

News Release

Title

TREM2/DAP12 signal exacerbates neuropathic pain by promoting proliferation and pro-inflammatory response of microglia

Key points

1. Dementia-associated molecules TREM2/DAP12 promoted microglial activation after nerve injury and exacerbate neuropathic pain.
2. Suppression of TREM2/DAP12-mediated signals could be a therapeutic target for neuropathic pain.

Summary

Prof. Hiroshi Kiyama, Assist. Prof. Hiroyuki Konishi and Postdoctoral Fellow Masaaki Kobayashi (first author) (Department of Functional Anatomy and Neuroscience, Nagoya University Graduate School of Medicine; Dean: Masahide Takahashi, M.D., Ph.D.) and a collaborator Prof. Toshiyuki Takai (Institute of Development, Aging and Cancer, Tohoku University) have reported that dementia-associated molecules TREM2/DAP12 promote proliferation and pro-inflammatory response of microglia after nerve injury, and exacerbates neuropathic pain.

Neuropathic pain is a chronic pain caused by nerve injury. Recent studies have shown that microglia activated in the spinal dorsal horn after peripheral nerve injury exacerbate neuropathic pain. Receptors expressed on microglial surface are assumed to induce microglial activation; however, only a few receptors have been identified as the inducer. The group focused on a receptor complex of TREM2 and DAP12, both of which are expressed by microglia and implicated in the pathogenesis of dementia. Because microglial activity affects the pathogenesis of dementia, TREM2/DAP12 complex is assumed to be a critical regulator of microglial activity. The authors analyzed functions of TREM2/DAP12-mediated signals in microglial activation by using an agonistic antibody for TREM2 and DAP12-deficient mice, and demonstrated that TREM2/DAP12-mediated signals promoted proliferation and pro-inflammatory response of microglia, resulting in exacerbation of neuropathic pain. These results

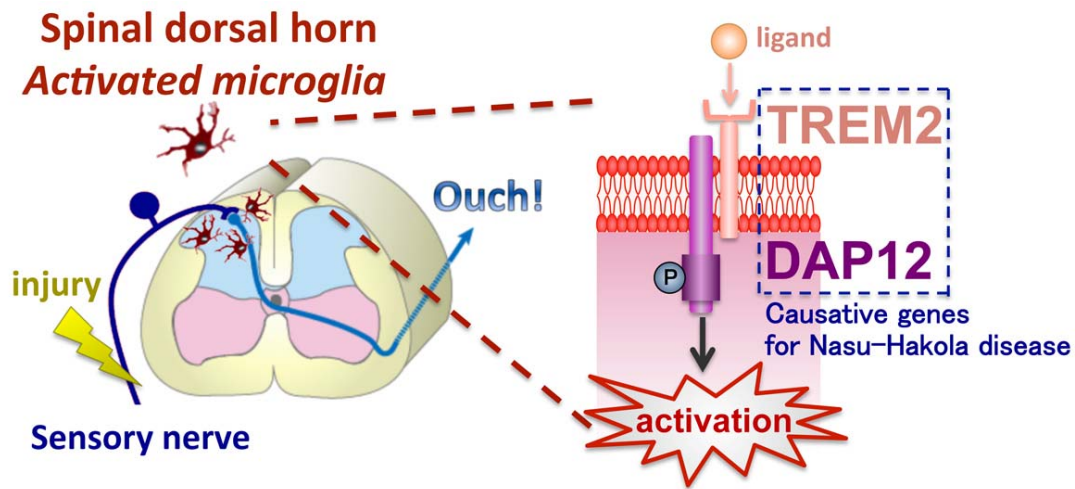
suggest that suppression of TREM2/DAP12-mediated signals could be a therapeutic target for neuropathic pain.

Research Background

Neuropathic pain (allodynia) caused by nerve injury impairs activities of daily life, and the establishment of a promising therapeutic strategy is an urgent issue. Recent studies have revealed that microglia activated in the spinal dorsal horn after peripheral nerve injury exacerbate neuropathic pain. Receptors expressed on microglial surface are assumed to induce microglial activation; however, only a few receptors have been identified as the inducer. The authors assumed a complex of TREM2 and DAP12 as a candidate receptor. Both TREM2 and DAP12 are causative gene for Nasu-Hakola disease, which is characterized by presenile dementia associated with bone cysts. Furthermore, a mutation of TREM2 is reported to be a risk factor for late onset Alzheimer's disease. Because microglial activity affects the pathogenesis of dementia, the authors assumed TREM2/DAP12 complex as a critical regulator of microglial activity and examined effects of TREM2/DAP12-mediated signals on microglial activation after nerve injury.

Research Results

Neuropathic pain was induced in mouse hindlimb by L4 spinal nerve transection. Pain behaviors after nerve injury were significantly suppressed in DAP12-deficient mice. Nerve injury-induced proliferation and upregulation of pro-inflammatory molecules in the dorsal horn were inhibited in DAP12-deficient mice. Furthermore, intrathecal administration of TREM2 agonistic antibody induced neuropathic pain and expression of pro-inflammatory cytokine in mice without nerve injury. However, the agonistic antibody-induced responses were abolished in DAP12-deficient mice. Taken together, TREM2/DAP12-mediated signals exacerbate neuropathic pain by promoting proliferation and pro-inflammatory response of microglia.



Future Perspective

1. Some phospholipids and ApoE protein are assumed as intrinsic ligands for TREM2 in the central nervous system. Further studies are needed to evaluate these molecules as functional ligand(s) for TREM2 in the neuropathic pain model.
2. Inhibitors of TREM2/DAP12 signaling have not been established yet. Development of such inhibitors would be helpful in the treatment of neuropathic pain.

Publication

Masaaki Kobayashi, Hiroyuki Konishi, Akira Sayo, Toshiyuki Takai, Hiroshi Kiyama
 “TREM2/DAP12 signal elicits pro-inflammatory response in microglia and exacerbates neuropathic pain”

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