Glioblastoma multiforme is the most aggressive form of brain cancer. The standard of care treatment for newly diagnosed patients with glioblastoma is tumour de-bulking by surgery, followed by combined therapy consisting of radiation and temozolomide chemotherapy. The tumour invariably recurs, often in the same area or adjacent to the original surgical-resected tumor. Tumour recurrence or progression is currently assessed by magnetic resonance imaging (MRI), which may include spectroscopy studies and blood flow. However, MRI has limitations for determining recurrence or treatment response. Therefore, identifying peripheral biomarkers that can predict tumor prognosis, tumor recurrence/progression and instruct personalised treatment strategies would be an important advance for improving overall patient outcomes in glioblastoma patients and other cancers.

Although several more established types of biomarker have been explored, including circulating tumour cells, growth factor and cytokines, miRNA and circulating tumour DNA, the detection of various long non-coding RNA (LncRNA) have rapidly emerged as potential candidates for optimized glioma diagnosis, prognosis and targeted therapy. LncRNAs are approximately 200 nucleotides in length and have emerged as novel gene regulators that interact with nucleic- or protein-molecules and regulate transcription or posttranscriptional processes. LncRNAs are thought to function via four potential mechanisms: (I) guiding chromatin-modifying enzymes; (II) providing a scaffold for RNA-protein complexes; (III) acting in conjunction with transcription factors and (IV) acting as molecular decoys. Further information of these four mechanisms of actions are discussed by Bhat et al. as it is beyond the scope of this editorial.

Several LncRNAs have been implicated in promoting glioblastoma progression. The study by Zhang and colleagues identified a correlation between the expression of the LncRNA HOX Transcript Antisense Intergenic RNA (HOTAIR) with tumour grade, where the highest expression of HOTAIR was observed in serum collected from glioblastoma patients compared with low grade glioma patients and healthy controls. HOTAIR is part of the homeobox superfamily and transcribed within the HOXD locus on chromosome 12q13. One of its known functions includes acting as a gene silencer on the HOXD locus by forming a complex with polycomb-repressive complex (PRC2) chromosome 2. HOTAIR was found to be up-regulated in primary colorectal cancer biopsies and matched serum samples compared to controls. HOTAIR was found to be up-regulated in primary colorectal cancer biopsies and matched serum samples compared to controls. HOTAIR has also been identified as a strong predictor of breast cancer progression and metastasis. Recent evidence demonstrated that HOTAIR is also involved in the progression of other solid tumours including cervical and bladder cancer. HOTAIR expression has subsequently been shown to enhance cell cycle progression and is associated with poor overall outcome of glioblastoma patients. Likewise, the study by Pastori et al. demonstrated that HOTAIR is over-expressed in human glioblastoma specimens compared to

**Peripheral biomarkers in glioblastoma patients—is it all just HOTAIR?**

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Provenance: This is an invited Editorial commissioned by the Section Editor Quying Dai (MetroWest Medical Center, Framingham, MA, USA)


Received: 17 May 2018; Accepted: 25 May 2018; Published: 13 June 2018.
doi: 10.21037/ncri.2018.05.05

View this article at: http://dx.doi.org/10.21037/ncri.2018.05.05
normal brain samples. Furthermore, they also showed that the knockdown of HOTAIR led to enhanced apoptosis and reduced colony formation in vitro, in addition to reduced intracranial tumour growth in vivo compared to control transfected glioblastoma cells (22).

These findings highlight the potential role of intratumoural HOTAIR expression in glioblastoma progression and the identification of HOTAIR LncRNA in peripheral samples such as serum, representing a likely important non-invasive biomarker for glioblastoma diagnosis and recurrence. Importantly, a follow-up article by the same group evaluated the expression levels of HOTAIR as a serum biomarker for glioblastoma diagnosis (23). HOTAIR were found to be located in exosomes and potentially not as free molecules, as it was detected in whole serum and purified exosomes, but not in serum supernatant depleted of exosomes. However, the authors did not state how many serum samples were used to harvest exosomes when displaying this data. Nevertheless, Tan et al. compared serum samples of 43 glioblastoma patients with 23 low grade glioma and 40 healthy controls and observed that HOTAIR expression was up-regulated in the glioblastoma patients (23). The sensitivity and specificity of HOTAIR expression was 86.1% and 87.5% respectively and the area under the ROC curve was 0.913 (P<0.001). The authors found a moderate correlation of HOTAIR in GBM tumors and serum (r=0.7342, P<0.01) (Figure 1B). To validate serum HOTAIR as a potential biomarker, HOTAIR products was amplified and sequence mapped to its original site on chromosome 12q13 of the human genome along with the HOTAIR-205 splice variant. Serum HOTAIR expression was also monitored in one recurrent GBM patient longitudinally from before surgery to post-treatment; and found that the level of serum HOTAIR was reduced after surgery and further reduced 2-week post-surgery, suggesting its prognostic potential. The authors acknowledged that the data presented was very preliminary (n=1 recurrent), thus it is necessary to repeat this analysis with more GBM patients. More importantly, analysis of HOTAIR expression in patient serum taken at several time-points post-surgery until recurrence is detected by MRI would be critical to determine whether the re-emergence of increased HOTAIR expression correlates with the detection of tumour recurrence (or ideally found to increase prior to detection of recurrence by MRI). These longitudinal findings in a large cohort of retrospective patient serum samples would therefore determine if HOTAIR can truly be used as a peripheral biomarker for glioblastoma recurrence; and perhaps represent an improved detection method than MRI, which is currently utilized worldwide.

In summary, data from this study provides promising evidence that HOTAIR can be used as a potential diagnostic and prognostic biomarker in glioblastoma, a devastating cancer with very poor prognosis (24). It is likely that LncRNA including HOTAIR may be used as a single biomarker or a combination of biomarkers for early diagnosis and tumor monitoring. However, research in this field is still in its infancy and more experiments are required to confirm the validity of HOTAIR as a universal biomarker.

Acknowledgements

RB Luwor is a recipient of the Victorian Cancer Agency.
Mid-Career Research Fellowship (MCRF15017).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/ncri.2018.05.05

Cite this article as: Nguyen HP, Morokoff AP, Stylli SS, Kaye AH, Luwor RB. Peripheral biomarkers in glioblastoma patients—is it all just HOTAIR? Non-coding RNA Investig 2018;2:32.