Free Radical Biology and Medicine 64 (2013) 20–30

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

Hypoxia: A master regulator of microRNA biogenesis and activity

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ARTICLE INFO

Available online 24 May 2013

Keywords:
Hypoxia
MicroRNA
Hypoxamir
HIF
Free radicals

ABSTRACT

Hypoxia, or low oxygen tension, is a unique environmental stress that induces global changes in a complex regulatory network of transcription factors and signaling proteins to coordinate cellular adaptations in metabolism, proliferation, DNA repair, and apoptosis. Several lines of evidence now establish microRNAs (miRNAs), which are short noncoding RNAs that regulate gene expression through posttranscriptional mechanisms, as key elements in this response to hypoxia. Oxygen deprivation induces a distinct shift in the expression of a specific group of miRNAs, termed hypoxamirs, and emerging evidence indicates that hypoxia regulates several facets of hypoxamir transcription, maturation, and function. Transcription factors such as hypoxia-inducible factor are upregulated under conditions of low oxygen availability and directly activate the transcription of a subset of hypoxamirs. Conversely, hypoxia selectively represses other hypoxamirs through less well characterized mechanisms. In addition, oxygen deprivation has been directly implicated in epigenetic modifications such as DNA demethylation that control specific miRNA transcription. Finally, hypoxia also modulates the activity of key proteins that control posttranscriptional events in the maturation and activity of miRNAs. Collectively, these findings establish hypoxia as an important proximal regulator of miRNA biogenesis and function. It will be important for future studies to address the relative contributions of transcriptional and posttranscriptional events in the regulation of specific hypoxamirs and how such miRNAs are coordinated in order to integrate into the complex hierarchical regulatory network induced by hypoxia.

Contents

Abbreviations: 3′UTR, 3′ untranslated region; Ago2, Argonaute 2; CCN5, cysteine-rich 61/connective tissue growth factor/nephroblastoma overexpressed 5; ChIP, chromatin immunoprecipitation; CUL2, cullin2; DGCR8, Di George syndrome critical region 8; DMNT, DNA methyltransferase; E2F3, E2F transcription factor 3; HIF, hypoxia-inducible factor; HUVEC, human umbilical vein endothelial cell; HRE, hypoxia-responsive element; mTOR, mammalian target of rapamycin; miRNA, microRNA; miRISC, miRNA-induced silencing complex; NF-κB, nuclear factor-κB; ODD, oxygen-dependent domain; PTM, posttranslational modification; pre-miRNA, precursor miRNA; pri-miRNA, primary microRNA; ROS, reactive oxygen species; TF, transcription factor; TRAF6, TNF receptor-associated factor 6; TWIST1, Twist-related protein 1; UPR, unfolded protein response; VHL, von Hippel-Lindau tumor suppressor protein

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http://dx.doi.org/10.1016/j.freeradbiomed.2013.05.022

Introduction

The processes that govern cellular adaptation to hypoxia, or low oxygen availability, are complex and incompletely defined. Recently, several lines of evidence directly implicate microRNAs (miRNAs), which are short noncoding RNAs that regulate gene expression through posttranscriptional mechanisms, in these molecular events [1–3]. Approximately 1–2% of the transcriptome in eukaryotic organisms consists of miRNAs [4,5]. They coordinate complex posttranscriptional regulatory events relevant to a variety of fundamental cellular processes, including proliferation, apoptosis, and differentiation. Mature miRNAs are approximately 18–23 nt in length and control gene expression through degradation and repression of translation of primary messenger RNA (mRNA) [6].

Hypoxic stress regulates the expression of an expanding but specific subset of miRNAs, termed hypoxamirs [3,7]. Although the specific miRNA hypoxic signature can vary based on the cellular or physiological scenario, a core group of hypoxamirs appears to be modulated consistently by hypoxia in diverse contexts [2] (Table 1). Among these, multiple hypoxamirs directly target important gene transcripts that coordinate metabolic reprogramming, DNA repair, apoptosis, and angiogenesis, among many other cellular adaptations to low oxygen availability [1,8–10].

Hypoxic insults can be acute, transient, and/or localized, and miRNAs are uniquely suited to participate in the rapid, adaptive responses to oxygen deprivation. The posttranscriptional regulatory mechanisms employed by miRNAs facilitate an expedient, precise, and quickly reversible fine-tuning of the cellular response to environmental stress. In addition, the network of hypoxamirs and their direct targets offer the potential for a dynamic and robust biological response to hypoxia through the coordinated regulation of host genes and miRNA clusters, with each miRNA potentially controlling multiple and often functionally related mRNA transcripts. Thus, to maintain such exquisite coordination of these adaptive programs, important molecular crosstalk has evolved between hypoxic signaling cascades and miRNA biogenesis and function. In this review, we summarize our current understanding of such hypoxia-mediated regulation of miRNA expression via alterations in miRNA biogenesis, maturation, processing, and, potentially degradation.

Table 1
Verified hypoxamirs in mammalian cells.

Upregulated by hypoxia	Downregulated by hypoxia
Let-7b,e,I [32]	Let-7a,c,d,f [32]
MiR-7 [104]	MiR-15b [104]
MiR-21 [2]	MiR-16 [32]
MiR-23a,b [2]	MiR-19a [32]
MiR-24 [2]	MiR-20a,b [32]
MiR-26a,b [32]	MiR-29b [104]
MiR-27a [104]	MiR-30e [104]
MiR-30b [32]	MiR-92 [105]
MiR-93 [2]	MiR-101 [104]
MiR-98 [104]	MiR-122a [104]
MiR-103 [2]	MiR-135a [109]
MiR-106a [2]	MiR-141 [104]
MiR-125b [2]	MiR-186 [2]
MiR-130 [105]	MiR-197 [104]
MiR-146a,b [8]	MiR-199a [27]
MiR-148a,b [104]	MiR-200b [110]
MiR-151 [32]	MiR-224 [32]
MiR-320 [104]	MiR-374 [32]
MiR-181a,b,c [2,32]	MiR-422b [104]
MiR-188 [32]	MiR-449a,b [111]
MiR-191 [104]	MiR-565 [104]
MiR-192 [2]	
MiR-195 [104]	
MiR-199a-5p [106]	
MiR-204 [107]	
MiR-205 [108]	
MiR-210 [2,32,86]	
MiR-213 [2]	
MiR-335 [108]	
MiR-373 [104]	
MiR-424 [10,103]	
MiR-429 [104]	
MiR-451 [94]	
MiR-491 [108]	
MiR-498 [104]	
MiR-563 [104]	
MiR-572 [104]	
MiR-628 [104]	
MiR-637 [104]	

Cellular adaptations to hypoxia

Hypoxia evokes stereotyped and highly coordinated cellular responses in the acute setting to preserve cell viability [11]. These adaptive responses are orchestrated by a variety of global molecular regulators, including the hypoxia-inducible factor (HIF), a "master" regulator of the hypoxic response [12]. HIF is a heterodimeric transcription factor (TF) consisting of HIFα and HIFβ subunits. Unlike HIFβ, which is stable regardless of cellular oxygen tension, HIFα is rapidly degraded under normoxic conditions. The HIFα isoforms—HIF1α, HIF2α, and HIF3α splice variants—undergo efficient prolyl hydroxylation of an oxygen-dependent degradation domain (ODD) by prolyl hydroxylation domain proteins. This posttranslational modification (PTM) leads to HIF1α binding to the von Hippel-Lindau tumor suppressor protein (VHL) and its subsequent ubiquitination and degradation by the 26S proteasome. In contrast, under hypoxic conditions, hydroxylation of proline residues in the ODD of HIFα is significantly diminished. As a result, HIFα accumulates in the cytosol and translocates to the nucleus where it forms a functional HIF heterodimer with HIFβ. The HIF heterodimeric complex then binds to consensus hypoxia-responsive elements (HREs) in the promoters of a number of target genes to activate wide-scale gene programs that coordinate a switch to glycolysis, angiogenesis, erythropoiesis, and apoptosis. Therefore, HIFα fulfills roles as a critical oxygen sensor and regulator of the hypoxic-adaptive response.

Recent evidence indicates HIF alone is insufficient to implement the full program of adaptive changes required for cell survival under hypoxic stress. Rather, HIF-independent pathways involving p53 [13–16], mTOR [17–19], endoplasmic reticulum stress, and the unfolded protein response (UPR) [20,21] play important complementary roles that promote cell survival under conditions of low oxygen availability. These HIF-independent pathways facilitate energy conservation and cell survival measures in the setting of low oxygen levels. Accumulating evidence indicates that miRNAs interface with both HIF-driven and HIF-independent pathways to form a highly interconnected regulatory network during hypoxic stress.

The diverse roles of miRNAs in cellular adaptation to hypoxia

Although individual miRNAs mediate relatively modest inhibitory effects on protein translation via 30–50% reductions in target protein levels [22,23], they collectively constitute an important component of the cellular response to hypoxia through combinatorial and coordinated regulation of key targets. An exhaustive discussion of the constantly expanding portfolio of hypoxamir functions is beyond the scope of this report. Yet, it is worth reviewing the broad themes that characterize their general actions in overall hypoxic reprogramming (Table 2), including the reinforcement of HIF adaptive responses and the regulation of the levels