

Programmed death ligand 1 reverse signaling in dermal dendritic cells promotes dendritic cell migration required for skin immunity.

Erin D. Lucas (PhD., GS)^{1,2}, Johnathon B. Schafer¹, Jen Matsuda³, Madison Kraus², Matt A. Burchill² and Beth A. Tamburini^{1,2}.

University of Colorado Anschutz Medical Campus, School of Medicine, Department of Medicine: Division of Gastroenterology and Hepatology¹ and Department of Immunology and Microbiology², Aurora, CO. National Jewish Health Center for Genomics³, Denver, CO.

Abstract

While the function of extracellular region of programmed death ligand 1 (PD-L1) through its interactions with PD-1 on T cells is well studied, little is understood regarding the intracellular domain of PD-L1. Here, we outline a major role for PD-L1 intracellular signaling in the control of dendritic cell (DC) migration from the skin to the draining lymph node (dLN). Using a mutant mouse model, we identify a TSS signaling motif within the intracellular domain of PD-L1. The TSS motif proves critical for chemokine mediated DC migration to the dLN during inflammation. This loss of DC migration, in the PD-L1 TSS mutant, leads to a significant decline in T cell priming when DC trafficking is required for antigen delivery to the dLN. Finally, the TSS motif is required for chemokine receptor signaling downstream of the Gα subunit of the heterotrimeric G protein complex, ERK phosphorylation and actin polymerization in DCs.

Figure 1. Loss of PD-L1 impairs dendritic cell accumulation in the draining lymph node

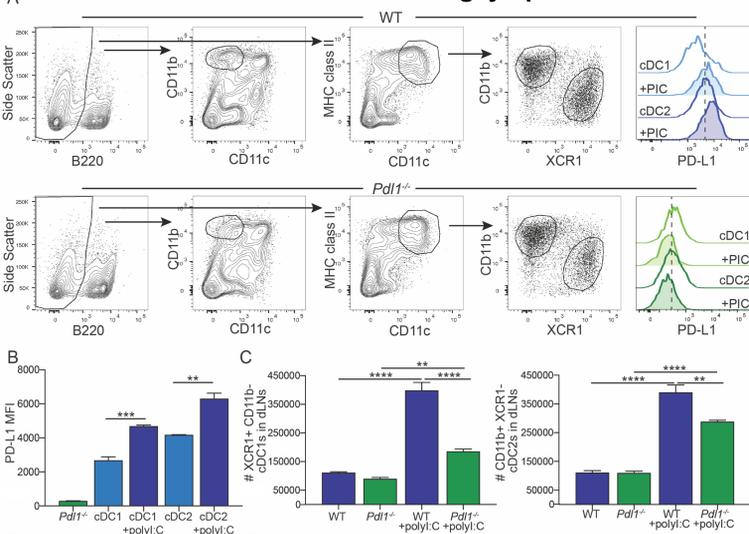


Figure 2. Loss of PD-L1 on dendritic cells impairs migration to the lymph node

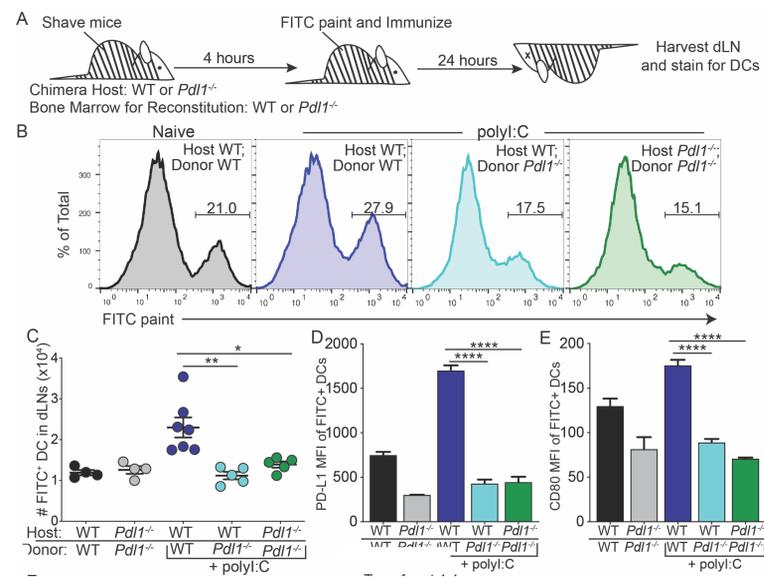


Figure 3. Mutation of three amino acids in the cytoplasmic tail of PD-L1 leads to impaired dendritic cell migration during an immune responses

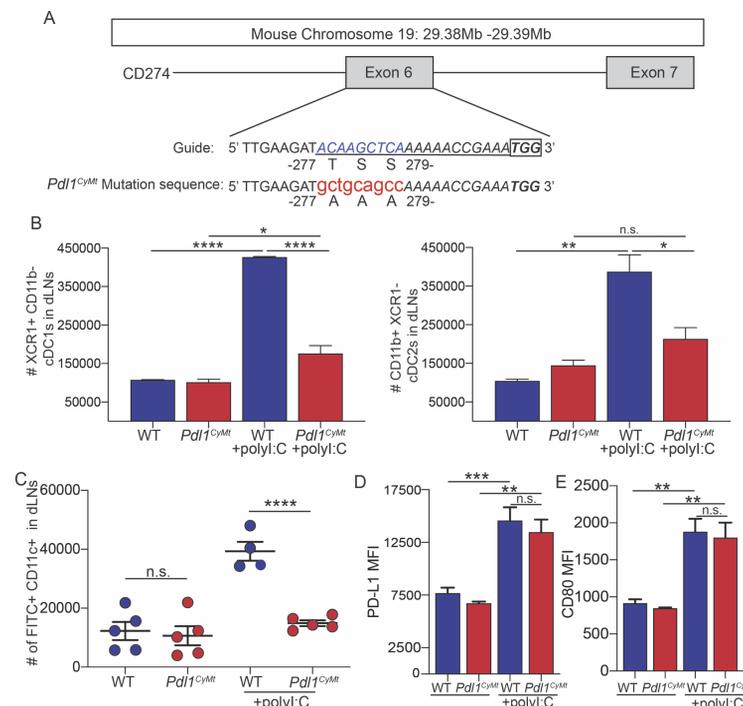


Figure 4. T cell responses to a non-draining antigen are impaired following loss of PD-L1 reverse signaling.

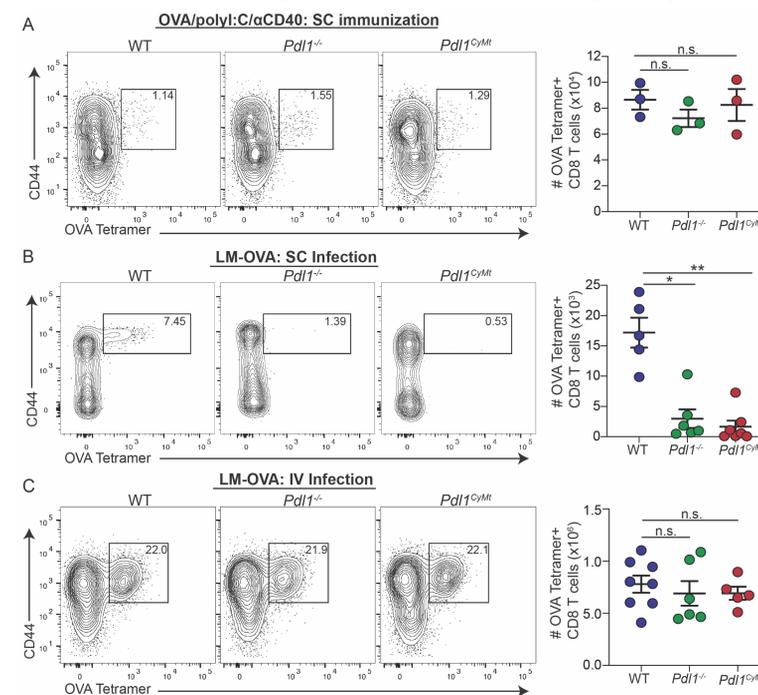


Figure 5. Chemokine mediated dendritic cell migration is impaired following loss of PD-L1 reverse signaling

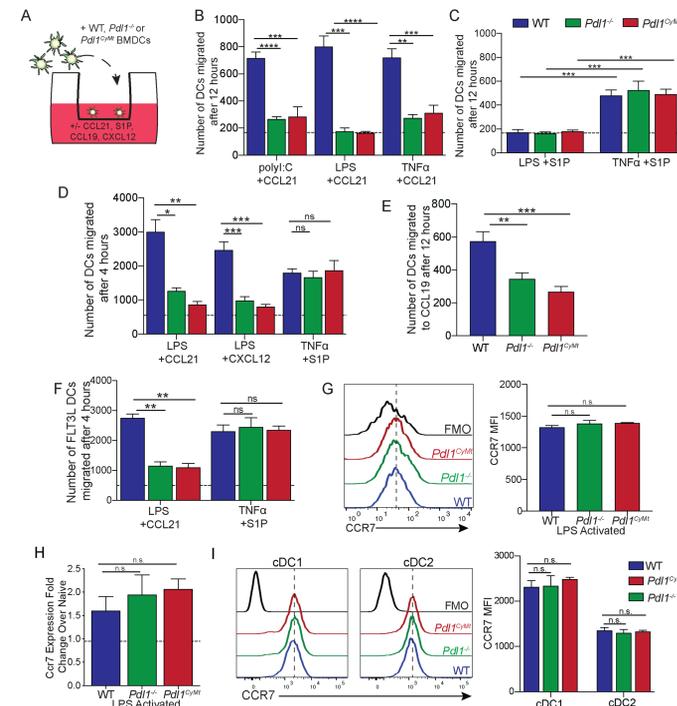


Figure 6. Chemokine signaling downstream of the Gα subunit GPCR signaling is disrupted following loss of PD-L1 reverse signaling.

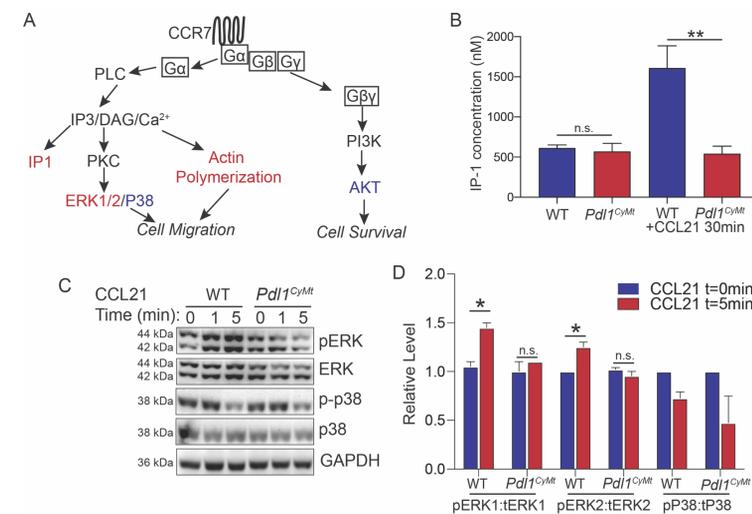


Figure 7. Loss of PD-L1 reverse signaling in dendritic cells impairs chemokine signaling leading to impaired immune responses.

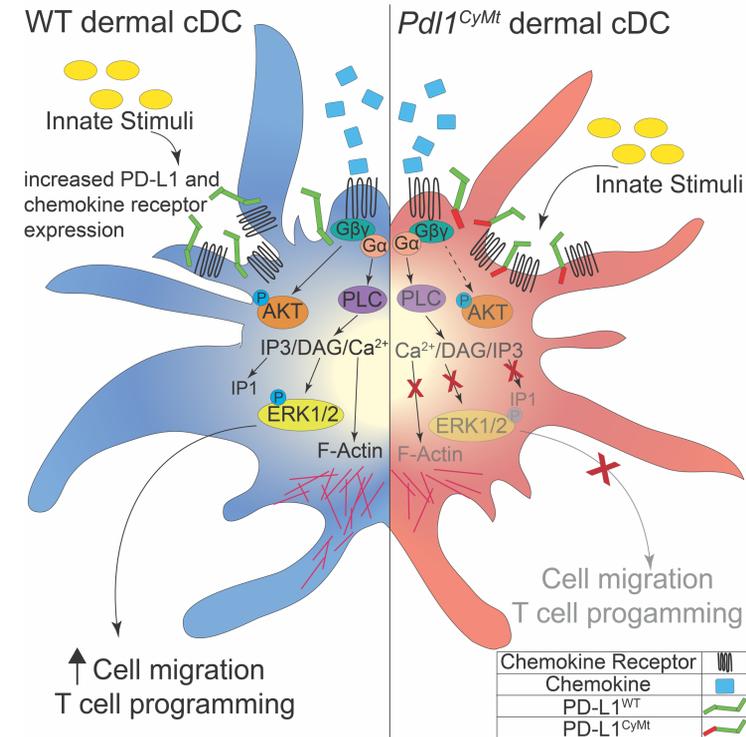


Figure 8. Future Questions: How does PD-L1 antibody blockade impact dendritic cell migration?

