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microRNA-449a acts as a master regulator of the brain tumour phenotype

Introduction: Combinations of genetic mutations in tumour initiating cells determine the phenotype of brain tumours. In our experimental model, deletion of both *Pten* and *p53* genes in the stem cells of murine subventricular zone (SVZ) gave rise to glial phenotype tumours, whereas deletion of *Rb* and *p53* generated predominantly primitive neuroectodermal tumours (PNET's) (1, 2). This suggests that a switch may exist that directs differentiation to glial or neural lineage and may depend on individual oncogenic signals. Here we aimed at identifying the role of microRNAs, strong post-transcriptional regulators, in determining the phenotypic characteristics of the brain tumour.

Material and methods: MicroRNA arrays were performed on solid brain tumours. Subsequent validation experiments were done with Neural stem cells cultures from *p53^{lox/lox}*; *Pten^{lox/lox}* or *p53^{lox/lox}*; *Rb^{lox/lox}* mice, recombined *in vitro* with adeno-cre. Allografts were generated by grafting the stem cells into to the brain of nude mice.

Results: We found that microRNA-449a is upregulated in experimental PNETs (tumours from *Rb/p53* grafted cells) and *in vitro* recombined cells with the same mutations. Inhibition of microRNA-449a in *Rb/p53* deficient cells increased invasiveness, proliferation and self-renewal. The mice with tumours generated from miR-449a inhibitor treated *Rb/p53* cells showed shorter survival and a phenotypic switch from PNET to glioma. The downstream targets of microRNA-449a revealed multiple signalling molecules involved in neurogenesis. The results were confirmed in human brain tumour tissues with PNET components.

Conclusions: Our study demonstrates that microRNA-449a is important in inhibiting growth and invasion of brain tumour-initiating cells and is a key regulator in sustaining PNET like phenotype of the brain tumour. The role of the downstream targets of this microRNA have been identified and are being validated.

References:

1. Jacques *et al.* *EMBO J* 2010; **29**:222-235
2. Henriquez *et al.* *Cancer Research* 2013; **73**:5834-5844