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Review

The tumour hypoxia induced non-coding transcriptome

Hani Choudhry [a], Adrian L. Harris [b,*], Alan McIntyre [c,**]

[a] Department of Biochemistry, Faculty of Science, Center of Innovation in Personalized Medicine, King Fahd Center for Medical Research, King Abdulaziz University, Jeddah, Saudi Arabia
[b] Molecular Oncology Laboratories, Department of Oncology, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, OX3 9DS, UK
[c] Cancer Biology, Division of Cancer and Stem Cells, QMC, University of Nottingham, Nottingham, NG7 2UH, UK

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ABSTRACT

Recent investigations have highlighted the importance of the non-coding genome in regions of hypoxia in tumours. Such regions are frequently found in solid tumours, and are associated with worse patient survival and therapy resistance. Hypoxia stabilises the transcription factors, hypoxia inducible factors (HIF1α and HIF2α) which coordinate transcriptomic changes that occur in hypoxia. The changes in gene expression induced by HIF1α and HIF2α contribute to many of the hallmarks of cancer phenotypes and enable tumour growth, survival and invasion in the hypoxic tumour microenvironment. Non-coding RNAs, in particular microRNAs (miRNAs), which regulate mRNA stability and translation, and long-non-coding RNAs (lncRNAs), which have diverse functions including chromatin modification and transcriptional regulation, are also important in enabling the key hypoxia regulated processes. They have roles in the regulation of metabolism, angiogenesis, autophagy, invasion and metastasis in the hypoxic microenvironment. Furthermore, HIF1α and HIF2α expression and stabilisation are also regulated by both miRNAs and lncRNAs. Here we review the recent developments in the expression, regulation and functions of miRNAs, lncRNAs and other non-coding RNA classes in tumour hypoxia.

Contents

1. Introduction 36
2. Hypoxic regulation of miRNAs 36
3. Regulation of the miRNA machinery in hypoxia 38
4. Regulation of HIF by miRNAs 38
5. Impact of miRNAs in hypoxia 41
   5.1. The impact of HIF regulating miRNAs 41
   5.2. Angiogenesis 42
   5.3. Metabolism 42
   5.4. Autophagy 42
   5.5. Invasion and metastasis 42
   5.6. Growth and survival 42

* Corresponding author. Molecular Oncology Laboratories, Department of Oncology, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, OX3 9DS, UK. Tel.: +44 (0)1865 222457; fax: +44 (0)1865 222 431.
E-mail address: aharris.lab@imm.ox.ac.uk (A.L. Harris).
** Corresponding author. Cancer Biology, Division of Cancer and Stem Cells, QMC, University of Nottingham, Nottingham, NG7 2UH, UK. Tel.: +44 (0)115 8231307.
E-mail address: alan.mcintyre@nottingham.ac.uk (A. McIntyre).

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6. Hypoxic regulation of lncRNAs and their impact on cancer biology 43
6.1. H19 43
6.2. LincRNA-p21 43
6.3. HINCUTs 45
6.4. lncRNA-LET 45
6.5. HOTAIR 45
6.6. WT1 45
6.7. AK058003 45
6.8. HIF2PUT 46
6.9. ENST00000480739 46
6.10. EFNA3 lncRNA 46
6.11. lncRNA-UCA1 47
6.12. RERT-lncRNA 47
6.13. linc-RoR 47
6.14. MALAT1 47
6.15. aHIF1α 48
6.16. NEAT1 48
7. Hypoxic regulation of other noncoding RNA classes 48
8. Summary and perspectives 49
Acknowledgements 50
References 50

1. Introduction

Regions of low oxygen (hypoxia) occur in solid tumours due to insufficient vascularisation, and high tumour metabolic and proliferative rates (Semenza, 2014). To survive, tumour cells need to adapt to this tumour microenvironmental stress and molecular adaption occurs through the stabilisation of the hypoxia inducible factor proteins HIF1α and HIF2α (Semenza, 2014; Shen and Kaelin, 2013). HIF1α and HIF2α are constitutively expressed, however, in conditions of adequate oxygenation they are degraded. They are hydroxylated by the prolyl hydroxylases which require oxygen as a co-factor (Shen and Kaelin, 2013). Upon hydroxylation, HIFs are ubiquitinated by von Hippel–Lindau (VHL) syndrome protein and degraded by the proteasome (Shen and Kaelin, 2013). In addition, the expression of HIFs are also regulated by growth factor signalling and a number of studies have shown their dependence upon growth factors (such as EGF and FGF-2) and MAPK and AKT signalling (Agani and Jiang, 2013; Feldser et al., 1999). Clinically, hypoxia is associated with metastasis, chemotherapy and radiotherapy resistance and worse survival (Multhoff et al., 2014; Rebucci and Michiels, 2013). HIF1α and HIF2α heterodimerise with HIF1β (ARNT) and transcriptionally activate many genes involved in processes that contribute to the hallmarks of cancer and increase tumour survival in the hypoxic tumour microenvironment including: angiogenesis, metabolism, autophagy, invasion and metastasis (Brahimi-Horn et al., 2011; De Bock et al., 2011; Favaro et al., 2011; Semenza, 2014; Singleton et al., 2014). In addition to regulating protein coding RNA, it is clear that non-coding RNAs are also differentially expressed in hypoxia and that these play major roles in the hypoxic tumour microenvironment (Choudhry et al., 2014, 2015; Gee et al., 2014; Ivan and Huang, 2014).

Recent advances in human transcriptome analysis revealed that less than 2% of the transcriptional output encodes proteins and the remaining 98% encode different classes of non-coding RNAs (Djebali et al., 2012). These non-coding RNAs can be categorized based on their length into small non-coding RNAs (<200 nucleotides), such as miRNA, piwiRNAs, snRNA, and tRNAs, and long non-coding RNAs (lncRNAs) (>200 nucleotides) such as MALAT1, NEAT1, and many antisense transcripts. Many of these non-coding RNAs have potential transcriptional, post-transcriptional, and epigenetic regulatory functions and are often deregulated in many diseases, including cancer. Alterations of the expression of these non-coding RNAs contribute to cancer formation and progression and has key roles in the hypoxic tumour microenvironment. Furthermore, many miRNA and a limited number of hypoxia responsive lncRNAs have been reported to play a regulatory role in the hypoxia/HIF pathway, which contributes to cancer development and metastasis. In this review, we will summarize the current knowledge regarding hypoxia-regulated miRNAs and lncRNAs and their impact on cancer biology. In addition, we will review the current literature regarding the effects of hypoxia on other non-coding RNA classes.

2. Hypoxic regulation of miRNAs

miRNAs are short 22 nucleotide duplexes that regulate mRNA stability and translation (Camps et al., 2014; Nallamshetty et al., 2013). miRNA expression is changed in tumours compared to normal tissues and in a parallel with coding genes many oncogenic and tumour suppressive roles for miRNA have been identified (Lin and Gregory, 2015). Furthermore, differential miRNA expression and biogenesis is observed under hypoxic conditions (Choudhry et al., 2014; Rupaimoole et al., 2014; van den Beucken et al., 2014). The biogenesis of miRNA and the processes by which they degrade mRNA and repress mRNA translation are complex (Camps et al., 2014; Nallamshetty et al., 2013). miRNA containing transcripts known as pri-miRNA are initially transcribed mostly by polymerase II under transcription factor regulation (Iorio and Croce, 2012). pri-miRNAs are