Big applications for a microRNA signature: the diagnostic, prognostic and predictive biomarker potential of a novel 5-miR signature associated with cisplatin resistant NSCLC

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Introduction:

MicroRNAs are a class of small non-coding RNAs that range in size from 19–25 nucleotides. They have been shown to regulate a number of processes within tumour biology, including metastasis, invasion and angiogenesis. More recently, miRNAs have been linked to chemoresistance in solid tumours, including lung cancer. Their role in cisplatin resistance and their potential as biomarkers has yet to be determined.

Methods:

MicroRNA expression within a panel of age-matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines was profiled and validated by qPCR. Significantly altered miRNAs within the CisR sublines were manipulated using antagomiRs and Pre-miRs and functional studies carried out in the presence and absence of cisplatin. To examine the translational relevance of these miRNAs, their expression was examined in a cohort of chemo-naïve patient-matched normal and lung tumour tissue and serum from NSCLC patients of different histologies. A xenograft model of cisplatin resistance was carried out in which 1×103 H460 PT or CisR cells were injected into 5–7 week old NOD/SCID mice. Tumours were harvested and formalin-fixed and paraffin embedded (FFPE). Expression of the 5-miR signature was analysed within FFPE sections and compared between PT and CisR tumours.

Results:

Validation revealed a 5-miR signature associated with cisplatin resistance (miR-30a-3p, miR-30b-5p, miR-30c-5p, miR- 34a-5p, miR-4286). Genetic manipulation did not alter cisplatin response. The signature displayed diagnostic and prognostic biomarker potential in tumour tissue. miR-4286 showed diagnostic potential in sera. Similarly to the cell line expression of the miRNAs, the miR-30 family members and miR-34a-5p were up-regulated in the CisR xenograft FFPE tissue relative to PT.

Conclusion:

A novel miRNA signature found to be associated with cisplatin resistance was identified in vitro, genetic manipulation of which did not alter response to cisplatin. The 5-miR

signature shows diagnostic, prognostic and predictive biomarker potential across a number of diagnostically relevant mediums. Disclosure: All authors have declared no conflicts of interest.