INVESTIGATING VISTA'S ROLE INTRINSIC TO T CELLS IN THE TUMOR MICROENVIRONMENT

Cassandra Gilmour*, Li Wang, Juan Dong, Sarah Stone, Keman Zhang, Hieu Ta. *Cleveland Clinic Foundation, Cleveland, OH, USA*

Background Cancer immunotherapies, specifically checkpoint blockade therapies, have demonstrated clinical importance for long term patient survival. One of the major limitations to checkpoint blockade therapies, is the low response rate: ~30% with anti-CTLA4 and anti-PD1 treatment. This may be due to heterogeneity of the patients' immune system and the tumor microenvironment including T cell inhibitions. There is a clear need to study this phenomenon and develop additional therapies for long term survival to include a broad range of patients. V-domain Immunoglobulin Suppressor of T-cell Activation (VISTA) is a suppressive protein expressed on many cell types in the tumor microenvironment including cytotoxic T cells. VISTA's role on T cells has been described as maintaining quiescence and peripheral tolerance in a graft vs host disease model, but is not fully understood in context of the tumor microenvironment.

Methods We use a series of in vivo experiments, including T cell specific VISTA knock outs, to understand the role of VISTA on T cells in the tumor microenvironment.

Results Here we show a series of in vivo experiments that suggest VISTA has a potent intrinsic role on T cells and therefore anti-tumor immunity. Using a T cell specific VISTA knock out, our results suggest that the absence of VISTA on T cells in combination with anti-CTLA4 and vaccine is a very powerful tumor suppressor compared to vaccine and anti-CTLA4 treatment alone. These results also indicate that the absence of VISTA alters the phenotype of cytotoxic T cells in several ways including the production of inflammatory cytokines.

Conclusions Our preliminary data provides foundation to study VISTA's role intrinsic to T cells in the tumor microenvironment and how disrupting VISTA's influence intrinsic to T cells may be advantageous for anti-tumor immunity and long term patient survival.

Ethics Approval All in vivo studies were reviewed and approved by Institutional Animal Care and Use Committee (Approval number 2019–2142).

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