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論　文　内　容　の　要　旨

氏　名　（　永梅　）	
論文題名	**Interleukin-6 Deficiency Does Not Affect Motor Neuron Disease Caused by Superoxide Dismutase 1 Mutation** （SOD1 変異によって生じる運動ニューロン疾患におけるIL-6欠損の作用検討）

論文内容の要旨

Background & Aim：Amyotrophic Lateral Sclerosis (ALS) is an adult-onset, progressive, motor neuron degenerative disease. Recent evidence indicates that inflammation is associated with many neurodegenerative diseases including ALS. Previously, abnormal levels of inflammatory cytokines including IL-1β, IL-6 and TNF-α were described in ALS patients and/or in mouse ALS models. In addition, one study showed that blocking IL-1β could slow down progression of ALS-like symptoms in mice. My lab members revealed that IL-6 blockade was effective in a mouse model of autoimmune arthritis and a mouse model of central neuron system disease, experimental autoimmune encephalomyelitis. In humans, anti-IL-6 receptor antibody tocilizumab is effectively used in treating rheumatoid arthritis and was recently reported to be effective in Neuromyelitis Optica (NMO), an autoimmune disease of the central nervous system mainly affecting spinal cord and optic nerves. The latter finding suggests that tocilizumab can ameliorate immune disease in central nervous system. Fiala et al recently started a clinical trial of IL-6 inhibition therapy in sporadic ALS. In this study, I examined a role for IL-6 in ALS, using an animal model for familial ALS.

Methods: Mice with mutant SOD1 (G93A) transgene, a model for familial ALS, were used in this study. The expression of the major inflammatory cytokines, IL-6, IL-1β and TNF-α, in spinal cords of these SOD1 transgenic (TG) mice were assessed by real time PCR. Mice were then crossed with IL-6(-/-) mice to generate SOD1TG/IL-6(-/-) mice. SOD1 TG/IL-6(-/-) mice (n=17) were compared with SOD1 TG/IL-6(+/-) mice (n=18), SOD1 TG/IL-6(+/+) mice (n=11), WT mice (n=15), IL-6(+/-) mice (n=5) and IL-6(-/-) mice (n=8), with respect to neurological disease severity score, body weight and the survival. I also histologically compared the motor neuron loss in lumber spinal cords and the atrophy of hamstring muscles between these mouse groups.

Results: Levels of IL-6, IL-1β and TNF-α in spinal cord of SOD1 TG mice was increased compared to WT mice. However, SOD1 TG/IL-6(-/-) mice exhibited weight loss, deterioration in motor function and shortened lifespan (167.55 ± 11.52 days), similarly to SOD1 TG /IL-6(+/+) mice (164.31±12.16 days). Motor neuron numbers and IL-1β and TNF-α levels in spinal cords were not significantly different in SOD1 TG /IL-6(-/-) mice and SOD1 TG /IL-6 (+/+) mice.

Conclusion: These results provide compelling preclinical evidence indicating that IL-6 does not directly contribute to motor neuron disease caused by SOD1 mutations.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

近年、免疫難病治療薬として炎症性サイトカインを標的とする生物学的製剤が多数実用化され、神経難病を含む様々な疾患へ効果を上げている。その機序として、IL-6の抑制が重要であると知られてきている。永梅は、神経難病である筋萎縮性側索硬化症（ALS）の病態に炎症が関与するという最近の知見を元に、炎症性サイトカインIL-6がALSの病態に関与するという仮説を立てた。その検証のため、ALSのモデル動物SOD1(G93A)トランスジェニック（TG）マウスを入手し、IL-6欠損マウスとの交配によりSOD1 TG IL-6（-/-）マウスを作製して、神経症状、脊髄病理像、炎症性サイトカイン産生について検討した。その結果、仮説に反して、ALSモデルマウスはIL-6欠損下においても通常と同様の病状を呈することが示され、本モデル動物の病態においてIL-6の関与は乏しいことが明らかになった。本研究の成果はALSの新規治療薬開発には直結しないが、難病ALSの病態解明と治療法探索を進める上で重要な意義があり、アクセプトされた英文誌からも同様の評価を得ており博士課程卒業論文として相応しいものと認める。本研究を遂行した永梅は学位取得に値すると考える。