【Grant-in-Aid for Scientific Research (S)】

Elucidation of the mechanism for biological resilience to neuropathic pain and their application to diagnosis and treatment

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Purpose and Background of the Research

●Outline of the Research

Neuropathic pain develops by a lesion or disease affecting the somatosensory system. Many patients suffer from this pain. The mechanisms of its development and chronicity should be elucidated. Although accumulating evidence has advanced our understanding of the onset of neuropathic pain, little is known about the mechanisms underlying its chronicity. Recently, we identified CD11c$^+$ microglia in the spinal cord as cells that have a suppressing effect on the chronicity of neuropathic pain using its mouse model (Science 376: 86-90, 2022). This finding has opened an avenue for the establishment of a strategy to control neuropathic pain by activating these cells and also for the discovery of a new mechanism of pain chronicity caused by their abnormality. In this study, we will investigate the origin, induction, and functional acquisition of CD11c$^+$ microglia and their regulation of pain signaling neurons, and further analyze the relationship between these cells and neuropathic pain in patients. The purpose of this study will be to clarify the mechanism of biological resilience to the chronicity of neuropathic pain and establish a foundation to develop innovative diagnostics and therapeutics.

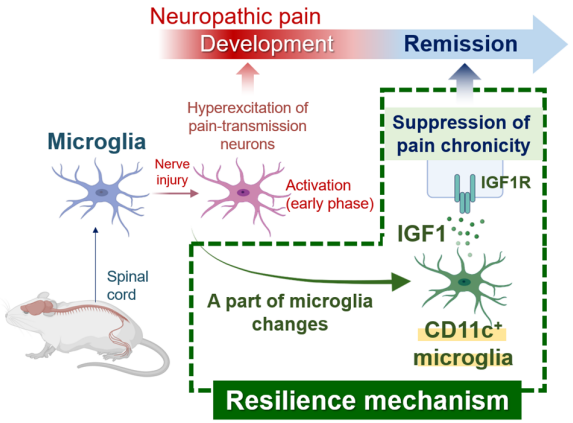

Figure 1. Outline of this research project (created with BioRender.com.)

●Background and Purpose

Neuropathic pain has been considered to involve dysfunction of the pain network system. Previously, we demonstrated that microglia, which are immune cells in the central nervous system that are activated in the spinal cord early (a few days) after nerve injury, are necessary for the network dysfunction and the development of neuropathic pain (Nature 2003, 2005). We also elucidated the molecular and cellular mechanisms underlying the microglia-mediated neuropathic pain onset (Nat Rev Neurosci 2018). Our understanding of the pain development has improved; however, the mechanism underlying its chronicity remains unclear. Recently, using a mouse model of neuropathic pain that sequentially exhibits the development, maintenance, and remission of pain symptoms over several months after nerve injury, we identified a microglial subpopulation, CD11c$^+$ microglia, emerging in the spinal cord after the development of neuropathic pain (Science 2022). Notably, contrasting to microglia, which are activated early after nerve injury, CD11c$^+$ microglia suppress the chronicity of neuropathic pain. Indeed, the removal of this microglial subset results in long-lasting pain symptoms. These new findings led us to hypothesize that CD11c$^+$ microglia are induced to counteract sensory system alterations caused by nerve injury and play a central role in biological resilience to neuropathic pain.

This study aims to elucidate the mechanisms underlying the induction of CD11c$^+$ microglia, acquisition of pain-suppressing functions, and suppression of pain chronicity by CD11c$^+$ microglia. Furthermore, the association between CD11c$^+$ microglia and pain chronicity will be analyzed in patients with neuropathic pain.

Expected Research Achievements

This study aims to identify the origin of CD11c$^+$ microglia in the spinal cord after nerve injury, and to elucidate the mechanisms underlying the transition of microglia from CD11c^{neg} to CD11c$^+$ and the acquisition of pain-suppressing functions (IGF1 production). We will also clarify the mechanism of pain suppression by CD11c$^+$ microglia based on the interaction of these cells with other cell-types in the nervous system. Furthermore, we will analyze the relationship between CD11c$^+$ microglia and chronic pain using pathological tissues and cerebrospinal fluid samples from patients with neuropathic pain.

From the achievements of this study, it can be expected to find new mechanisms of pain chronicity related to changes in CD11c$^+$ microglia-dependent resilience. Furthermore, if an association between CD11c$^+$ microglia and pain chronicity is shown in patients with neuropathic pain, it can also be expected to lead to a new concept that abnormalities in these cells are a risk factor for the chronicity of neuropathic pain and also to establish a foundation to develop innovative diagnostics and therapeutics.

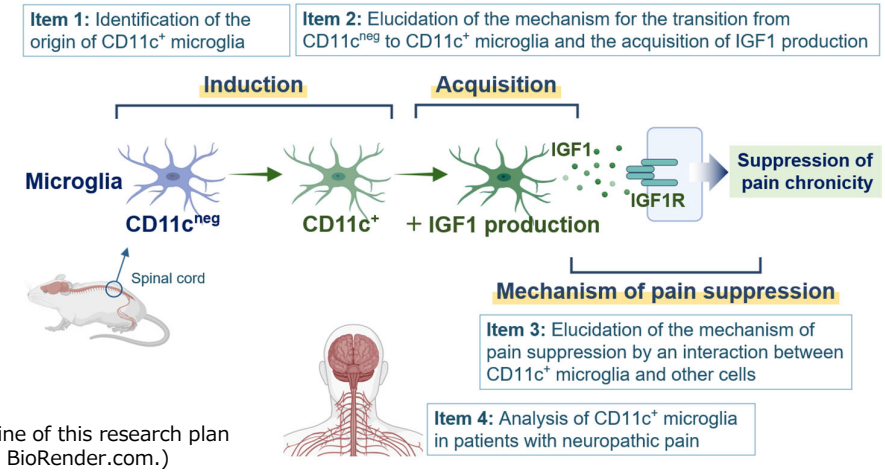

Figure 2. Outline of this research plan (created with BioRender.com.)

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