Programmed death ligand-1 is an endogenous pain inhibitor and silences mouse and human nociceptive neurons

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Abstract: Objective Mounting evidences suggests that cancers, such as melanoma express the checkpoint inhibitory protein PD-L1, which can suppress T cell function and induce immune tolerance via its receptor PD-1. However, it is unclear whether and how the PD-L1/PD-1 pathway can regulate pain sensitivity via non-immune modulation such as neuronal modulation. In this study, we assessed the expression and function of PD-1 in primary sensory neurons of mouse and human DRG. Methods Adult mice (males, 8-10 weeks) were used for behavioral and biochemical studies. Pd1 knockout mice with C57BL/6 background were purchased from the Jackson laboratory. Non-diseased human DRGs were obtained from donors through NDRI with permission of exemption from Duke IRB. Cell culture, models of pain and cancer, in situ hybridization, immunohistochemistry, ELISA, RT-PCR, Western blot, patch clamp recordings and behavioral analysis were used in this experiment. Results We find that PD-L1 is produced by melanoma and normal neural tissues including dorsal root ganglia (DRG) and acts as a
Intraplantar injection of PD-L1 evokes analgesia in naïve mice, whereas PD-L1 neutralization or PD-1 blockade induces mechanical allodynia. PD-1 activation in DRG nociceptive neurons by PD-L1 induces SHP-1 phosphorylation, inhibits sodium channels, and causes hyperpolarization through activation of TREK2 K+ channels. PD-L1 potently suppresses excitability of mouse and human DRG nociceptive neurons. Inoculation of B16 melanoma cells induces profound skin cancer lesion and increases serum PD-L1 levels but does not cause cancer pain. Remarkably, blocking PD-L1 or PD-1 elicits spontaneous pain and mechanical allodynia in melanoma-bearing hindpaw. **Conclusion** Our findings identify PD-L1 as a novel endogenous pain inhibitor that silences nociceptive neurons and masks melanoma-induced pain.

**Keywords:** Programmed death ligand-1, inhibit, pain, melanoma