Case Report

Transient Receptor Potential Channels as Blood Biomarkers for Pain Characteristics in Patients with Chronic Pain

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Abstract

Transient receptor potential (TRP) channels play key roles for the transition from acute to chronic postoperative pain after surgery. To evaluate TRP channels in the peripheral blood cells as blood biomarkers for chronic pain, we collected blood samples for genome-wide assays of the mRNA expression and assessed pain intensity and the number of pain symptoms in 13 patients with chronic pain. There was a significant association between increases in the number of pain symptoms and increases in the TRP vanilloid 1 (TRPV1) expression. Decreases in the TRP ankyrin 1 (TRPA1) expression, however, tended to increase the number of pain symptoms. There was likely an inverse relationship for TRPV1 and TRPA1 expressions with regard to the number of pain symptoms in chronic pain patients.

Keywords: Biomarker, chronic pain, transient receptor potential ankyrin 1, transient receptor potential vanilloid 1

INTRODUCTION

Transient receptor potential (TRP) channels reportedly play key roles for the transition from acute to chronic postoperative pain, which includes neuropathic pain, after surgery. To reveal an association between TRP channels and chronic pain states would be beneficial for the future treatment of chronic postoperative pain. The previous studies reported that increased expression of either TRP vanilloid 1 (TRPV1) or TRP ankyrin 1 (TRPA1) expression in human blood cells was related to suppress pain in healthy humans. In contrast, TRPV1 and TRPA1 might have opposite effects on the blood cell functions in patients with inflammatory bowel disease. When taken together, the previous results suggest that a further investigation of the correlation between TRPV1 and TRPA1 in the human blood cells of chronic pain patients might reveal a more precise association between potential biomarkers and the pain states.

CASE REPORT

Thirteen patients, who were suffering from chronic low back pain without malignant diseases, completed the self-rating questionnaire for depression, the State-Trait Anxiety Inventory 1, which assessed anxiety levels, the Barthel Index, which evaluated daily living activities, and the Mini-Mental State Examination, which evaluated the cognitive impairment. We also assessed the chronic pain states using either the douleur neuropathique 4 (DN4) questionnaire or the short-form McGill pain questionnaire (SF-MPQ). DN4 is for assessing the number of pain symptoms, and SF-MPQ is for pain intensity. The DN4 questionnaire comprises 10 items that are used to determine the neuropathic pain symptoms. The SF-MPQ consists of the sensory pain rating index (S-PRI), the affective PRI, the total PRI (T-PRI), the visual analog scale, and the present pain intensity (PPI).

After collecting whole blood samples from the 13 patients, all of the samples were stored at −80°C until analyzed. Genome-wide assays of the mRNA expression assays were performed by Oncomics Ltd., (Nagoya, Japan) using the SurePrint G3 Human Gene Expression 8×60K v2 Microarray Kit (Agilent Technologies, Santa Clara, CA USA). Seven of TRPA1 data in the previous data was registered in the present ones.

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This protocol was approved by the Ethics Committee of the Hyogo College of Medicine, and written informed consent was obtained from all patients. This protocol was registered in the UMIN Clinical Trial Registry (UMIN000014908).

We analyzed the relationship between the two variables using Pearson’s correlation. The statistical significance was set at \( P < 0.05 \). SPSS Statistics 21 software (IBM, Chicago, IL, USA) was used for all statistical analyses.

Table 1 presents the characteristics of the patients and their pain states. The results showed that the increase in the number of the pain symptoms determined by the DN4 (DN4 score) was significantly related to the increase in the TRPV1 expression \( [P = 0.018, \text{Table 1 and Figure 1a}] \). On the other hand, the DN4 score tended to be oppositely related to the decrease in the TRPA1 expression \([P = 0.058, \text{Table 1 and Figure 1b}]\). These results suggest that there is likely an inverse relationship between the TRPA1 and TRPV1 expressions in whole blood cells with regard to the DN4 score.

The increase in the TRPV1 expression also exhibited significant associations with the increases in pain duration, depression level, anxiety level, and pain intensities, which were assessed by S-PRI, T-PRI, and PPI [Table 1]. The decrease in the TRPA1 expression was significantly related to increases in a patient’s age [Table 1].

**DISCUSSION**

The increase in the mRNA expressions of TRPV1 in whole blood cells augmented the number of pain symptoms in patients suffering from chronic pain. In contrast, increases in TRPA1 mRNA expressions tended to suppress the number of symptoms, which was similar to what we observed in our previous report of chronic pain patients.\(^6\)

TRPA1 and TRPV1 are expressed on peripheral nervous cells and immune cells, and play a pivotal role in pain sensation and the regulation of immune response during and after surgery.\(^1\) It has been shown that neuroplasticity in the central nervous system is responsible for the development and maintenance of chronic pain, including chronic postoperative pain. In addition, there has been a recent focus on the potential role of the innate immune system in the blood for chronic pain.\(^7\) Therefore, chronic pain patients might exhibit changes in their nervous systems due to neuroimmune interactions, in conjunction with pain symptom augmentation.\(^7\) TRPV1 channels are associated with chronic pain in the central and peripheral nervous systems and play a relevant role in the innate immune system.\(^8\) Chemical compounds around tissue injury sites have been shown to activate TRPA1 channels in the immune cells and induce pro-inflammatory responses.\(^9\) Activated TRPA1 reportedly inhibits TRPV1 activity in CD4+ T-cells.\(^4\) The opposite effects reported for TRPA1 and TRPV1 on the immune system would explain the inverse relationship that was found for these TRP channels with regard to the number of pain symptoms in the present case report.

Our current report also demonstrated that increases in the TRPV1 expression exhibited significant associations with the increases in the pain duration, the levels of depression and anxiety, and pain intensity. It is well known that pain intensity is associated with depression and anxiety states in chronic pain patients. Since the increased mRNA expression of TRPV1 in peripheral blood leukocytes was reported to increase in patients with depression,\(^10\) there might be a pathological link among pain intensity, depression, anxiety, and the TRPV1 expression in the blood cells in chronic pain patients.

**CONCLUSION**

Our findings show that increases in the number of pain symptoms in chronic pain patients are likely related to increases in the TRPV1 expression and decreases in the TRPA1 expression in whole blood cells. Further investigations are needed to reveal the association between perioperative time-series changes in these biomarkers and chronic postoperative pain states.

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Conflicts of interest
There are no conflicts of interest.

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