Programmed Death-ligand 1 downregulates TRPV1 function in Dorsal root ganglion neurons and alleviates mice bone cancer pain

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Abstract:

Objective

Cancer is the leading cause of death worldwide, accounting for about 13% of all death according to the report from the World Health Organization. Advanced cancers are easy to spread to bone, causing cancer induced bone pain, which is unbearable.

Transient receptor potential vanilloid 1 (TRPV1) is a non-selective cation channel which is mainly expressed in small-diameter dorsal root ganglion (DRG) neurons. TRPV1 on the peripheral nociceptors is considered to act as transducers and molecular integrators of peripheral nociceptive stimuli, which is known to play an important role in inflammatory pain, neuropathic pain, and bone cancer pain.

The occurrence and metastasis of tumor has a close relationship with tumor microenvironment. Recent evidence applied that nerve-cancer cell interaction promote tumor progression. Mounting evidences suggest that a lot of cancers produce programmed death-ligand 1 (PD-L1) to suppress immunity via interaction with PD-1 receptor expressed on T cells and then modulating protein tyrosine phosphatase such as SHP1. Blocking PD-L1/PD1 pathway has been a promising immunotherapy with the goal to enhance the host’s own immune anticancer response. However, pain is
one of the major side effects of PD-L1/PD-1 immune therapy in cancer patients. In this research, we focus on the topic that whether PD-L1/PD1 pathway could modulate nociceptor activities.

**Methods** Bone cancer pain model was established by injecting Lewis lung carcinoma cells into the tibia in mice. By means of immunohistochemistry, western blotting and in situ hybridization, the expression level of PD-L1, PD1, SHP-1 and TRPV1 was detected. The development of pain behavior (mechanical allodynia and thermal hyperalgesia) was observed in wild-type mice, cancer mice and TRPV1 knockout mice. Whole cell patch-clamp recordings and Calcium imaging experiment displayed to explore the function of TRPV1.

**Results** (1) PD-L1 alleviates mice bone cancer pain. (2) PD-1 receptor is expressed in primary sensory neurons in mouse DRGs and alleviates mice bone cancer pain by inhibiting the current of TRPV1. (3) PD-L1/PD1 pathway down-regulated TRPV1 function by activating the tyrosine-phosphorilation of SHP1 in DRG neurons.

**Conclusion** In our study, we found that PD-L1 down-regulated TRPV1 function in cancer mice and alleviates mice bone cancer pain.

**Keywords:** Programmed Death 1; Dorsal Root Ganglion; Transient Receptor Potential Vanilloid 1; Src homology region 2 domain-containing phosphatase-1; Bone cancer pain