東北医科薬科大学

審査学位論文（博士）要旨

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Importance of core fucosylation in regulating neuroinflammation

(神経炎症の調節におけるコアのフコシル化の重要性)

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α1,6-Fucosyltransferase (Fut8) catalyzes the transfer of fucose to the innermost *N*-acetylglucosamine residue of *N*-glycan to form core fucosylation, and is associated with numerous physiological and pathological processes. Our previous studies showed that lipopolysaccharide (LPS) treatment highly induced neuroinflammation in Fut8 homozygous knockout ($Fut8^{-/-}$) or heterozygous knockout ($Fut8^{+/-}$) mice, compared with the wide-type ($Fut8^{+/+}$) mice. To understand the underlying mechanism, we utilized a sensitive inflammation-monitoring mouse system that contains the human interleukin-6 (*hIL6*) bacterial artificial chromosome (BAC) transgene modified with luciferase (*Luc*) reporter cassette. We successfully detected LPS-induced neuroinflammation in the central nervous system by exploiting this BAC transgenic monitoring system. Then we examined the effects of L-fucose on neuroinflammation in the $Fut8^{+/-}$ mice. The lectin blot and mass spectrometry analysis showed that L-fucose pre-administration increased the core fucosylation levels in the $Fut8^{+/-}$ mice. Notably, exogenous L-fucose attenuated the IL-6 mRNA and *Luc* mRNA expression in the cerebral tissues induced by LPS, confirmed using the *hIL6-Luc* bioluminescence imaging system. The activation of microglial cells, which provoke neuroinflammatory responses upon LPS stimulation, was inhibited by L-fucose pre-administration. L-Fucose also suppressed the downstream intracellular signaling of IL-6, such as the phosphorylation levels of JAK2, Akt, and STAT3. L-Fucose administration increased gp130 core fucosylation levels and decreased the association of gp130 with the IL-6 receptor in $Fut8^{+/-}$ mice, which was further confirmed in BV-2 cells. These results indicate

that L-fucose administration ameliorates the LPS-induced neuroinflammation in the Fut8$^{+/-}$ mice, suggesting that core fucosylation plays a vital role in anti-inflammation and that L-fucose is a potential prophylactic compound against neuroinflammation.

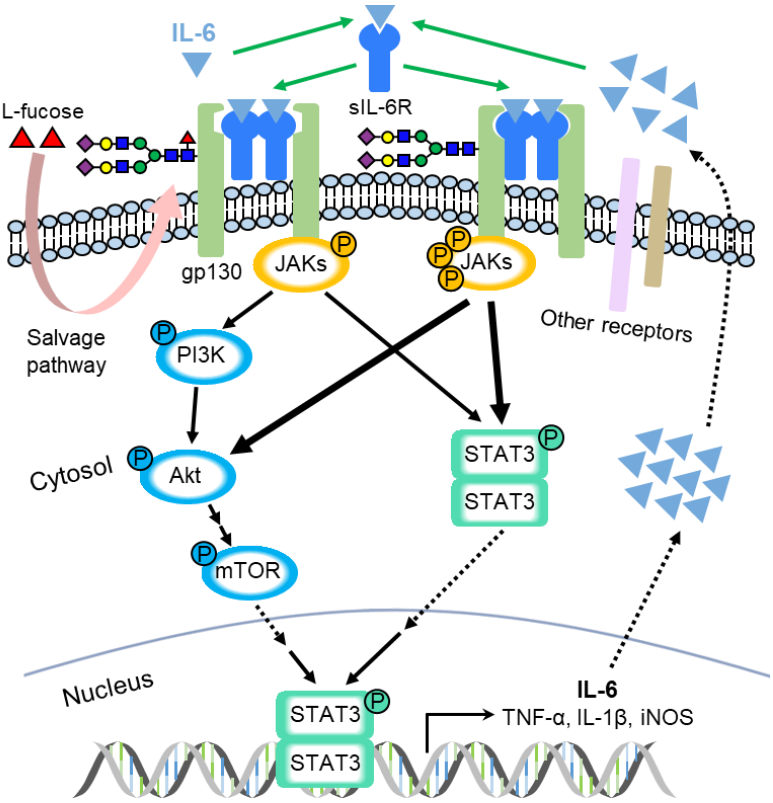

Fig. 1. Schematic diagram of the proposed molecular mechanism for neuroinflammation regulated by core fucosylation.

Reference

Xu, X., Fukuda, T., Takai, J., Morii, S., Sun, Y., Liu, J., Ohno, S., Isaji, T., Yamaguchi, Y., Nakano, M., Moriguchi, T., and Gu, J. (2023) Exogenous L-fucose attenuates neuroinflammation induced by lipopolysaccharide. J. Biol. Chem., 105513