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【 EDITORIAL 】

Implications for White Matter Vulnerability to Anti-interleukin-6 Receptor Antibody Treatment

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The brain is composed of gray and white matter. Gray matter consists of neuronal cell bodies and synapses, while white matter consists of axons and myelin. Oligodendrocytes are major glial cells that wrap around the axons to form myelin, which provides electrical insulation to regulate conduction velocity. Consequently, these myelinated axons act as cable connecting distinct brain regions for effective information transmission (1). Recent studies using brain magnetic resonance imaging (MRI) in humans have shown that learning and training, such as with juggling and playing piano, induce changes in signals from white matter, indicating that neuronal activities promote structural plasticity in white matter (2). In addition, impairment of white matter plasticity is associated with an impaired learning process and abnormal neuronal activities (3). Thus, impaired regulation in white matter owing to leukoencephalopathy caused by viral infections, radiation and chemotherapy can be expected to result in cognitive impairment (4-6). However, the underlying mechanisms triggering the pathology in white matter are still being debated.

The study published by Ryo Sasaki of the Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, showed that tocilizumab, a humanized anti-interleukin-6 (IL-6) receptor antibody, causes cognitive dysfunction associated with leukoencephalopathy in patient with rheumatoid arthritis (RA), and discontinuation of this drug leads to improvement in both the cognition and brain MRI findings (7). This report suggested that disruption of IL-6 signaling might be involved in leukoencephalopathy damage to the white matter (myelinated axons). IL-6 is a cytokine that is elevated in patients with RA and other auto immune diseases. It promotes the pathogenicity of T helper cells in patient with multiple sclerosis (MS; the most common demyelinating disease) (8), and high levels of IL-6 result in reduced white matter integrity in old age (9). Blocking the IL-6 signaling pathway thus seems to be beneficial for the white matter. However, in demyelinating lesions from human MS patients, the number of IL-6-positive cells suggested to be macrophages and astrocytes (a type of glial cell in the brain) due to their morphology correlated with the extent of oligodendrocyte preservation (10). Consistent with this observation, IL-6 and the soluble IL-6 receptor complex form were shown to lead to oligodendrocyte differentiation (11, 12), suggesting that inhibiting the IL-6 signaling pathway is detrimental for oligodendrocyte linage cells. These findings are important for improving our understanding of the mechanism underlying leukoencephalopathy caused by IL-6 receptor antibody treatment.

Recently, astrocytes and microglia (another type of glial cell) have been considered key regulators of myelin production and maintenance under normal conditions and of remyelination under pathological conditions (13, 14). The astrocyte-targeted production of IL-6 improved demyelination, astrogliosis and microglial accumulation in the white matter because the level of CXCL10, a key microglial attracting chemokine, was lower in the cuprizone treated glial fibrillary acidic protein IL-6 transgenic mice [GFAP-IL6 tg mice (15)] (14). Indeed, colony-stimulating factor-1 receptor gene mutations induce leukoencephalopathy via microglial activation (16). Furthermore, a deficit of astrocyte, microglia and oligodendrocyte function contributes to chemotherapy-related cognitive impairment, which is mainly caused by leukoencephalopathy (6). These observations highlight the potential utility of the effective modulation of the glial cell function for treating leukoencephalopathy.

Finally, tocilizumab is very beneficial for treating not only autoimmune diseases (17) but also the cytokine storm associated with coronavirus disease 2019 (18), so it is expected to be used more frequently in the future. However, leukoencephalopathy, although very rare, is a serious adverse effect once it occurs, so it is necessary to use tocilizu-

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mab safely in patients with autoimmune responses, keeping in mind the possibility of leukoencephalopathy.

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