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Background

In the absence of a targetable mutation, cisplatin based chemotherapy is the backbone of NSCLC treatment. However, a diverse patient population combined with complex tumor heterogeneity is hampering its' clinical utility. Although intrinsic and acquired resistance to cisplatin is common, the mechanisms have not yet been fully elucidated. However, some studies have suggested that inflammatory pathways may play a key role in chemo-resistance. The aim of this project is to increase our understanding of inflammatory mediated cisplatin resistance in NSCLC.

Methods

A number of isogenic cell line models of NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma) cisplatin resistance were utilized to assess the role of inflammation in chemo-resistance. These included a sensitive parental cell line (PT) and a matched resistant subtype (CisR). The cell lines were screened for NFKB and a number of inflammatory mediators including chemokines and TLRs at the mRNA (RT-PCR/qPCR) and protein level (Western Blot/ELISA). A specific NFKB inhibitor, DHMEQ, and recombinant chemokines were employed to further characterize inflammatory pathways in PT and CisR cells in terms of cisplatin sensitivity, proliferation (BrdU ELISA), cellular viability (Cytell Cell Imaging System) and DNA damage response (Comet). An *in vivo* study was also completed using DHMEQ alone and in combination with cisplatin.

Results

A number of NFKB targets and responsive pathways are deregulated in CisR cells compared with their matched sensitive PT cell line. Amongst others, CCL2 and CCL5 were altered across all NSCLC subtypes. Preliminary data suggests that DHMEQ enhances cisplatin sensitivity in both PT and CisR cells, conversely recombinant chemokines elicit a protective effect. Additionally, DHMEQ treatment resulted in opposite effects on CCL2 and CCL5 mRNA levels in the PT and CisR cell lines. This may reflect an alternative pathway hierarchy within the cells. Further characterization is ongoing assessing chemokine specific inhibitors. Although, *in vivo* data suggests a trend of decreased tumor growth in the DHMEQ cohorts compared with vehicle control, the data was not significant. However, tumor samples appeared more necrotic with DHMEQ and are currently being characterized using IHC for necrosis and proliferation.

Conclusion

Targeting chemokines downstream of NFKB may provide a means to overcome inflammatory mediated acquired and intrinsic NSCLC chemo-resistance. Given the increased significance of immuno-oncology agents to harness the body's own immune system in the fight against cancer, these agents may also prove fruitful in re-sensitizing patients to chemotherapy.

Keywords

non-small cell lung cancer, inflammation, Chemokines, Cisplatin resistance