EXTRAFOLLICULAR EXPANSION AND DIFFERENTIATION OF B CELLS DRIVES ANTI-TUMOR RESPONSES IN METASTATIC CANCER

Noor Nader*, Dongyan Liu, Hye Mi Kim, Ayana Ruffin, Xiaron Zhang, Daniel Dunlap, Roy Semaan, Adam Soloff, Tullia Bruno. University of Pittsburgh, Pittsburgh, PA, United States; Tsinghua University, Beijing, China

Background Recent studies have demonstrated that B cell infiltration in patients with primary tumors is associated with increased survival and superior response to immune checkpoint blockade (ICB). Further, B cells play a significant role in the tumor microenvironment, such as the production of tumor-specific antibodies, antigen presentation, modulation of the cellular immune response by the production of specific cytokines, and formation of tertiary lymphoid structures (TLS). One knowledge gap in the field is determining how B cells function within microenvironments that don’t have TLS, specifically in metastatic spaces that occur because of a primary tumor. Malignant pleural effusions (MPEs) are metastatic microenvironments that are marked by the accumulation of interstitial fluid and the infiltration of tumor and immune cells into the pleural space of the lung of patients with advanced disease. Currently, there is no treatment for patients with MPE; thus, there is a need to improve our understanding of the complete MPE microenvironment. B cells highly infiltrate MPE, and antibody accumulation is significant in this space. Thus, our studies have geared to functionally interrogate MPE B cells to better understand how to target B cells in metastatic disease.

Methods We aimed to assess B cell subsets in MPEs and correlated these subsets with the initial primary tumors of origin for patients with benign and MPE fluids. Specifically, we compared the infiltration of memory and naïve B cells within these patients, antibody isotype and production in the paired fluids, antigen specificity of the antibodies, and differentiation of B cells in the presence or absence of MPE fluid. When cellually possible, we also interrogated antigen presentation by B cells subsets to CD4+ and CD8+ T cells.

Results We observed increased levels of naïve B cells in MPE compared to benign fluids and a high level of double negative 3 (DN3) memory B cells, suggesting potential extrafollicular B cell differentiation in the MPE microenvironment. Furthermore, we quantified tumor antigen-specific IgG antibodies in MPE fluid and matched plasma reactive to extracellular antigens of breast and lung tumor cell lines. Moreover, we determined that MPE-associated B cells are often superior to professional antigen-presenting cells (APCs) at educating CD4+ T cells.

Conclusions Understanding B cell composition and function in metastatic spaces is critical for engineering future immunotherapies. Here we highlight B cells in metastasis as a potential immunotherapeutic target given increased extrafollicular B cell expansion and differentiation into tumor antigen-specific plasmablast in MPE.