T CELL INTRINSIC CASPASE 1 SIGNALING NEGATIVELY REGULATES T CELL ANTI-TUMOR RESPONSE

Young Kim, Michael Korner, Cara Lang*. *Vanderbilt University, Antioch, TN, United States*

Background The inflammasome is a multi-protein signaling pathway in immune and epithelial cells that is important for activation of the innate immune system and protection from pathogens. This pathway is well characterized in myeloid cell populations, however the T cell intrinsic effects of the inflammasome are not well understood.

Methods In this study we utilize an inflammasome null mouse model to investigate the functional and phenotypic differences in inflammasome null and wildtype T cells. We utilize a whole cell vaccine against B16 mouse tumors to generate B16 tumor antigen specific T cells. In addition, we utilize clinically relevant PD-1 inhibitory antibodies to model checkpoint inhibition with inflammasome null T cells.

Results Here we show that the inflammasome is expressed and activated in tumor infiltrating T cells in both humans and mice. We find that inflammasome null T cells have an altered phenotype causing them to become more proliferative and increase killing capacity. In addition, caspase 1 null T cells are present in the TME at a greater frequency than wildtype T cells. We also show that caspase 1 knockout T cells have higher checkpoint expression, most notably an increase in PD-1 expression, and combination caspase 1 and PD-1 blockade results in a significant reduction in tumor burden.

Conclusions Therefore, we propose that T cell intrinsic inflammasome signaling acts as a negative regulator to inhibit T cell activation and cytotoxicity. Together our findings reveal the inflammasome as an attractive pathway that can be targeted in combination with checkpoint blockade therapies to improve anti-tumor T cell responses.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.648>