

2018

High miR-9 levels represent a novel prognostic biomarker to predict development of malignant meningioma

Baiz, D

<http://hdl.handle.net/10026.1/12316>

All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Please cite only the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.

High miR-9 levels represent a novel prognostic biomarker to predict development of malignant meningioma

Baiz D¹, Negroni C¹, Ferluga S¹, Ercolano E¹, Adams C¹ and CO Hanemann¹.

¹Plymouth University, Peninsula Schools of Medicine and Dentistry, the Institute of Translational and Stratified Medicine, the John Bull Building, Plymouth Science Park, Research Way, Plymouth UK, PL6 8BU

Introduction: Meningioma is the most common primary tumour affecting the central nervous system; it is classified as benign (WHO I, ~80%), atypical (WHO II, ~15-20%) and anaplastic/malignant (WHO III, ~1-3%). The 3-year recurrence rate in WHO I meningioma is estimated in about 50% and it is much greater in WHO II and III tumours. MicroRNAs (miRNAs) represent a large class of small RNAs driving regulation of gene expression at post-transcriptional level and playing a role in cell proliferation, differentiation, apoptosis and carcinogenesis. Several studies showed that miRNAs are involved in tumour progression and therefore proposed as diagnostic tools. Here, we evaluated miRNAs signature in meningioma to identify novel biomarkers of tumour progression.

Material and Methods: Meningioma (MN) specimens were collected from consented patients, according to the ethics. The 96-miRNA profiling was performed using the QuantimirTM Cancer MicroRNA qPCR Array (System Biosciences, UK) following the instructions of the supplier. Validation studies were achieved using TaqMan[®] MicroRNA reagents (Applied Biosystems). Bioinformatic analysis was done using the NormFinder software and *in silico* studies were performed using the following datasets for putative miRNA targets: TargetScanHuman7.1, DIANA TOOLS microT-CDS, mirDIP and the UTRdb tool. Probability (p) values were calculated using the Student's t-Test, led by the GraphPad Prism 5.01 ($p < 0.05 \pm \text{SEM}$).

Results and discussion: We established a new miRNA dataset by identifying six miRNA signatures ($p < 0.01$) differentially regulated in benign versus malignant meningioma cells (miR-9, -10b, -125b, -143, -145 and -199). Validation studies by qPCR confirmed that the miR-9 was upregulated in malignant KT21-MG1 cells (10.71 folds; Log₂ scale, $p = 0.0006$) and WHO III tissues (3.75 folds versus WHO I=0, Log₂ scale, $p = 0.044$). Finally, highly stringent *in silico* studies suggested that the miR-9 targets and downregulates the ubiquitin-protein ligase E3C (UBE3C), as confirmed by proteomic analysis in malignant KT21-MG1 and IOMM-Lee cells.

Conclusion: In this study, we identified the miR-9 as significantly upregulated in WHO III tumour-derived meningioma cells and tissues when compared to lower grades. Since miR-9 targets the ubiquitin-protein ligase E3C, involved in the ubiquitin-proteasome pathway and therefore regulating protein homeostasis, this protein, together with miR-9, could represent potential novel diagnostic and/or prognostic biomarkers in meningioma.