	HIF2α	Promotes growth	(95)
miR-30c-2-3p	Down	Renal cancer	HIF2α	Promotes growth	(95)
miR-31	Up	HNSCC	FIH	Promotes proliferation and migration	(94,96)
miR-92-1	Up	Chronic lymphocytic leukemia	VHL	ND	(97)
miR-99a	Down	Hepatoma and breast cancer	mTOR	Regulates glycolytic activity	(70,98)
miR-100	Down	Bladder cancer	FGFR3	Promotes proliferation	(99)
miR-101	Down	Prostate cancer	Ezh2	Promotes proliferation and invasion	(58)
miR-125b	Down	Ovarian cancer	HER2 and HER3	Promotes angiogenesis	(46)
miR-128	Down	Glioma and prostate cancer	p70S6K1 and RPS6KB1	Regulates proliferation, angiogenesis and glycolytic activity	(49,100)
miR-130b	Down	Breast cancer stem cell	DDX6	Regulates inflammation	(80)
miR-135b	Up	HNSCC and multiple myeloma	FIH	Promotes proliferation, migration and angiogenesis	(33, 101)
miR-138	Up	Ovarian and renal cancer	SOX4 and HIF1α	Regulates apoptosis, invasion and migration	(54,102)
miR-145	Down	Neuroblastoma, colon cancer	HIF2α, p70S6K1, IRS1 and N-RAS	Regulates growth, invasion, metastasis and angiogenesis	(50,56,103)
miR-150	Down	Hepatocyte	VEGF-A	ND	(104)
miR-155	Up	Cervical and renal cancer	HIF1α	ND	(92)
miR-155	Up	Lung cancer	FOXO3A	Radiosensitizes	(85)
miR-181a	Up	Chondrosarcoma	VEGF	Promotes angiogenesis	(105)
miR-183	Up	Gliomas	IDH2	ND	(69)
miR-184	Up	HNSCC	FIH	Promotes proliferation and migration	(94)

Table I. Continued.

miRNAs	Regulation	Type	Targets	Action	Refs.
miR-185	Up	Pancreatic cancer	ND	ND	(106)
miR-199a	Down	Hepatocyte, lung and ovarian cancer	HIF1α and HIF2α	Regulates proliferation and migration	(30,31,55)
miR-199a	Down	Ovarian cancer	HER2 and HER3	Promotes angiogenesis	(46)
miR199a-5p	Down	Lung cancer and multiple myeloma	HIF1α and COX2.	Promotes angiogenesis	(19,107)
miR-199b	Down	Liver and prostate cancer	HIF1α	Regulates proliferation and apoptosis	(32,87)
miR-210	Down	Glioma stem cells	MNT	Inhibits cell cycle progression and viability, promotes differentiation	(79)
miR-210	Up	T cells	HIF1α	Promotes differentiation	(73)
miR-210	Up	Neuroblastoma, lung, colon, renal, cervical, ovarian and breast cancer	VMP1, ISCU, Bcl-2, COX10, E2F3, RAD52, MNT, PTPN1	Regulates metastasis, apoptosis, mitochondrial function, cell cycle, genetic instability; correlates with radioresistance, prognosis	(14-16,27,59, 64,108-110)
miR-210-3p	Up	GBM	HIF3α	Hypoxic survival and chemoresistance	(13,22)
miR-218	Down	Mesenchymal tumors	RTK	Promotes angiogenesis	(111)
miR-320	Down	Oral cancer	Neuropilin 1	Promotes angiogenesis	(42)
miR-338-3p	Down	Hepatocarcinoma	HIF-1α	Correlates with chemoresistance and apoptosis	(112)
miR-373	Up	Cervical and breast cancer	RAD23B	DNA repair and genetic instability	(109)
miR-374b	Up	Prostate cancer	HIF-1α and VEGF	Inhibits angiogenesis	(113)
miR-382	Up	Gastric cancer	PTEN	Promotes angiogenesis	(114)
miR-424	Up	Colon cancer and melanoma	PDCD4	Inhibits apoptosis	(115)
miR-485-5p	Up	Soft tissue sarcoma	HIF-3α	ND	(22)
miR-503	Down	Hepatoma	FGF2 and VEGFA	Regulates angiogenesis	(48)
miR-519c	Up	Renal cancer	HIF-1α	Inhibits angiogenesis	(51)
miR-566	Down	Glioblastoma	VHL	ND	(82)
miR-3195	Up	Prostate cancer	HIF-1α and VEGF	Inhibits angiogenesis	(113)

IRS1, insulin receptor substrate-1; VMP1, vacuole membrane protein 1; PTEN, phosphatase and tensin homolog; RPS6KB1, ribosomal protein S6 kinase 1; IDH2, isocitrate dehydrogenase 2; RTK, receptor tyrosine kinase; ND, not determined.

Table II. miRNAs involved in AHRs associated carcinogenic processes.

miRNAs	Regulation	Type	Targets	action	Refs.
miR-24	Up	Hepatocellular carcinoma	ARNT	ND	(116)
miR-25	Up	Multiple myeloma	p53	ND	(24)
miR-107	Up	Pituitary adenomas	AIP	Inhibits proliferation	(35)
miR-124	Down	Neuroblastoma	AHR	Promotes differentiation, cell cycle arrest and apoptosis	(117)
miR-125b	Up	Renal cancer	AhRR	ND	(89)
miR-196a	Up	Hepatocellular carcinoma	ARNT	Promotes proliferation	(61)
miR-221	Up	Breast cancer	SOX4	Inhibits metastasis	(37)
miR-335	Up	Bronchial epithelial cells	AHR	ND	(53)
miR-375	Up	Fibroblast	ND	Inhibits apoptosis	(77)

transport, and oxidative phosphorylation (62). Upregulated miR-210 by HIF plays a pivotal role in the regulation of the components that are necessary for this 'Pasteur effect', which can minimize the impact of hypoxia on energy production and benefit tumor growth (63,64). miR-210 caused a shift to glycolysis by controlling a series of components of mitochondrial oxidative phosphorylation, these components included iron-sulfur cluster scaffold homolog (ISCU) (63), COX10 (16), mitochondrial complex I and aconitase (65,66), subunit D of succinate dehydrogenase complex (SDHD) (67), glycerol-3-phosphate dehydrogenase 1-like (GPD1-L) (68). In addition to miR-210, miR-183 upregulated HIF1α by targeting isocitrate dehydrogenase 2 (IDH2): mitochondrial enzymes catalyze the conversion of isocitrate to α-ketoglutarate in TCA cycle (69). Downregulated HIF1α by miR-99a in hepatocarcinoma cells inhibited insulin-induced glucose consumption by suppressing pyruvate kinase M2 (PKM2), a rate-limiting enzyme in the glycolytic pathway (70). miR-203 negatively regulated AHR expression and had a putative binding site in the 3'UTR of indoleamine 2,3-dioxygenase (IDO) (71). IDO is a rate-limiting enzyme in extrahepatic catabolism of tryptophan, thus miR-203 may be involved in AHR/IDO axis-mediated metabolism of tryptophan (72).

Inflammation and immunity. Wang *et al* reported that there was a negative-feedback between miR-210 and HIF1α and they could regulate each other. When induced by hypoxia, miR-210 negatively regulated HIF1α expression and TH17 cell differentiation through reducing HIF1α transcript abundance and the proportion of cells producing inflammatory cytokines, which could limit immunopathology (73). miR-17 and miR-20a mediated post-transcriptional suppression of HIF1α and HIF2α expression in tumor-associated monocytes and macrophages and played an important role during a wide range of cellular physiological as well as pathophysiological processes such as monocyte-to-macrophage differentiation (74,75). Csak *et al* revealed that downregulation of miR-122 attenuated the inhibitory effect on HIF1α and played a pathogenic role in steatohepatitis (76).

Bleck *et al* reported that upregulated miR-375 by environmental pollutants could target AhR and downregulate its expression, thus regulating a pivotal cytokine, thymic stromal lymphopoietin (TSLP), which associated with innate and Th2 adaptive immune disorders (77). The overexpression of miR-132/212 cluster induced by AHR promoted differentiation of Th17 cells by targeting a negative regulator of Th17 differentiation, the B-cell lymphoma 6 (78).

Stem cells. Stem cells are found in all multicellular organisms, that can self-renew and differentiate into diverse specialized cell types, and cancer stem cells are critical drivers of tumor progression (38). Yang *et al* found that hypoxia led to induction of HIF2α and miR-210 in glioma stem cells (GSCs), while knocking down of miR-210 decreased stemness, viability, neurosphere formation capacity, invasive capacity and induced differentiation, apoptosis, G0/G1 cell cycle arrest of hypoxic GSCs, and participated in regulating myc-antagonist (MNT) protein expression and caspase-3/7 activity (79). The enhancement of peroxisome proliferator activated receptor-α (PPARα) and HIF1α interplay in breast cancer stem cells sustained expression of the pro-inflammatory cytokine interleukin-6 (IL-6), the hypoxia survival factor carbonic anhydrase IX and the plasma lipid carrier apolipoprotein E. Moreover, the PPARα/HIF1α interplay was regulated by miR-130b through targeting DDX6 (a HIF1α translation inhibitory protein) and miR-17-5p via directly targeting PPARα (80). Overexpression of miR-21 induced by HIF1α played a positive role for epithelial-mesenchymal transition (EMT), invasion and migration of breast cancer stem cell-like cells (81).

4. Clinical application

The resistance of hypoxic cells to radiotherapy and chemotherapy is a major problem in the treatment of cancer. Induction of miR-210 by HIF1α in hypoxia conferred resistance to radiation via rapidly repairing DNA double-strand breaks after radiation in NSCLC cells (14). The induction of miR-210-3p by HIF1α in GBM cells showed increased resistance to temozolomide (a chemotherapeutic drug) mediated death while miR-210-3p inhibition made cells more sensitive (13). Inhibition of miR-566 was demonstrated to sensitize GBM cells to nimotuzumab by targeting VHL and activating the β-catenin/HIF1α complex which can suppress the activity of epidermal growth factor receptor (EGFR) pathway (82). Bao *et al* reported that

the treatment of pancreatic cancer cells with a novel synthetic derivative of curcumin showed an obvious antitumor effect through decreasing gene expression of miR-21, miR-210, IL-6, HIF1α, VEGF under hypoxia (83,84). In low-oxygen conditions, overexpression of miR-155 induced by HIF1α enhanced radioresistance in lung cancer cells and correlated with poor patient prognosis (85). Pyrrolopyrazine metabolite of oltipraz, a cancer chemopreventive agent, was found to play its antineoplastic function via inducing miR-199a-5p and miR-20a and these two miRNAs mediated inhibition of HIF1α by preventing its *de novo* synthesis (86). A case-control study including 35 matched HCCs and cirrhosis tissues showed that underexpressed miR-199b regulated by the upregulation of HIF1α in HCCs was inversely correlated with survival and directly correlated with the malignant status of HCC patients (87).

Hu *et al* demonstrated that upregulation of miR-302 in response to tranilast treatment was dependent on AHR, which was able to bind to miR-302 promoter and active its expression (88). Transcriptionally activated miR-125b by nuclear factor erythroid-2-related factor 2 (Nrf2) served as an inhibitor of AhRR and attenuated its control on AhR, thus, upregulated AhR inhibited p53 activity by targeting an inhibitor of p53 (Mdm2) and contributed to protecting the kidneys from cisplatin-induced injury (89).

5. Conclusions and future directions

There is increasing evidence that the bHLH-PAS proteins and its ligands play important roles in cell normal homeostasis and malignant tumor formation. miRNAs can consistently and rapidly sense and respond to environmental and physiological signals (such as B[a]P and hypoxia) by regulating multi-variety of genes and influencing numerous components of cellular signaling pathways extensively and simultaneously, thus research on the interactional role of miRNAs and bHLH-PAS proteins is worthy to clarify the mechanism that underlies the regulation of these environmental and physiological signals. However, the complicated physiological and pathophysiological molecular mechanisms between miRNAs and bHLH-PAS proteins are still unclear. Therefore, further study is needed to uncover the basic mechanisms and should focus on the following directions. First, we need to find more miRNAs and demonstrate their target genes and functions involved in bHLH-PAS proteins. Then, inflammation and stem cells are very valuable and promising fields in cancer. Further in-depth investigations are needed to understand the underlying mechanisms of this interaction in stem cell transformation, CSCs maintainence, and the relationship between inflammation and cancer. The ultimate goal is to look for specific diagnostic markers and selective preventive and therapeutic drugs thus promoting anticancer pharmaceutical development and benefit the prognosis of cancer patients.

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