DIFFERENCES IN THE SUSCEPTIBILITY OF HUMAN SMALL CELL LUNG CANCER VARIANTS TO NK CELL-MEDIATED LYSIS CAN BE OVERCOME WITH THE ADDITION OF N803 (IL-15 SUPERAGONIST)

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Background: Small cell lung cancer (SCLC) is a highly aggressive tumor with a 5-year survival rate of less than 5%. Traditionally characterized as a neuroendocrine (NE) cancer, several subtypes have now been identified which vary in their phenotypic and transcriptional profiles. Classical NE tumors are molecularly defined as ASCL1+ or NEUROD1+ and exhibit an epithelial phenotype, expressing cytokeratin and E-cadherin (E-Cad). In contrast, non-classical variants express POU2F3 or YAP1 and are enriched in mesenchymal features, such as high levels of vimentin (Vim). Prior studies describe that non-NE variants of SCLC are less susceptible to chemotherapy and may arise via therapeutic selection. With the addition of immune checkpoint blockade to first-line chemotherapy for the treatment of advanced SCLC, understanding whether SCLC variants respond differently to immunotherapy is crucial.

Methods: We utilized a range of pre-clinical models to investigate whether molecular and phenotypic variants of SCLC differ in their susceptibility to immune-mediated lysis. Following extensive characterization at the RNA and protein levels for expression of ASCL1, NEUROD1, POU2F3, YAP1, epithelial E-Cad, mesenchymal Vim, and other markers of cell phenotype, a panel of cells including each variant subtype were selected for further study.

Results: Upon exposure to healthy donor effector NK cells, the more epithelial cells were highly susceptible to NK-mediated cytotoxicity while all mesenchymal SCLC cells remained highly refractory to NK-mediated lysis. This prompted us to investigate immunotherapy approaches such as the addition of N803, a mutant IL-15 superagonist, to improve the activation and proliferation of NK cells. In a xenograft model utilizing the mesenchymal YAP1+ H841 cell line subcutaneously implanted into nude mice devoid of all immune cells except for NK cells, we observed that the weekly administration of N803 resulted in a significant increase in the number of activated NK cells within the spleens of treated mice. Additionally, NK cells from treated mice produced significantly higher levels of IFN-gamma and granzyme B, resulting in a significant decrease in overall tumor burden.

Conclusions: Our data indicates that N803-activated NK cells effectively mediate lysis of SCLC across all variant types, including those previously completely refractory to traditional NK cell lysis. These results highlight the potential of N803 as a novel immune-based intervention for the treatment of all variants of SCLC.

Ethics Approval: PBMCs were obtained from healthy donors at the NIH Clinical Center Blood Bank (NCT00001846). All animal studies were approved and conducted in accordance with an IACUC-approved animal protocol (LTIB-57) with the approval the NIH/NCI Institutional Animal Care and Use Committee.

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