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RNA Binding Protein And Microrna: Key Players In Hypoxia Signaling

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Abstract

MicroRNAs (miRNAs) are small, non-coding RNA molecules involved in post-transcriptional regulation of genes by binding to the miRNA recognition site of 3' untranslated region (UTR) of the target transcript. RNA binding proteins (RBPs) are involved in number of functions including post-transcriptional regulation of genes. They have also affect the messenger RNA stability by binding to their recognition sequences. Specific RBPs and miRNAs have shown to be key players in hypoxia signaling.

Key Words: miRNA, UTR, RBPs, non-coding RNA

Introduction

Hypoxia has emerged as an important factor in tumor biology identified as a driver of angiogenesis, tumor aggressiveness, cancer stem cells etc and a negative prognostic factor for several cancers, primarily breast cancer, glioblastoma, cervical cancer etc. [1]. Hypoxia-inducible genes have been show to regulate several biological processes including but not limited to cell proliferation, metabolism, angiogenesis, apoptosis etc. [2]. Cancer cells have the ability to make the best of this physical condition by ignoring some pathways like apoptosis while taking advantage of certain others as angiogenesis [2]. Many of the understood oncogenic signaling pathways and the hypoxia-induced pathways show certain similar features. Studies delineating the expression profiles of genes have identified many genes that regulated by hypoxia and HIF-1α, the master regulator of Hypoxia-inducible genes. These include genes involved in proliferation, angiogenesis and cell-adhesion [2]. Considering all of these things, targeting hypoxic responses becomes an important tool in cancer therapy and development of cancer therapeutics.

Post-transcriptional regulation: Post-transcriptional regulation plays an important role in the regulation of gene expression under hypoxia. Post-transcriptional regulation can occur through a variety of means, mainly centered on the 3' UTR. Two of those means are modulation through RNA binding proteins (RBP) and a small class of non-coding RNAs called micro RNAs (miRNAs).

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Micro RNAs: Micro RNAs are 18-25 nt long small RNAs which share sequence similarity with 3'UTRs of specific mRNAs and depending on the extent of complementarity, they either completely degrade the transcript (complete complementarity) or inhibit translation (partial complementarity) [3].

RNA binding proteins: RNA binding proteins bind to double stranded or single stranded RNAs and can perform a variety of functions including RNA processing and modification, RNA editing, binding and recognition features including zinc-finger binding etc. [4]. They also play a role in the regulation of mRNA translation by a variety of mechanisms.

Interactions between microRNAs and RNA binding proteins: Nascent studies have shown that microRNAs and RNA binding proteins may show some interactions. *Kedde et al.* have demonstrated, in MCF7 cell line, that the RBP Pumilio augments the regulatory effects of miR-221/222 on the mRNA transcript of p27Kip1 by inducing a change in conformation of the sequence at the 3' UTR to facilitate the binding of miR-221/222 [5]. Conversely the activity of miRNAs can inhibited by certain RBPs. *Bhandari et al* showed that in squamous cell carcinoma, the RBP DND1 impairs miR-21 action on target transcript MSH2 which ultimately results in suppression of tumorigenesis [6]. *Nairismägi et al.* also identified an augmenting effect of RBP CPEB2 on the miRNA-580. They found a cooperative effect of the RBP in the negative regulation of TWIST1, an oncogene that also happens to be a miR-580 target [7]. It has shown that Dnd1, an RNA binding protein, binds to the 3' UTR of mRNAs such as p27Kip1 and LATS2 and blocks the miRNAs targeting these transcripts thereby maintaining p27Kip1 and LATS2 protein levels [8].

With regards to the interaction between RBP and miRNAs, it has also been shown that miRNAs can have regulatory effects on RBPs. *Morgan et al.* demonstrated that CPEB2, which is an RBP, was shown to undergo regulation by miR-92 and miR-26, in the neuroblastoma cell line SK-N-BE [9]. Another miRNA, miR-550a, has been shown to target CPEB4 in human hepatocellular carcinoma. They found that there is an inverse correlation between miR-550a and CPEB4 expression [10]. *Liu et al.* also demonstrated the regulation of an RBP by miRNA and found that miR-24 specifically downregulates the RNA-binding protein DND1, thereby yielding reduced p27Kip1, which in turn results in reduced apoptosis and enhanced proliferation [11].

Kulshreshtha et al. were the first to report that hypoxia induces a specific spectrum of miRNAs, with various roles in cell fate, in breast and colon cancer and found that HIF-1 (Hypoxia inducible factor 1), a master regulator of gene expression in hypoxia is the transcription factor involved in their introduction [12]. *Bhatt et al.* found that miR-687, a key regulator in renal ischemia-reperfusion injury, is noticeably upregulated in kidney cells during hypoxia [13].Another study found that miR-146a was upregulated in myeloid leukemic cell lines [14]. Certain RBPs have implicated and have found to regulate mRNA transcripts in the presence of hypoxia [15]. *Wellmann et al.* highlighted that during the

presence of mild (8% O_2) and severe (1% O_2) hypoxia, there was significant upregulation of RBPs CIRP and RBM3 in Hepa-1 c4, a murine HIF-1B-deficient cell line [16]. It has also been shown that some RBPs can regulate HIF-1 during hypoxia. Under hypoxia, PTBP interacted with the 5'UTR of the HIF-1a mRNA and promoted its translation in human embryonic kidney cells [17].

With the recent spate of research in underlying mechanisms and interactions of RBPs and miRNAs, it seems that the effect of hypoxia on these interactions has received scant attention. Given that hypoxic conditions have been known to regulate specific miRNAs and RBPs, the study of their interactions under hypoxia would add a new dimension to this already growing aspect of cancer biology.

Hypoxia is known to play an important role in affecting the fate of cells. The mechanisms by which cellular adaption to hypoxic conditions becomes possible are yet to be fully explored. One of the ways by which this happens is through micro RNAs. Studies have found that the master regulator of Hypoxia, hypoxia inducible factor 1 (HIF1), regulates a range of micro RNAs. MicroRNAs have also been found to be regulated in a HIF1-independent manner. The result of this regulation of miRNAs is the effect on translation of genes involved in various cellular processes like apoptosis (e.g. BAK1, CASP3), DNA repair (e.g. CHK1, MGMT), and metabolism (e.g. GPD1L1L, ATP50) and cell cycle (e.g. E2F1, PLK1). This in turn affects these crucial processes that affect the fate of the cell [1].

Some hypoxia-regulated micro RNAs (HRMs) in turn regulate HIF 1. For e.g., it was reported that downregulation of miR-199, miR-20b and miR-17-92resulted in stability of HIF1 because these HRMs under normoxic conditions could target and repress the HIF1 transcripts [2]. These interactions have an obvious effect on the downstream target genes of HIF1 that have observable effects on processes like cell signaling (VEGF), energy metabolism (e.g. GLUT1 and GLUT3), cell differentiation (OCT4 and EPO) etc. [2, 3]. While these studies are relatively new, they do promise an interesting insight into the effect of a physical process like hypoxia and its role in determining the fate of cells. This is especially relevant in tumour cells as microenvironments of hypoxia regularly created inside tumors and cells adapt accordingly [4].

CONCLUSION:

Cooperative interactions between RBPs and miRNAs regulate the critical factors of hypoxia, targeting both pathways might achieve a more effective control of hypoxia. Indeed, RNA-based therapeutics to control have been successfully implemented and Further study in this area will likely yield novel therapeutic agents to control hypoxia.

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