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Small molecule modifiers of microRNA: In search of new therapeutics for cancer

Debasmita Mukhopadhyay, Nishant Jain, S Chandrasekhar and Manika Pal Bhadra
Indian Institute of Chemical Technology, India

Micro RNA are endogenous small non coding RNA with 20-22 nucleotide long that are transcribed from the chromosomal DNA. They exhibit their effect after getting partially attached to the cogent mRNA of a particular gene. Although there are numerous evidences which established that miRNa behave as onco genes as well as tumour suppressors, however there is lack of evidence in the role of miRNa on tumour metastasis. Here, it is shown anaza-flavanones group of compound containing an unnatural amino acid that negatively regulates mir-10b activity. MiR10b is predominantly expressed in metastatic breast cancer cell line, Pharmacological inhibitor of miR10b resulting in reducing tumour invasion and metastasis of breast carcinoma in vitro. Initially it was analysed for mir-10b levels in transfected mir-10b luciferase reporter gene construct in MDAMB-231 cell line in the presence of AZT-DMAD. It was observed that the cells treated with this compound have remarkably lower level of mir-10b using dual luciferase assay system. Further we checked the expression of different Epithetical – mesenchymal marker both in treated and untreated condition since EMT play an essential role in cancer metastasis. Notably inhibition of miR 10b expression by AZT-DMAD consequently reduces the expression of cell proliferation marker. Interestingly, over expression of miR10b in breast cancer cell line, exhibit very high level of angiogenesis and formation of new vasculature. It was shown decreased miR10b activity in cells treated with AZT-DMAD lowered angiogenesis. Expression of mir10b is induced by the transcriptional factor Twist1 which directly bind to the promoter of this miRNa. Hence it was tried to find out the expression of TWIST1 after treatment with this compound and surprisingly found that mir10b inhibition leads to TWIST1 down regulation as well as the pro metastatic gene RHOC and up regulation of HoxD10. These finding suggest that the aza Flavanononones specifically targets mir-10b by modulating its upstream transcriptional factor, which in turn reduces EMT marker, cell proliferation and decently inhibits the pro-metastatic gene, leading to reducing tumour cell invasion and metastasis.

Biography

Debasmita Mukhopadhyay is pursuing her PhD from Indian Institute of Chemical Technology, Hyderabad. She has been awarded as ICMR-SRF in the year 2013. She has published 5 papers in reputed international journals.

debasmitag2009@gmail.com