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Indoleamine 2,3-dioxygenase regulates anti-tumor immunity in lung cancer by metabolic reprogramming of immune cells

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Introduction & Aim: Myeloid derived suppressor cells (MDSCs) are major contributors of immunosuppression by inducing oxidative stress and by modulating amino acid metabolism. Indoleamine 2,3-dioxygenase (IDO) is a key regulator of tryptophan (Trp) metabolism. Poor prognosis in lung cancer patients is associated with elevated IDO expression and activity. We have previously shown that a combination strategy of gemcitabine and a superoxide dismutase mimetic promoted anti-tumor immunity by enhancing metabolism of CD8⁺ memory T cells and prolonging survival in mice with lung cancer. In this study, we aim to elucidate how modulation of IDO pathway alters metabolic signaling in the tumor microenvironment (TME) and influence mitochondrial dynamics to promote long term immunity against lung cancer.

Methods: Lewis lung carcinoma cells were injected by intracardiac route into wild type (WT) and IDO^{-/-} mice. We assessed tumor burden, infiltration of MDSCs and CD8⁺ T cells by flow cytometry. Protein analyses of metabolic signaling pathways were performed on whole tissue and sorted cell lysates. Peripheral blood samples from Stage III–IV lung cancer patients and healthy normal relatives were used to measure serum IDO activity and percent circulating MDSCs.

Results: Circulating human MDSCs and serum IDO activity correlated with lung cancer. In a preclinical lung cancer mouse model, MDSCs were the significant contributors of IDO in the TME. Combination therapy targeted IDO signaling, specifically in MDSCs, tumor cells, and CD8⁺ T cells infiltrating the TME. Deficiency of IDO caused significant reduction in tumor burden, tumor-infiltrating MDSCs, GM-CSF, MDSC survival and infiltration of programmed death receptor-1 (PD-1)-expressing CD8⁺ T cells compared to controls. IDO^{-/-} MDSCs downregulated nutrient-sensing AMP-activated protein kinase (AMPK) activity, but IDO^{-/-} CD8⁺ T cells showed AMPK activation associated with enhanced effector function. Additionally, our studies showed that IDO pathway directly modulated mitochondrial dynamics to enhance memory T cell response.

Conclusions: Our study revealed a novel role of IDO in regulation of AMPK activation, distinct from Trp sufficiency and deficiency signaling. These data also provide mechanistic evidence that a combination treatment of gemcitabine and a SOD mimetic can metabolically reprogram the cellular components of the TME including suppressor cells, effector T cells, and tumor cells.

Biography

Jessy S Deshane is currently an Associate Professor of Medicine at University of Alabama at Birmingham. Her work is focused on immune regulation by myeloid-derived regulatory cells (MDRCs) in chronic inflammatory lung diseases. Her team has recently identified and characterized free radical producing myeloid-lineage cells as master regulators of allergic airway inflammation. She is currently investigating the novel hypothesis that MDRCs can produce neo-antigens that trigger dysregulated immune responses in asthma.

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