BACKGROUND

As immunotherapies are now used to treat a large proportion of NSCLC patients, defining mechanisms of immune resistance is critical.

Immune resistance may arise from extrinsic or intrinsic mechanisms of immune resistance. Previous work showed that acquisition of a more mesenchymal (MES) phenotype after EMT can be associated with an increased propensity to resist cytotoxic T lymphocytes (CTL) and Natural killer (NK) cells attacks (Terry S. et al. Oncolimunology 2017).

AXL, a member of the TAM receptor tyrosine kinase family is widely expressed human cancers and increasingly recognized for its role in drug resistance and immune suppression.

In this study, we asked whether AXL could impact on tumor resistance to cytotoxic immune effectors such as NK cells and Cytotoxic T Lymphocytes (CTLs).

RESULTS

Selective expression of AXL in MES lung carcinoma cells is associated with resistance to cell-mediated cytotoxicity

Treatment of AXL-hi MES and AXL-med lung carcinoma clones with AXL inhibitor results in increased susceptibility to NK and CTL-mediated lysis

Treatment of the AXL expressing MES carcinoma clones with the AXL inhibitor is accompanied by perturbation of certain NK-receptors-ligands

CONCLUSION

The results suggest that increased AXL expression in mesenchymal lung carcinoma correlates with increased cancer cell intrinsic resistance to both NK and CTL-mediated killing, and that small molecule AXL targeting can sensitize these cells to cytotoxic lymphocyte-mediated killing in a manner involving a novel molecular network comprising NF-κB activation, increased ICAM1 expression, and upregulation of ULBP1 expression coupled with MAPK inhibition. These results support AXL targeting to optimize immune response in NSCLC.