

POSTER PRESENTATION

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IFN γ -induced PD-L1 expression is JAK2 but not JAK1 dependent and its inhibition enhances NK-cetuximab mediated ADCC of HNSCC cells

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Programmed death ligand 1 (PD-L1) is an immunosuppressive molecule expressed by many cancer types, including a large proportion of head and neck cancers (HNC), and ligation of its receptor, programmed death 1 (PD-1), induces exhaustion of effector T cells. It has been shown that interferon gamma (IFN γ) induces PD-L1 expression in many cancer types including glioblastoma, melanoma, lung and kidney cancer. Importantly, the stimuli and mechanism for PD-L1 upregulation in HNC cells are not well characterized. IFN γ signals through Janus Kinase 1/2 (JAK1/2) heterodimer complex and mediates signal transducer and activator of transcription 1 (STAT1) phosphorylation, leading to type I cytokine expression, upregulation of antigen presentation, and tumor cell recognition by cytolytic T lymphocytes (CTL). We investigated basal PD-L1 expression and the mechanism by which IFN γ signaling upregulates PD-L1 in HNC cells including dependence on JAK/STAT pathway. We observed that IFN γ signaling increased PD-L1 expression in a JAK2 but not JAK1 dependent fashion. In addition, interferon alpha (IFN α), which signals via JAK1/TYK2 did not upregulate PD-L1 expression while still upregulated HLA class I. Specific JAK2 inhibition downregulated NK cell-derived IFN γ induced PD-L1 expression and enhanced cetuximab mediated ADCC. Our data suggest a crucial role for JAK2/STAT1 in IFN γ mediated PD-L1 upregulation. JAK2 inhibition provides a promising strategy to increase tumor cell lysis through maintaining HLA class I while suppressing tumor cell expressed PD-L1 in combination with anti-EGFR cetuximab therapy.

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