891 IMMUNE RELATED VULNERABILITIES OF NON-NEUROENDOCRINE SMALL CELL LUNG CANCER

Ryan Kowash*, Mingrui Zhu, Benjamin Drapkin, John Minna, Luc Girard, Esra Akbay. *UT Southwestern Medical Center, Dallas, TX, United States*

Background Small Cell Lung Cancer (SCLC) is primarily a neuroendocrine (NE) cancer, however there is a subtype of SCLC that displays non-neuroendocrine (non-NE) phenotype. This subtype displays a unique immune and metabolic signature. Specifically, immune related vulnerabilities of this subtype are increases in expression of MHC-I and natural killer (NK) cell activating ligands. We discovered that there are additional immune modulators differentially produced in this subtype such as *NT5E*. *NT5E* encodes for CD73. CD73 acts as an ectoenzyme and is involved in adenosine production within the tumor microenvironment. Accumulation of adenosine limits the function of T and NK cells. Our recent studies suggest targeting CD73 in combination with immune checkpoint blockade results in an additive effect through decreased adenosine production in Non Small Cell Lung Cancer. However, the role of CD73 is yet to be explored in SCLC.

Methods We analyzed expression of *NT5E* for both SCLC cell lines and patient derived xenograft (PDX) models. Expression of CD73 at the protein level was validated in mouse and human cell line models. Mouse and human SCLC cell lines were used in co-culture experiments. Syngeneic mouse models were utilized for *in vivo* experiments. Flow cytometry was used to analyze changes in the tumor microenvironment.

Results Non-NE SCLC cell lines and PDX's express significantly higher levels of CD73 compared to NE models. Co-cultures of tumor cells with NK cells demonstrated that SCLC's with increased NK cell activating ligands display increased response to NK cell killing. Blockade of CD73 further enhanced activation of cytotoxic T cells in peripheral blood mononuclear cell (PBMC) co-cultures. When combined with immune checkpoint blockade treatment, syngeneic tumor growth was inhibited in mice. Combination treatment resulted in significantly increased activated T cells and NK cells within the tumor microenvironment as well as changes in myeloid cell populations.

Conclusions Our results argue that increased NK cell activating ligands and CD73 inhibition is a potential therapeutic target for non-NE SCLC. Increased NK cell activating ligands makes non-NE SCLC more susceptible to NK cell killing compared to NE SCLC. CD73 inhibition in combination with immune checkpoint blockade resulted in decreased tumor growth. This response was attributed to increased T cell and NK cell populations within the tumor microenvironment.

Acknowledgements Mingrui Zhu, Luc Girard, John Minna, Benjamin Drapkin, Esra A Akbay

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0891