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The Effect of DICAM Gene on Neuroinflammatory modulation in CRPS model using DICAM-knockout Mice.

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Background

Although complex regional pain syndrome (CRPS) is described as a single disease, it is usually categorized into two distinct phases: an acute stage of CRPS and a chronic stage of CRPS. In addition to changes in the clinical symptoms and signs, these two distinct stages are accompanied by different biochemical changes in both human patients and mouse models of CRPS. Although the mechanisms of this transition from the acute to the chronic stage of CRPS are still very poorly understood, propagation of neuroinflammation in the peripheral nervous system (PNS) (neuroinflammation by peripheral immune cells, ex. macrophage) to CNS (neuroinflammation by astrocyte and microglia) through a weakened blood-brain barrier (BBB) has been identified as one of the major causes of central sensitization, and has been regarded as one of the causes of the chronic stage of CRPS in previous studies. DICAM, a dual immunoglobulin domain containing cell adhesion molecule, is a type I transmembrane protein is found to be expressed ubiquitously in various organs and cell lines. DICAM is also known to be involved in cell-cell adhesion through direct interaction with αVβ3 integrin, such as in the blood-brain barrier (BBB). In addition, DICAM is known to reduce pro-inflammatory cytokine production in lipopolysaccharide (LPS)-mediated macrophage by modulating macrophage M1 polarization. Although DICAM protein has a positive effect on BBB integrity and anti-inflammatory effects on macrophages, it has not yet been determined how it plays a role in CNS immune cells, such as macrophage and astrocyte.

Objective

We aimed to investigate the role of DICAM gene in the acute and chronic stage of CRPS, and to investigate the possibility of DCAM gene as a therapeutic target in CRPS.

Methods

The authors constructed CRPS rodent model involving tibia fracture/cast immobilization using wild-type (WT) and DICAM knock-out (KO) mice to investigate the role of DICAM gene in the acute and chronic stages of CRPS. Behavioral testing, gene expression studies, and immunohistochemistry were performed to compare between two groups (WT vs. DICAM KO) at acute and chronic stages of CRPS.

Results

In both the acute and chronic stages of CRPS, DICAM KO mice tend to be more painful in behavioral pain tests. Immunohistochemistry and gene expression studies of the spinal cords showed that more severe pain patterns in both acute and chronic stages of CRPS in DICAM KO mice than in WT mice may be due to deteriorated neuroinflammation by

DICAM KO astrocytes through increasing secretion of CXC chemokine ligand 10 (CXCL 10) and inhibition of microglial M2 polarization.

Conclusions

The loss of the DICAM gene has a negative effect on the modulation of neuroinflammation in the CNS. These results suggest that DICAM gene can be a therapeutic target in CRPS. Further studies will be required to determine whether modulating DICAM gene may be effective in the treatment of CRPS.

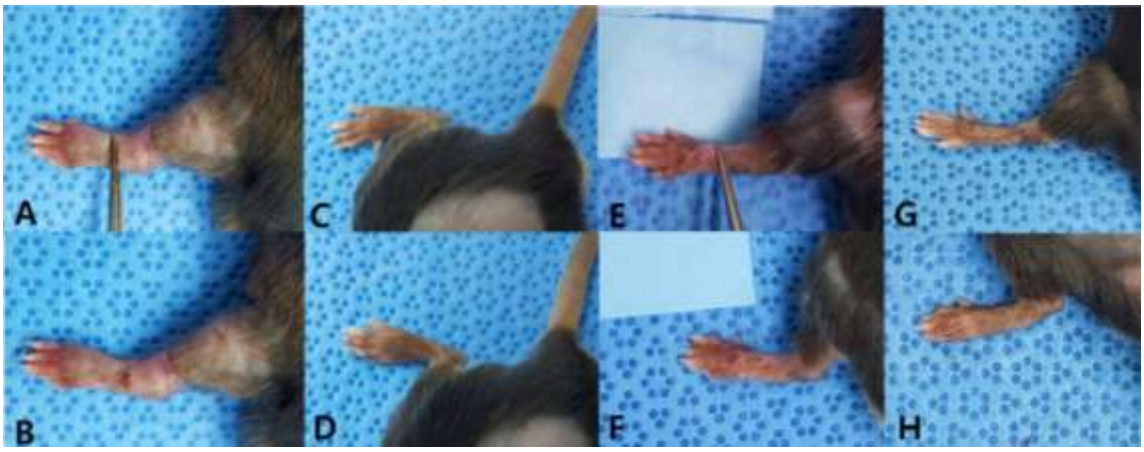

Fig 1. The image of bilateral hind paw in CRPS of WT mice (A,C,E,G) and DICAM KO mice (B,D,F,H). There was no significant differences in hind paw volumes between WT and DICAM KO mice CRPS model.

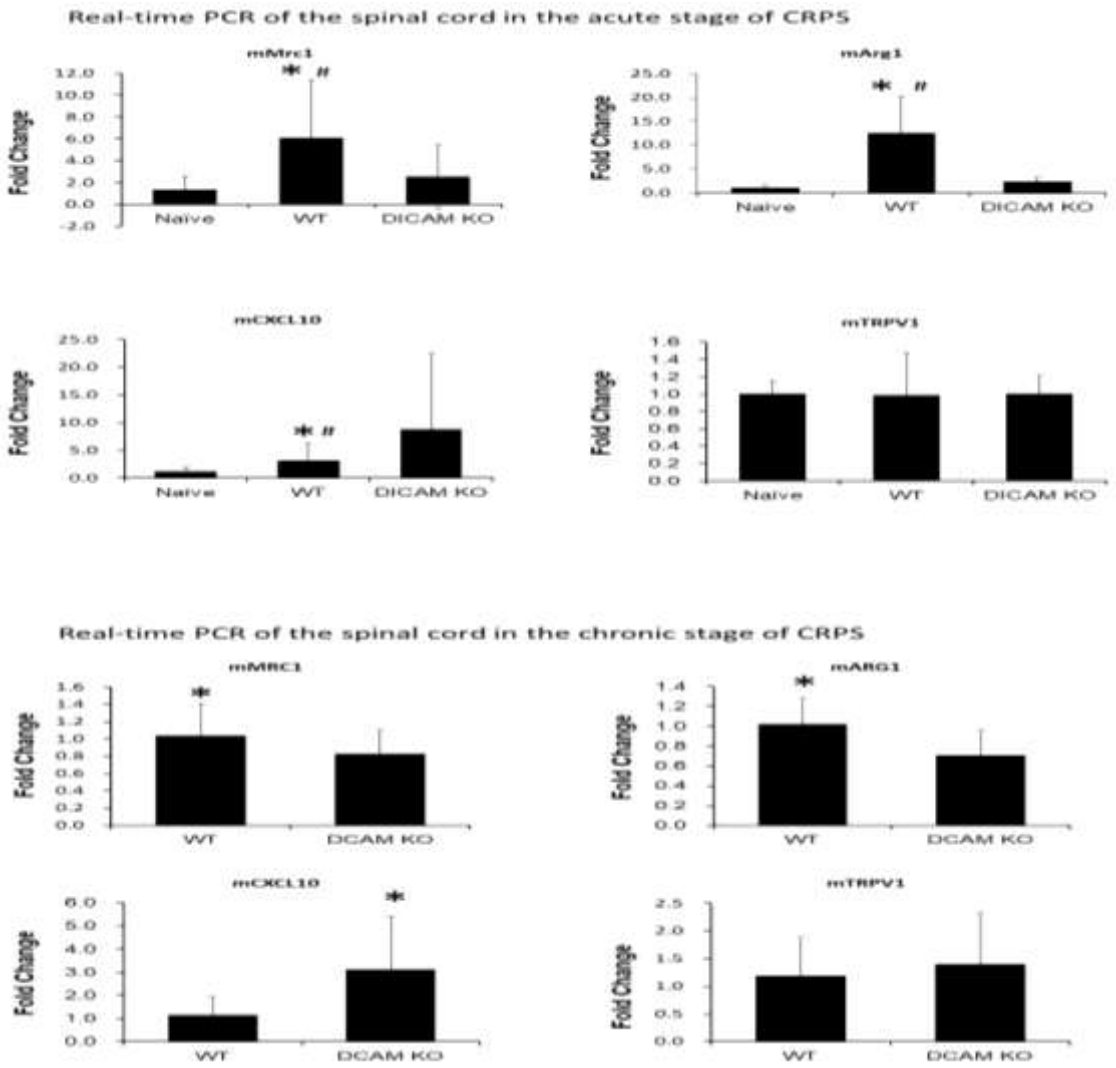

Fig 2. Real-time PCR data of the spinal cord in both the acute and chronic stages of CRPS using WT and DICAM KO mice. Real-time PCR data revealed that increased CXCL 10, and decreased mARG1 and mMRC1 in the spinal cord of the acute and chronic stages of CRPS using DICAM KO mice

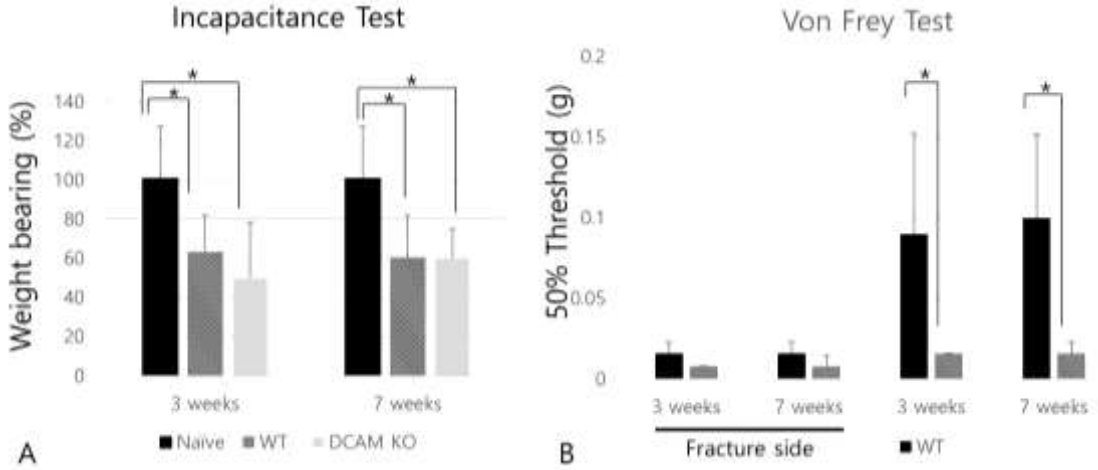

Fig 3. Behavioral pain tests in CRPS model of WT mice and DICAM KO mice. There was no difference in behavioral pain tests in ipsi-lateral hind paw between WT and DICAM KO CRPS mice. However, there were significant differences in contra-lateral hid paw between WT and DICAM KO CRPS mice.