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P01.01 ECTOPIC EXPRESSION OF MICRORNA-1300 IN ADULT AND PAEDIATRIC GLIOMA CELLS INDUCES CYTOKINESIS FAILURE AND APOPTOSIS VIA ECT2

M. Boissinot, H. King, M. Adams, J. Higgins, L. P. Steele, H. Wurdak, J. Bond, D. C. Tomlinson, S. E. Lawler, S. C. Short

MicroRNAs are proving to be potent tumour suppressors in cancer. Many microRNAs are in pre-clinical and clinical validation.

A high-throughput screen was performed to identify microRNAs with potent anti-proliferative and/or pro-apoptotic effect in a panel of glioma cell lines. MicroRNA-1300 was identified as a potent pro-apoptotic candidate. Its effect was validated in U251 (adult) and KNS42 (paediatric) established cell lines as well as two newly established patient-derived glioma stem-like cell lines. Initial validation showed that microRNA-1300 is not usually expressed in glioma and that ectopic expression of a mimic of its mature form leads to cytokinesis failure followed by apoptosis. Further characterization indicated that this effect is mediated through its target ECT2, a GTP exchange factor responsible for the recruitment of RhoA at the cleavage furrow in mitosis.

In addition, we confirmed that normal cells surrounding the tumour are not affected by the expression of microRNA-1300 in a model of quiescent brain cells, thus excluding off-target cytotoxicity.

Investigation of the physiological interaction and role of microRNA-1300 and ECT2 showed that the expression of microRNA-1300 is normally restricted to megakaryopoiesis, during endomitosis, to allow for the formation of plurinuclear megakaryoblasts. This is consistent with the effect we observed on ectopic expression of microRNA-1300 in which glioma cells become binucleated following cell cycle arrest and apoptosis ensues.

In conclusion, microRNA-1300 was identified as a potent, cytotoxic microRNA with potential therapeutic effect in glioblastoma. Ectopic expression of a microRNA in an abnormal cellular context is a novel approach to microRNA therapeutics. Research is ongoing, aiming to optimise the use of microRNA-1300 in a pre-clinical setting and to assess its in vivo cytotoxicity alone and in combination with radiation.