

## Importance of core fucosylation in FLT3-mediated cellular signaling

東北医科薬科大学 大学院薬学研究科

細胞制御学教室 段 程 偉

Fms-like tyrosine kinase 3 (FLT3) is a glycoprotein, that is a member of the class III receptor tyrosine kinase family. Approximately one-third of acute myeloid leukemia (AML) patients have mutations of this gene, and activation of the FLT3 downstream pathway plays an important role in both normal and malignant hematopoiesis. However, the role of N-glycosylation for FLT3 activation remains unclear. In this study, we found that the N-glycan structures on wild type (WT), internal tandem duplication (ITD), and tyrosine kinase domain (TKD) mutants of FLT3 were different. Interestingly, expression of either WT or mutant FLT3 in Ba/F3 cells, an interleukin-3 (IL-3)-dependent hematopoietic progenitor cell, greatly induced core fucosylation. To elucidate the function of core fucosylation in FLT3-mediated signaling, we used a CRISPR/Cas9 system to establish  $\alpha$ 1,6-fucosyltransferase (Fut8) knockout (KO) cells. Surprisingly, the Fut8KO resulted in cell proliferation in an IL-3-independent manner in FLT3-WT cells, which was not observed in the parental cells, and suggested that this proliferation is dependent on FLT3 expression. Fut8KO greatly increased cellular tyrosine phosphorylation levels, together with an activation of STAT5, AKT and ERK signaling, which could be completely neutralized by restoration with Fut8 in the KO cells. A tyrosine kinase inhibitor consistently and efficiently inhibited cell proliferation

induced by Fut8 KO or specific fucosylation inhibitor. Additionally, immunostaining with FLT3 showed that the proteins were mainly expressed on the cell surface in the KO cells, which is similar to FLT3-WT cells, but different from the ITD mutant. Finally, we found that Fut8KO could induce dimer-formation in FLT3 without ligand-stimulation. Taken together, the present study clearly defines the regulatory function of core fucosylation in FLT3, which could provide a valuable direction for the development of drugs that could be effective in the treatment of AML.

<参考文献>主論文, 参考論文

**Duan C**, Fukuda T, Isaji T, Qi F, Yang J, Wang Y, Takahashi S, Gu J. Deficiency of core fucosylation activates cellular signaling dependent on FLT3 expression in a Ba/F3 cell system. *FASEB J* 2020 Feb;34(2):3239-3252.

Lu X, Zhang D, Shoji H, **Duan C**, Zhang G, Isaji T, Wang Y, Fukuda T, Gu J. Deficiency of  $\alpha$ 1,6-fucosyltransferase promotes neuroinflammation by increasing the sensitivity of glial cells to inflammatory mediators. *Biochim Biophys Acta Gen Subj*. 2019 Mar;1863(3):598-608.