463 INVESTIGATING THE T CELL-INTRINSIC REGULATORY ROLE OF VISTA IN ANTI-TUMOR IMMUNITY

Cassandra Gilmour*, Yikun Wang, Sachin Patnaik, Sarah Stone, Li Wang. *Cleveland Clinic, Cleveland, OH, United States*

Background Cancer immunotherapies, specifically checkpoint blockade therapies, are extremely successful at treating subpopulations of specific cancers long term. The goal is to disrupt the negative regulation of T cells and restore cytotoxic abilities allowing killing of the cancer cells and formation of memory T cells. One major limitation to checkpoint blockade is that it is has limited response rate, one theory as to why this is the case, is that there are multiple non-redundant pathways of T cell suppression. In response to the heterogeneous and suppressive tumor microenvironment (TME), T cells may enter a dysfunctional state which results in the concurrent expression of many checkpoint proteins, altered metabolic state, and lack of cytotoxic abilities.[1, 2] One of the many checkpoint proteins which is expressed on these dysfunctional T cells and negatively regulates the T cell is V-domain Immunoglobulin Suppressor of T-cell Activation (VISTA). VISTA's expression on naïve CD4 T cells controls quiescence and peripheral tolerance, but VISTA's role on cytotoxic lymphocytes (CTL) populations in the TME is largely unknown.[3]

Methods Our studies explore VISTA's role on cytotoxic T cells in the TME in an antigen dependent and polyclonal manner using complementary in vivo models

Results Our results suggest that VISTA KO T cells proliferate more, persist longer, and maintain a more robust metabolic program which likely contributes to the observed reduced tumor burden and overall survival of the mouse. Additionally, our results indicate that genetic deletion of VISTA on T cells provide an advantage of protective immunity against a re-challenge of antigen compared to wildtype or naïvely challenged mice.

Conclusions These studies provide context to the mechanism by which VISTA contributes to the dysfunctional state of CTLs and reaffirms the value in studying VISTA on CTLs and developing VISTA blocking immunotherapies to broaden the scope in which checkpoint blockade immunotherapies are successful.

Acknowledgements Thank you to current and former members of the Wang lab whom I've inundated with questions and they so graciously answered: Hieu Ta, Dia Roy, Keman Zhang, and Jun Dong

REFERENCES

1. Blank CU, *et al*. Defining 'T cell exhaustion'. *Nature Reviews Immunology*, 2019. **19**(11): 665–674.
2. Yu Y-R, *et al*. Disturbed mitochondrial dynamics in CD8+ TILs reinforce T cell exhaustion. *Nature Immunology*, 2020. **21**(12): 1540–1551.
3. ElTanbouly MA, *et al*., VISTA is a checkpoint regulator for naïve T cell quiescence and peripheral tolerance. *Science*, 2020. **367**(6475): eaay0524.

Ethics Approval All human data and animal work was collected analyzed and presented in accordance with Cleveland Clinic's IRB and ethics committee standards.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0463