Suppression of B lymphopoiesis by myeloid-derived suppressor cells in tumor-bearing mice

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Rationale: Myeloid-derived suppressor cells (MDSCs) have been well established as regulators of anti-tumor immunity. MDSCs modulate amino acid metabolism in the tumor microenvironment and suppress T-cell function. However, it is less clear whether MDSCs regulate B-cell responses during tumor progression.

Methods: Using a syngeneic orthotopic model for lung cancer with murine Lewis Lung Carcinoma cells, we evaluated B-cell subsets in tumor bearing mice by multi parameter flow cytometry. The amount of serum IgG or IL-7 was determined by ELSIA. Phospho-STAT5 and total STAT5 were detected by immunoblotting. To investigate MDSC-mediated suppression of B cell lymphopoiesis, we adoptively transferred MDSCs derived from bone marrow of CD45.2+ tumor bearing mice intratibially into congenic CD45.1+ mice. B-cell subsets in recipient mice at day 7 post MDSC transfer were enumerated as above. In vitro B-cell inhibitory assay was performed by co-culturing CFSE-labeled pre-activated splenocytes with MDSCs purified from bone marrow of tumor-bearing mice at a ratio of 1:1 in the absence or presence of arginase inhibitor nor-NOHA (20 µM), iNOS inhibitor 1400W (500 nM) or IDO inhibitor 1-D-MT (1 mM) for 48 hours. The percentage of CD19+CFSElow cells (proliferating cells) was determined by FACS analysis.

Results: Percentages and absolute numbers of Pro-, Pre- and mature B-cells were reduced in bone marrow (BM) of tumor bearing mice. Moreover, percentage and absolute number of follicular B cells were reduced, while immature B-cells increased in the spleen of tumor bearing mice. Levels of serum IgG were reduced in tumor-bearing mice. Furthermore, IL-7 and downstream STAT-5 signaling were impaired in tumor bearing mice. Transfer of BM-derived MDSCs from tumor bearing mice into congenic recipients resulted in significant reduction in both percentages and absolute numbers of immature and mature B-cells in peripheral blood of recipient mice. Pre-B cells and immature B-cells also decreased in BM of MDSC transferred recipients. Additionally, MDSCs suppress B-cell proliferation and IgG production by B-cells in an arginase and iNOS dependent but IDO independent manner.

Conclusions: In the present study, we demonstrate that B-cell differentiation in vivo is impaired in the BM and spleen of mice with lung cancer. Adoptive transfer studies with congenic mice demonstrate that MDSCs derived from Lewis Lung Carcinoma bearing mice may suppress B-cell differentiation in tumor naive mice. These results together suggest that tumor-related MDSCs may potentially regulate humoral immune responses to promote tumor survival.

Biography
Jessy S Deshane is a pulmonary Immunologist with expertise in immune regulation in asthma. She investigates myeloid-derived regulatory cell biology and free radical mechanisms that regulate their differentiation and function. She pioneered these investigations both in mouse models and human asthma. She has authored 46 peer-reviewed publications, including high impact journals like Journal of Experimental Medicine, Journal of Clinical Investigations, Journal of Allergy and Clinical Immunology, Immunity and Cancer Research. She serves on the Editorial Boards for the journals Allergy and American Journal of Respiratory Cell and Molecular Biology and serves on grant review committees.