MIR PROFILING IDENTIFIES CDK6 DOWN-REGULATION AS A POTENTIAL MECHANISM OF ACQUIRED CISPLATIN RESISTANCE IN NON-SMALL CELL LUNG CARCINOMA


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Aim: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death. NSCLC systemic treatment usually includes platinum-based chemotherapeutic drugs. Resistance to these drugs is common and multi-factorial. We aimed to gain insight into the molecular mechanisms involved in platinum-resistance.

Methods: A set of NSCLC platinum resistant cell-lines was created from Calu6 and NCI-H23 cell lines. Cell viability was quantified by MTT assay. Differentially expressed micro RNAs (miRs) in these lines were identified by Affymetrix miR array. Potential genes targeted by these miRs were searched by TargetScan algorithm. miRs and mRNA levels were tested by real-time PCR.

Results: miR-145 was reproducibly elevated in all the resistant sub-lines tested within one of the experimental sets; however, modulation of miR-145 levels alone in these cells did not affect their response to cisplatin. A potential target of miR-145 is cyclin dependent kinase 6 (CDK6), an important regulator of cell proliferation. Both mRNA and protein levels of CDK6 are down regulated in the resistant sub-lines. An inhibitor of CDK4/6 (PD0332991) protected cells from cisplatin cytotoxicity.

Conclusions: We have identified a number of miRs differentially expressed in cisplatin-resistant cell lines including miR-145. A potential target of miR-145 is CDK6. Expression of CDK6 is down regulated in the resistant sub-lines, likely through multiple mechanisms that may include targeting by miRs. Inhibition of CDK6 antagonizes cisplatin-induced NSCLC cell cytotoxicity, suggesting that agents that inhibit CDK6 should be avoided during cisplatin therapy.

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