Hypoxia-Induced Non-Coding RNAs

Subjects: Genetics & Heredity

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Non-coding RNA induced by low oxygen partial pressure play a crucial role in cancer progression and therapeutic response.

Hypoxia HIF lncRNAs miRNAs cancer proliferation cell cycle

1. Introduction

Hypoxia-responsive ncRNAs have been found to play important roles in hypoxia-driven cancer progression modulating the hypoxic gene expression at transcriptional, and post-transcriptional levels, by acting as effectors of HIF or as direct modulators of the HIF-transcriptional cascade[1][2]. (Figure1)

Profiling techniques and bioinformatics analysis allowed us to unveil more and more hypoxia-regulated non-coding RNA by the presence of the hypoxia response elements (HREs) in their promoter regions[3]. Moreover, several studies have described hypoxic induction of non-coding RNAs lacking HREs indicating an indirect regulation often involving epigenetic mechanisms; HIF may control non-coding RNAs expression through histone deacetylase activation, or affecting miRNA maturation machinery[4][5]

Using microarray analysis on hypoxia-induced gastric cancer cell lines, Wang et al. identified several hypoxia-responsive lncRNAs in gastric cancer. In particular, they found that an intronic antisense lncRNA named lncRNA-AK058003 was among the most induced lncRNAs upon hypoxia treatment in all examined gastric cancer cell lines [6], data confirmed also in breast cancer[7]. In addition, recent data demonstrated that HIF-1α can directly regulate circRNAs at the transcriptional level[8][9] and that HIF-induced circRNAs may promote cancer growth as demonstrated in bladder[10]; however, unlike miRNAs and lncRNAs, the mechanisms of HIF-mediated circRNAs expression have been less investigated and will not be further addressed in this review.

Considering the different mechanisms through which ncRNAs might control tumour growth, these have been divided here into two different groups: 1) the hypoxia-induced ncRNAs that work as HIF effector in promoting cell growth or inhibiting cell death, and 2) the Hypoxia induce ncRNAs such as aHIF-1α, linc-ROR, and lincRNA-p21 which directly or indirectly regulate the HIFs proteins (Figure 2).

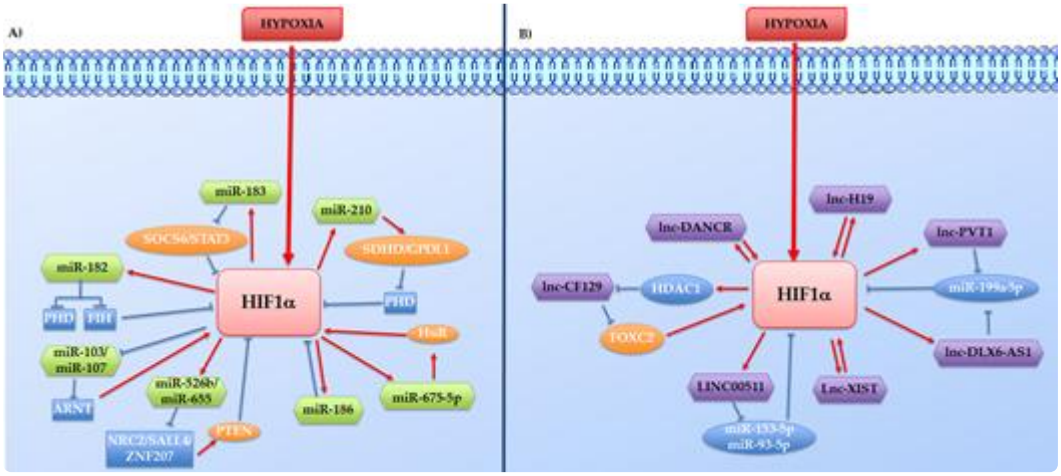

Figure 2. Direct or indirect feedback loops between HIF-1a and hypoxia-regulated ncRNAs. The hypoxia-regulated ncRNAs, HIF-1a, and other co-operators intertwine to form reciprocal feedback loops in both positive and negative manners, represented in the figure respectively with red arrows and blue lines. A) Reciprocal feedback loops between HIF-1a and hypoxia-regulated lncRNAs. B) Reciprocal feedback loops between HIF-1a and hypoxia-regulated miRNAs.

2. Hypoxia-Induced miRNAs with a Role in Tumour Growth

Hypoxic microenvironment can promote tumour growth in a dual mode: by inducing cell cycle deregulation and by allowing apoptosis escape. Several ncRNAs may act as molecular mediators through which, HIF complex controls these processes. Here we collected the most recent and relevant finding of hypoxia-induced miRNAs (hypoxiamiR), further summarized in Table 1.

Table 1. List of hypoxia-responsive miRNAs involved in cell proliferation, apoptosis and cell cycle regulation.

miRNAs	Cancer types	Regulation hypoxia-mediated	Targets	Functions	References
miR-210	Schwannoma cells	upregulation	NA	enhances tumour cell proliferation	[11]
	neuroblastoma cells	upregulation	Bcl-2	induces apoptosis	[12]
	Breast and melanoma	upregulation	Max's Next Tango (MNT)	inhibits hypoxia-induced cell cycle	[13]

	cancer cells,			arrest	
	Glioma stem cells	upregulation	MNT-Max complex	inhibits hypoxia-induced cell cycle arrest	[14]
	Epithelial ovarian cancer	upregulation	PTPN1	promotes cell proliferation and inhibits apoptosis	[15]
	Epatoma cells	upregulation	AIFM3	inhibits hypoxia-induced cell cycle arrest	[16]
	Glioma cells	upregulation	SIN3A	inhibits proliferation and promotes apoptosis	[17]
	triple-negative breast cancer	upregulation	p53	promotes cell proliferation	[18]
miR-210-3p	bladder cancer	upregulation	NA	induces apoptosis	[19]
miR-145	breast cancer	upregulation	TGFb2, HuR	promotes proliferation	[20]
miR-191	non-small cell lung cancer cells	upregulation	NF1A	promotes proliferation	[21]
	gastric cancer	upregulation	MDR1/P-gp, LRP and Bcl-2 pathways	promotes proliferation	[22]

miR-27a	gastric cancer	upregulation	PTEN	promotes proliferation	[23]
miR-382	breast cancer	upregulation	PDCD4	inhibits apoptosis	[24]
miR-424	colorectal cancer	upregulation	DAPK, KLF4	promotes hyperproliferation and decreases apoptosis	[25]
miR-103/107	pancreatic cancer cells	upregulation	NA	promotes proliferation and inhibits apoptosis	[26]
miR-21	cervical cancer cells	upregulation	PTEN/AKT pathway	promotes cell growth	[27]
	gastric cancer	upregulation	RASSF8	promotes cell growth	[28]
miR-224	bladder cancer cells	downregulation	FGFR3	upregulates proliferation	[29]
miR-100	pancreatic cancer cells	downregulation	Vimentin	inhibits proliferation	[30]
miR-548an	acute myeloid leukaemia cells	downregulation	p21, STAT3	inhibits cell growth	[31]
miR-101	glioblastoma	upregulation	NA	promotes cell proliferation	[32][33]
miR-675	colorectal cancer cells	upregulation	b-catenin localization	regulates cell cycle	[34][35]
	non-small cell lung cancer	upregulation	p53	promotes cell proliferation	[36]

	gastric cancer	upregulation	Caspase 3	inhibits apoptosis	[37]
miR-421	hepatocellular carcinoma	downregulation	VASP	promotes cell growth	[38]
miR-204	hepatocellular carcinoma	downregulation	TWIST1	induces tumour cell proliferation	[39][40]
miR-33a	hepatocellular carcinoma	downregulation	NA	upregulates tumour cell proliferation	[39][40]

The most studied hypoxiamiR is the miR-210, it is regulated by HIF in various cell types through the direct binding of the transcription factor to the HREs on its promoter. It was found to represses genes expressed under normoxia, and required to promote tumour growth[41]. The upregulation of miR-210 in solid tumours was associated with bad prognosis, indicating that the target genes affected by miR-210 have a functional impact on tumour malignancy and drug resistance[42][43]. Several studies, to date, have demonstrated its involvement in various kinds of tumours affecting a large number of cellular functions, including mitochondrial metabolism, angiogenesis, DNA repair, and cell survival. Wang et al. showed that, in schwannoma cells, hypoxia-induced miR-210 promotes autophagy activation, tumour cell proliferation and angiogenesis, while inhibits apoptosis; intriguingly, in this study, the authors noted that miR-210 promoter region, containing the HREs, was hypermethylated in normoxia, while demethylated in hypoxia thus suggesting a double control on miR-210 expression[11]. Concerning the molecular mediators, firstly, the Grandori group identified in breast and melanoma cancer cells that hypoxia-induced miR-210 targets the Max's Next Tango (MNT) mRNA, a key transcriptional repressor of the MYC-MAX network. MNT downregulation allows c-MYC to push cells through the cell cycle[13]. Similar results were obtained by Yang and colleagues in glioma stem cells, in which they observed that hypoxia upregulated miR-210 avoided G0/G1 cell cycle arrest via MNT-Max complex-dependent transcription repression[14]. In an in vitro model of ovarian cancer, Li et al. demonstrated that hypoxia upregulates miR-210 thus promoting tumour cell proliferation and cell clone generation via targeting PTPN1 (tyrosine-protein phosphatase non-receptor type 1) and inhibiting apoptosis[15]. It is notable that several studies highlighted the predicted miR-210 seed sites in apoptosis-related mRNA transcripts such as AIFM3 (Apoptosis-Inducing Factor Mitochondrion-associated 3), CASP8AP2 (Caspase-8-Associated Protein-2) and SIN3A (a transcription repressor that forms a complex with histone deacetylase 1)[16][17][44][45].

Recently, an interesting manuscript of Du et al. demonstrated that hypoxia-induced miR-210-3p controls cell proliferation by promoting Warburg effects and, concomitantly by inhibiting p53 activity in triple-negative breast cancer[18].

Taken together, these studies support a model in which, through the regulation of a single miRNA, HIF can simultaneously target multiple factors with a key role in the apoptotic process, ultimately promoting uncontrolled cell proliferation and carcinogenesis.

Another highly expressed hypoxiamir, regulated by both HIF-1 a and HIF-2a, is miR-21. It is considered to act as oncomirs by targeting many tumour suppressor genes involved in cell proliferation, apoptosis, and invasion in several types of cancer[26][27]. The pro-oncogenic role of miR-21 was in deep studied in the last years since to propose anti-miR-21 as a strategy to fight tumour growth[46]; here is interesting to note that hypoxia-induced miR-21 shows an elevated level in hypoxic exosomes. Li et al., demonstrated that tumour-derived exosomes enriched in miR-21 are internalized by normoxic cells driving recipient cells toward a pro-metastatic phenotype[47].

One of the miRNAs, which expression increases in the hypoxic tumour, is the miR-675. It was found up-regulated by HIF in several tumours including Glioblastoma[32][33] and colorectal cancer[34]. Recently it was described its role in controlling cell cycle by regulating Glycogen Synthase Kinase 3b (GSK-3b) activity and allowing b-catenin nuclear localization[35]. MiR-675 was found up-regulated in hypoxic non-small cell lung cancer where in addition to promoting cell proliferation, it acts on apoptosis by directly inhibiting the expression of p53[36]; also in this case, through the induction of a single miRNA, HIF promotes tumour growth by acting simultaneously on several molecular pathways.

In a study conducted by Zhao et al., miR-191 was found to be upregulated by HIF-1a. They showed that miR-191 promoted the proliferation and migration of non-small cell lung cancer cells (NSCLC) by targeting of NF1A (Nuclear factor 1 A-type) under chronic hypoxic conditions[21]. In breast cancer, Nagpal and colleagues showed that miR-191 is upregulated by both HIF-1a and HIF-2a and its overexpression is responsible for cancer aggressiveness by promoting cell proliferation, and survival under hypoxia; moreover, they demonstrated that miR-191 promotes TGFb expression thus revealing a molecular link between HIF and TGFb signalling pathways, both pivotal in the regulation of breast cancer metastasis[20].

He et al. highlighted the role of HIF-1α in transcriptional upregulation of the miR-224 in gastric cancer cells. Through target gene validation, these authors revealed that miR-224 directly targets RASFF8 (Ras association domain family member 8), stimulating p65 nuclear translocation and NF-kB transcriptional activity to confer gastric cancer cells with more aggressive phenotype[28]. Their results suggest that hypoxia-inducible miR-224 promotes gastric cancer cell growth by downregulating RASSF8 and acts as an oncogene, implying that inhibition of miR-224 may have potential as a therapeutic target for patients with hypoxic gastric tumours[28].

Several studies conducted on gastric cancer cells using different approaches (i.e., ChIP assay, luciferase assay, as well as qRT-PCR) revealed the direct relationship between HIF-1a and different miRNAs. Ge et al. observed that miR-421, up-regulated by HIF-1α, can promote tumour behaviour in gastric cancer by targeting the caspase-3 thus inhibiting apoptosis[37]. Zhao and colleagues revealed that HIF-1α can directly bind the miR-27a promoter increasing the activity of some antiapoptotic pathways (i.e., the MDR1/P-gp, Bcl-2, LRP) and promoting multidrug resistance [22].

It is notable that while several miRNAs are directly induced by HIF, a great number of non-coding RNAs were found to be down-regulated in hypoxic conditions.

Liu et al. showed that in hepatocellular carcinoma miR-204 expression is inhibited by HIF-1a. These authors proved that hypoxia-induced down-regulation of miR-204 promotes malignant transformation through the up-regulation of Vasodilator-stimulated phosphoprotein (VASP); this is a regulator of cytoskeletal actin and cell migration, and its expression correlates with aggressive phenotype and metastasis both in vitro and in vivo[38]. MiR-33a and miR-199a-5p are found to be reduced under the regulation of HIF-1a in HCC[39][40]. Li et al. proved that mirR-199a-5p inhibition by HIF-1a regulates Warburg effect and induce tumour cell proliferation in hepatocellular carcinoma[40]. Also, miR-548an, a tumour suppressor miRNA, is down-regulated by HIF-1a in pancreatic cancer cells, and it is involved in increasing vimentin level and facilitating the pancreatic tumorigenesis[30].

Intriguingly, several studies have reported hypoxamirs working as tumour suppressors e.g., the miR-145 or the miR-215[19][48], thus suggesting the existence of an intricate network of interactors not yet fully revealed. To solve this, some aspects that have been neglected so far must be taken into account: i) here we reviewed only a fraction of HIF-induced miRNA but several other miRNAs are induced under hypoxic condition in a HIF-independent manner, ii) a single miRNA has numerous targets in the same cell, and iii) hypoxia-induced lncRNAs can sequester multiple miRNAs preventing them from reaching their target.

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