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Editorial

The analgesic effect of programmed cell death protein-1

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In the last issue of the Korean Journal of Pain, an experimental research paper about the heparanase and cancer pain progression was presented [1]. Heparanase treatment aggravated mechanical allodynia, cold response, and spontaneous pain. Additionally, the contents of inflammatory cytokines (TNF-α, NF-κB, IL-1β, and IL-6) was increased, and programmed death-ligand 1 (PD-L1) level was decreased in tumor tissue. Inversely, the heparanase inhibitor (SST0001) exhibited opposite results [1].

Programmed cell death protein 1, also known as PD-1, is a type I transmembrane glycoprotein and a cell surface receptor. PD-1 is broadly presented on cytotoxic T cells, regulatory T cells, B cells, natural killer cells, microglia, macrophages, and certain types of neurons [2–4].

PD-1 has a role in suppressing the inflammatory actions of T cells. Therefore, the immune system is downregulated, self-tolerance is promoted, autoimmune diseases are attenuated, and killing actions against cancer cells by the immune system could be prevented [5].

PD-1 is an essential and negatively acting regulator related to diverse biological effects and diseases, such as cancer immunotherapy, brain tumors, Alzheimer's disease, stroke, multiple sclerosis and cognitive dysfunctions [6,7].

PD-1 signaling modulates synaptic plasticity, synaptic transmission, and neuronal excitability in neurons [2]. The neuronal signaling of PD-1 regulates pain by modulating dephosphorylating transient receptor potential subtype V1 (TRPV1) [8], GABAergic neurotransmission [4], and sodium/potassium channels [3]. In an experiment with *Pd1* knockout mice, *Pd1* knockout mice were more sensitive to pain stimulation than wild type mice, and it presented that PD-1 performs a crucial role in the modulation of pain [3]. Additionally, the activation of PD-1 signaling by PD-L1 is related to the regulations of μ-opioid receptor signals in the nociceptive neurons, and it enhances the antinociceptive actions of morphine [9]. Therefore, small molecular peptides targeting PD-1 could be an alternative medicine for treating chronic pain.

On the other hand, PD-1 inhibitors, a newly developed class of anticancer medicine that block PD-1, could activate the immune system to attack cancer cells and could be used to treat special types of cancers [5]. For example, Pembrolizumab is a humanized IgG4 isotype antibody, and it blocks a protective mechanism of cancer cells and allows the immune system to destroy cancer cells. It targets the PD-1 receptor of lymphocytes and acts by targeting the cellular pathway of proteins, known as PD-1/PD-L1, found on the immune cells and certain cancer cells. Pembrolizumab is used as an immunotherapy medicine

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for treatments of lung cancer, head and neck cancer, melanoma, Hodgkin's lymphoma, gastric cancer, cervical cancer, and some kinds of breast cancer. The common adverse effects of Pembrolizumab are tiredness, skin rash, severe itching of the skin, gastrointestinal disturbance, retching, joint pain, muscular pain, and limb pain. During the treatment of cancer with PD-1 inhibitors, joint pain or muscle pain could occur.

Clinically it's very difficult to differentiate PD-1 inhibitor-induced pain from cancer pain itself. However, we should bear in mind that some anticancer medicines, such as PD-1 inhibitors, could aggravate the patients' pain and unpleasant feelings.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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