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Grant Title: A new tactic to inhibit leukemia cell growth via the function of NOTCH O-glycans

Abstract

Aberrant enhancement of Notch signaling is observed in many types of cancer, including T-ALL and high-grade breast cancer (1), and activating mutations in NOTCH1 have been found in more than 50% of T-ALL patients (2). We and others have shown that glycosylation at the extracellular site of Notch plays an important role in its activation (3). However, the molecular mechanism by which O-glycosylation regulates the activation of NOTCH1 remains elusive. We hypothesized that the molecular mechanism by which glycosylation regulates NOTCH1 transport to the cell surface could be used to selectively suppress the constitutive activation of mutated NOTCH1 seen in T-ALL. Therefore, the purpose of this study was to gain a better understanding of the molecular function of O-linked glycans, i.e., their role in the trafficking of Notch receptors to the cell surface, and to identify a new molecular target for T-ALL and its potential therapeutic application. In this study, we investigated the role of *O*-glucosylation in the intracellular behavior of the Notch receptor and Notch signaling using Jurkat cells, a cultured T-ALL cell line, as a model. Knockout of the xylosyltransferase gene in T-ALL cells did not alter the level of cell surface expression of endogenous NOTCH1. In *Drosophila*, it has been suggested that it acts in an inhibitory manner on Notch signaling. We reported that in HEK293T cells, loss of xylosyltransferase reduced the trafficking of overexpressed NOTCH1 and NOTCH2 to the cell surface (4). Additionally, we performed a screening for small molecule inhibitors of the glycosyltransferases that are involved in the biosynthesis of *O*-glucosylation. It is expected that the discovered inhibitors will be further improved to be more specific and contribute to biochemical studies on the enzymatic reaction mechanism, molecular and cell biological studies on the molecular mechanism by which *O*-glucosylation on the Notch receptor extracellular domain regulates Notch signaling in various cells, tissues, and organisms, and future drug discovery studies for Notch-related diseases caused by aberrant *O*-glucosylation.

References

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