Aza-Flavanones as Small Molecule Inhibitors of MicroRNA-10b in MDA-MB-231 Breast Cancer Cells

Authors : Debasmita Mukhopadhyay, Manika Pal Bhadra

Abstract : MiRNAs contribute to oncogenesis either as tumor suppressors or oncogenes. Hence, discovery of miRNA-based therapeutics are imperative to ameliorate cancer. Modulation of miRNA maturation is accomplished via several therapeutic agents, including small molecules and oligonucleotides. Due to the attractive pharmacokinetic properties of small molecules over oligonucleotides, we set to identify small molecule inhibitors of a metastasis-inducing microRNA. Cytotoxicity profile of aza-flavanone C1 was analyzed in a panel of breast cancer cells employing the NCI-60 screen protocols. Flow cytometry, immunofluorescence and western blotting of apoptotic or EMT markers were performed to analyze the effect of C1. A dual luciferase assay unequivocally suggested that C1 repressed endogenous miR-10b in MDA-MB-231 cells. A derivative of azaflavanone C1 is shown as a strong inhibitor miR-10b. Blockade of miR-10b by C1 resulted in decreased expression of miR-10b targets in an aggressive breast cancer cell line model, MDA-MB-231. Abrogation of TWIST1, an EMT-inducing transcription factor also contributed to C1 mediated apoptosis. Moreover C1 exhibited a specific and selective down-regulation of miR-10b and did not function as a general inhibitor of miRNA biogenesis or other oncomiRs of breast carcinoma. Aza-flavanone congener C1 functions as a potent inhibitor of the metastasis-inducing microRNA, miR-10b. Our present study provides evidence for targeting metastasis-inducing microRNA, miR-10b with a derivative of Aza-flavanone. Better pharmacokinetic properties of small molecules place them as attractive agents compared to nucleic acids based therapies to target miRNA. Further work, in generating analogues based on aza-flavanone moieties will significantly improve the affinity of the small molecules to bind miR-10b. Finally, it is imperative to develop small molecules as novel miRNA-therapeutics in the fight against cancer.

Keywords : breast cancer, microRNA, metastasis, EMT

Conference Title : ICCST 2015 : International Conference on Cancer Science and Therapy

Conference Location : Singapore, Singapore **Conference Dates :** March 29-30, 2015