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Unlocking the complexity of hypoxia non-coding transcriptome landscape of breast cancer

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Transcriptional responses to hypoxia are central to the pathogenesis of many types of cancer. Today, pan-genome analyses of hypoxia have focused on protein-coding genes, however, the role of non-coding RNAs, in particular long non-coding RNAs (lncRNA) is not well characterised. We undertook an integrated pan-genomic analysis of the transcriptional responses to hypoxia in MCF7 breast cancer cells, employing total RNA-seq together with ChIP-seq for the hypoxia-inducible transcription factor (HIF) and for epigenetic marks of transcriptional activation (RNApol2 and histone H3K4me3). Analyses revealed that all classes of RNA are significantly regulated by hypoxia. We found significant numbers of lncRNAs are up-regulated in hypoxia and these are associated with epigenetic marks of increased transcription and HIF binding. We describe a number of hypoxia regulated non-annotated RNA species, including several that are antisense to hypoxia regulated protein-coding RNAs. The most hypoxia up-regulated lncRNA was NEAT1. The role of NEAT1 in cancer has not been previously studied. We demonstrate that NEAT1 induction is common in breast cancer cell lines and xenograft models. Finally, selected hypoxia regulated lncRNAs are analysed in a large cohort of breast cancers (n=2000) and found to be associated with poor clinical outcome and clinicopathological features. Our findings extend knowledge of the hypoxic transcriptional response into the spectrum of non-coding transcripts. These HIF-regulated non-coding transcripts have the potential to act as biomarkers for breast cancer as well as potential novel therapeutic targets.

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