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The Neuroblastoma Anti-Tumor Immune Response: Macrophage Modulation by Amyloid Precursor-Like Protein 2

Gabrielle L. Brumfield,[1,2] Shelby M. Knoche,[1,2] Alaina C. Larson,[1,2] Brittany Poelaert,[1,2] Benjamin T. Goetz,[1,2] Poomy Pandey,[1,2] Donald W. Coulter,[2,3,4] and Joyce C. Solheim[1,2]

[1]Eppley Institute, UNMC, Omaha, NE; [2]Fred & Pamela Buffett Cancer Center, UNMC, Omaha, NE; [3]Department of Pediatrics, UNMC, Omaha, NE; [4]Children's Hospital & Medical Center, Omaha, NE

Background: Neuroblastoma (NB), a cancer of immature sympathetic ganglion cells, is responsible for approximately 15% of cancer-associated deaths in the pediatric population. Macrophages have diverse functions in the anti-cancer response, either enhancing immune responsiveness (pro-inflammatory macrophages) or inducing tumor tolerance (anti-inflammatory macrophages). Increased infiltration of anti-inflammatory macrophages is observed in advanced stage NB, leading to a need for identification of factors that influence anti-inflammatory macrophage development. My preliminary findings associate the anti-inflammatory macrophage phenotype with higher expression of amyloid precursor-like protein 2 (APLP2), a member of the amyloid precursor protein (APP) family. In tumors, my laboratory has shown that APLP2 expression enhances cancer cell migration and reduces surface levels of major histocompatibility complex (MHC) class I, a T cell-activating molecule. These phenotypes (i.e., increased migration and lowered MHC expression) are also characteristic of anti-inflammatory macrophages, consistent with possible functional roles of APLP2 in tumor-associated anti-inflammatory macrophages.

Significance of Problem: High-risk NB patients over 18 months of age currently face an approximate 50% survival rate. Identification of factors to enhance pro-inflammatory macrophage activity and inhibit anti-inflammatory macrophage development and function within tumors has potential to reduce morbidity and high mortality associated with NB.

Hypothesis: The central hypothesis of this study is that APLP2 promotes an immunosuppressive phenotype in NB by affecting macrophage reactivity.

Experimental Design: Primary murine bone marrow-derived macrophages and U937 monocyte-like cells were analyzed by flow cytometry and western blotting for APLP2 expression and phenotypic shifts post stimulus (pro- and anti-inflammatory cytokines, NB cell-conditioned media, PMA). APLP2-knockout mice were generated through breeding of Aplp2 flox-flox mice with mice expressing Cre recombinase under the ubiquitously expressed viral Ella promoter. Functional markers in bone marrow-derived macrophages of these mice were observed by flow cytometry following cytokine treatment.

Results: Macrophage treatment with NB-conditioned media induces an anti-inflammatory phenotype. These anti-inflammatory macrophages are associated with increased APLP2 expression compared to pro-inflammatory macrophages, and upregulated APLP2 expression is also observed in a model of monocyte-to-macrophage transition.

Conclusions: The aggressive and refractory nature of NB invokes the need for more effective therapeutics, developed in part through mechanistic understanding of the disease process. We anticipate that identifying the influence of APLP2 in NB-reactive macrophages will contribute to future understanding of macrophage physiology and identification of a therapeutic target for reduction of morbidity and mortality from this pediatric cancer.