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Understanding the role of hypoxia regulated oncogenic microRNA-X in glioblastoma

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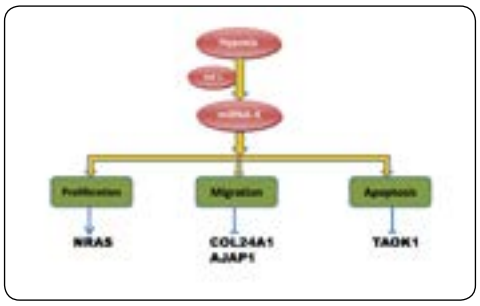
Glioblastoma (GBM) is the most common and aggressive malignant primary brain tumor in humans. Despite of advances in medical management of solid tumors, the mortality rates of GBM patients remain high, which urge for a better understanding of GBM pathogenesis and improvement in its therapeutic strategy. Hypoxia has been correlated with the aggressive form of glial tumors, their poor prognosis and resistance to various therapies. MicroRNAs (miRNAs) have emerged as key players in cellular transformation and tumorigenesis and have shown great potential for cancer diagnostics and therapeutics. The present study is based on our recently published deep sequencing technology based data showing alteration in the miRNA profile in GBM cell line U87MG in response to severe hypoxia. A total of 13 miRNAs were further validated by qRT-PCR to be hypoxia regulated in GBM cells. Among these, miRNA-X was found to be highly induced in response to hypoxia and also showed significant upregulation in GBM patients. The high expression of miRNA-X was shown to be associated with poor prognosis in GBM patients.We performed functional analyses of miRNA-X in GBM cell lines using both overexpression and inhibition approach. miRNA-X overexpression was shown to promote cellular proliferation, migration and colony formation and inhibit apoptosis in U87MG and A172 cell lines while miRNA-X inhibition using anti-miRNA-X showed opposite results suggesting oncogenic role of miRNA-X in GBM. We further identified targets of miRNA-X using a combination of bioinformatic and biochemical approaches. Notably, we found that miRNA-X not only down regulates tumor suppressor genes but may also be involved in up-regulating/stabilizing the levels of oncogenes. We further unveiled that NRAS, AJAP1, TAOK1 and COL24A1 are direct targets of miRNA-X. Overall, our work identifies novel role of hypoxia regulated miRNA in GBM and suggests their prognostic and therapeutic significance.



Recent Publications:

1. Agrawal, et al. (2014) Hypoxic signature of microRNAs in glioblastoma: insights from small RNA deep sequencing. BMC Genomics 15:686.
2. Ivan, et al. (2008) Hypoxia response and microRNAs: no longer two separate worlds. Journal of Cellular and Molecular Medicine 12:1426–1431.
3. Kulshreshtha, et al. (2007) A MicroRNA signature of hypoxia. Molecular And Cellular Biology 1859–1867.

Biography

Sonam Takkar is a PhD Scholar at Indian Institute of Technology, Delhi. Under the advisement of Dr. Ritu Kulshreshtha, her research is focused on unraveling the novel role of hypoxia regulated miRNA in GBM. Prior to joining IIT Delhi she has done MTech in Genetic Engineering from SRM University. Currently, she is working on identification and characterization of various hypoxia regulated miRNA in GBM; their gene targets and related pathways. Her passion is to develop miRNA-based biomarkers for predicting cancer risk, early detection, prognosis and response to therapeutic interventions.

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