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miRNAs as novel therapeutic adjuvants for treating high-risk medulloblastoma

Medulloblastoma is the most common malignant brain cancer in children. Although long-term survival has improved in recent years, only a modest percentage of patients survive high-risk disease. The quality of life for those who survive is substantially reduced due to the high toxicity associated with the radiation and chemotherapy. Recently, in a large unbiased genomic screen, we discovered that specific microRNAs (miRNAs) can mediate drug sensitivity in c-myc amplified high-risk medulloblastoma. Our functional screen of ~1900 miRNAs identified a candidate miRNA that uniquely sensitized high-risk medulloblastoma to radiation as well as Vincristine (VCR), a chemotherapy drug routinely used as a combination therapy to treat medulloblastoma patients. Our studies revealed that the candidate miRNA may act as a potent tumor suppressor as it inhibited medulloblastoma stem cell self-renewal as well as growth, migration and invasion of c-myc amplified high-risk medulloblastoma. Interestingly, our preliminary results show that candidate miRNA overexpression resulted in defective mitotic spindles as well as an altered tubulin isotype profile. Notably, we discovered that candidate miRNA may directly regulate the expression and activity of genes including *HDAC1*, *EIF4E3* and *PTTG1IP* that we found to be highly expressed in medulloblastoma patients and are known to play important roles in microtubule dynamics, metaphase-anaphase transition and cell cycle regulation. Furthermore, we show that silencing of either of these target genes resulted in sensitization of c-myc amplified medullaoblastoam cells to VCR and/or radiation. These findings are highly significant, unexpected and innovative as this miRNA and its target genes are the first to be shown to affect therapeutic efficacy of VCR and radiation in c-myc amplified high-risk medulloblastoma. Recent miRNA-based clinical trials have begun to establish miRNA therapeutics as a feasible approach for treating diseases in general and cancer in particular. We believe that successful completion of this study will not only identify novel gene targets that may regulate radio- and chemo-sensitivity in high-risk medulloblastoma but will also set the stage for a NEW paradigm of treating high-risk medulloblastoma using miRNA therapeutics.

Biography

Manjeet Rao has completed his PhD from University of Delhi and Postdoctoral studies from MD Anderson Cancer Center, Houston, TX, USA. He is currently an Associate Professor at Greehey Children's Cancer Research Institute, University of Texas Health Science Center at San Antonio, USA. He has published more than 38 papers in reputed journals including *Cell, PNAS, Blood, Leukemia, Oncogene* and *Clinical Cancer Research*.

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