RNA Editing Mistake Promotes Brain Tumour Development

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Despite relatively low incidence rates, brain tumours are of growing concern. Patients with the most common primary brain tumour, glioblastoma multiforme, have a median survival time of only around one year. In the hunt for effective treatments, Assoc Prof Wang Shu and his team recently discovered a potential new strategy for fighting this highly lethal disease.

The most aggressive of the gilomas, a group of tumours that affect the glial cells in the central nervous system, glioblastoma multiforme is extremely difficult to treat. Assoc Prof Wang explains that "despite surgical resection, combination radiation and chemotherapy, the disease usually recurs due to extensive invasion of tumour cells into the normal brain parenchyma and therapeutic resistance". There is an urgent need, he warns, to develop "adjuvant glioma therapies that are capable of targeting multiple infiltrative tumour foci intracranially".

Understanding the mechanism underlying brain tumour invasion is the first step in that process. Critical here are microRNAs (miRNAs), short (around 22 nucleotide) non-coding ribonucleic acid compounds that mediate the post-transcriptional silencing of a set of target genes. There is emerging evidence that miRNAs have a defining role in cancer initiation and progression. "Fifty per cent of miRNA genes map within cancer-associated genomic regions or fragile sties of chromosomes", Assoc Prof Wang notes, "providing a reasonable explanation for deregulated expression of miRNAs in various cancers". However, the roles of miRNAs in regulating the initial steps of cancer cell metastasis have not been well characterised.

In the human brain, miRNAs from the miR-376 cluster are subject to adenosine-to-inosine (A-to-I) RNA editing, an essential epigenetic mechanism that transforms the genomic information contained within RNA molecules. By sequencing these microRNAs, Assoc Prof Wang and his team found an association between overall A-to-I editing frequencies and the regulation of gliomas. The frequencies were reduced in gliomas, and in high-grade gliomas such as glioblastoma multiforme there was an accumulation of unedited miR-376a*. That accumulation correlated with the extent of invasive tumour spread, as measured by the magnetic resonance imaging of patients' brains. Using in vitro and orthotopic xenograft mouse models, the team also demonstrated that unedited miRNA-376a* promoted glioma cell migration and invasion, whereas edited miRNA-376a* suppressed them.

In short, a single mutation in miR-376a* affects the selection of its target genes and redirects its function from inhibiting to promoting glioma cell invasion. Assoc Prof Wang remarks that the "miRNA epigenetic classification of tumours is expected to better define subcategories of tumours with implications for diagnosis, treatment, and prognosis". The inherent reversibility of most epigenetic mechanisms, including A-to-I editing, certainly underscores their potential as targets for therapeutic intervention.

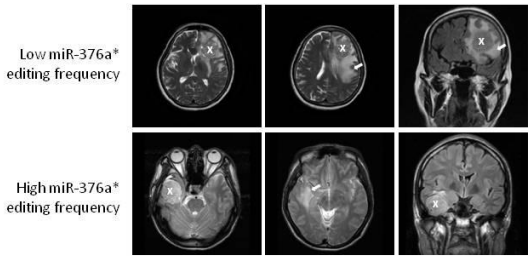

Figure 1. Frequency of miR-376a* editing and expression of its unedited form correlate with invasive glioma spread. Representative MRI scans of patients with gliomas with low or high editing frequency of miR-376a*. White cross indicates the main tumor mass and white arrow indicates region of invasive tumor spread.

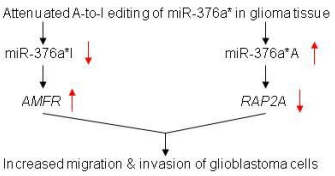

Figure 2. Roles of attenuated miR-376a* editing in regulation of glioma cell invasion and migration. Our findings indicate opposite roles of AMFR and RAP2A in regulating cell invasion, which are subject to epigenetic regulation by miR-376a*. When the A-to-I editing of miR-376a* is attenuated in glioblastoma, the accumulation of unedited miR-376a* (miR-376a*A) down-regulate RAP2A while a decreased level of edited miR-376a* (miR-376a*I/G) leads to up-regulation of AMFR, collectively resulting in increased migration and invasiveness of glioma cells.

Publication:

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