Neutrophil accumulation in the DRG contributes to the mechanical allodynia during the preclinical phase of EAE through a TLR4/CXCL1 pathway in the DRG

張, 競

（様式６－２）

氏　　名	張　競
論　文　名	Neutrophil accumulation in the DRG contributes to the mechanical allodynia during the preclinical phase of EAE through a TLR4-CXCL1 pathway in the DRG （多発性硬化症モデル動物で生じる DRG への好中球の集積および機械的アロディニアは DRG ニューロンにおける TLR4-CXCL1 経路によって生じる）
論文調査委員	主　査　　九州大学　　教授　　重村　憲徳 副　査　　九州大学　　教授　　久木田　敏夫 副　査　　九州大学　　教授　　前田　英史

論　文　審　査　の　結　果　の　要　旨

Multiple sclerosis (MS) is a potentially disabling disease of the central nervous system. Approximately half of the patients with MS experience severe pain; however, currently available therapeutics provide only insufficient relief. The mechanisms underlying the generation of neuropathic pain in patients with MS are not fully understood. Recently, we found that neutrophil elastase from accumulated neutrophils in the dorsal root ganglion (DRG) sensitizes DRG neurons and induces mechanical allodynia in a mouse model of experimental autoimmune encephalomyelitis (EAE). However, the mechanism underlying neutrophil accumulation in the DRG after myelin oligodendrocyte glycoprotein (MOG_{35-55}, immunogenic peptide) immunization remains unclear. Here, we found that C-X-C motif ligand 1 (CXCL1) was upregulated in DRG neurons after MOG_{35-55} immunization. Increased expression of CXCL1 protein was also observed in primary cultured DRG neurons treated with MOG_{35-55}, which was mediated through toll-like receptor 4 (TLR4). Gene silencing of TLR4 or CXCL1 in DRG neurons significantly attenuated neutrophil accumulation in the DRG and mechanical allodynia during the preclinical phase of EAE (around day 5 after immunization). Our results thus suggest that a TLR4-CXCL1 pathway in DRG neurons triggers neutrophil recruitment in the DRG and subsequent mechanical allodynia in response to MOG_{35-55}. This study contains novel findings and has been published in *Scientific Reports*. Therefore, the candidate deserves to be conferred the degree of DOCTOR OF PHILOSOPHY (Dental Science) in the Graduate School of Dentistry, Kyushu University.