News Release

Title

O-linked *N*-acetyl-glucosamine regulates Notch signaling and vascular development

Key Points

- ○ O-linked *N*-acetyl-glucosamine (O-GlcNAc) regulates Notch-ligand interaction
- ○ Notch O-GlcNAcylation regulates vascular development and its function
- ○ Notch signaling and vascular development are tightly regulated by glycans

Summary

Post-translational modification of proteins with sugar chains (glycans) adds functional diversity to the resultant glycoprotein. Specific glycans on signaling receptors are important for the precise regulation of signaling pathways that control cell fate decisions required for animal development and homeostasis. For example, several types of glycans are found on Notch receptors and regulate Notch signaling that is responsible for many developmental processes. One of the O-glycans on Notch is initiated by the transfer of O-GlcNAc by the enzyme EOGT, which is associated with Adams-Oliver syndrome. In this study, Shogo Sawaguchi, Mitsutaka Ogawa, and Tetsuya Okajima at Nagoya University School of Medicine (Dean: Masahide Takahashi) in collaboration with Professor Pamela Stanley at Albert Einstein Medical University and Koichi Kato at Okazaki Institute for Integrative Bioscience, found that the transfer of O-GlcNAc by EOGT to specific EGF repeats of NOTCH1 promotes DLL4 binding**,** Notch signaling, and retinal vascular development. The results will provide molecular insights into Adams-Oliver syndrome, whose pathological mechanisms are largely unknown. Furthermore, our study will suggest a new strategy for cancer therapy in which Notch signaling is a promising molecular target.

Research Background

Post-translational modification of proteins with sugar chains (glycans) adds functional diversity to the resultant glycoprotein. Specific glycans on signaling receptors are important for the precise regulation of signaling pathways that control cell fate decisions required for animal development and homeostasis. For example, several types of glycans are found on Notch receptors and regulate Notch signaling that is responsible for many developmental processes. Mutations that prevent the addition of these glycans lead to congenital diseases. One of the O-glycans on Notch is initiated by the transfer of O-GlcNAc by the enzyme EOGT. *EOGT* mutations are found in patients with Adams-Oliver syndrome. Our experiments were aimed at finding biological functions for the O-GlcNAc on Notch receptors.

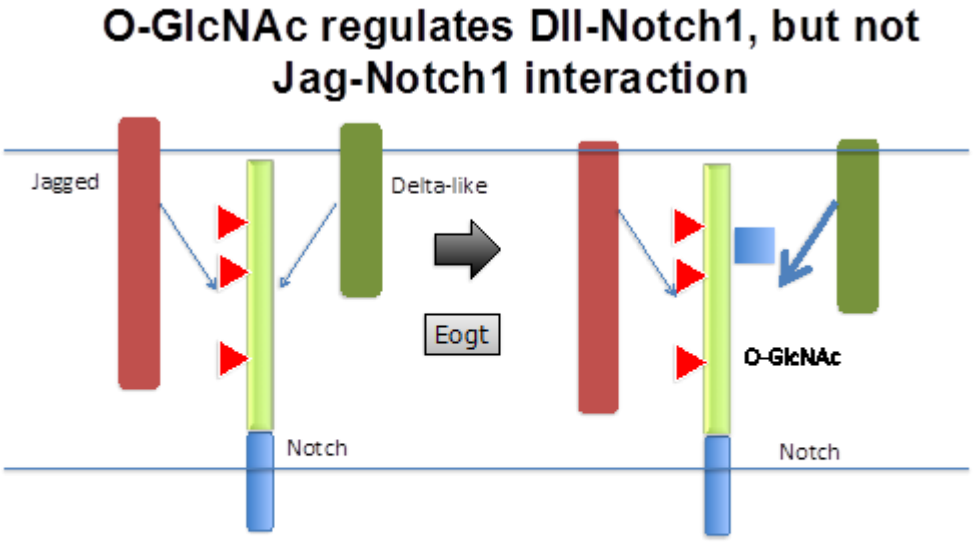
We wished to determine whether the recently identified addition of O-GlcNAc to Notch receptors regulates Notch signaling. Moreover, we aimed to define molecular mechanisms by which O-GlcNAc regulates the Notch signaling pathway.

Research Results

In cell-based ligand binding and ligand-induced signaling assays, we showed that EOGT regulates Notch ligand binding, Notch activation and signaling induced by the canonical ligands DLL1 and DLL4, whereas Notch activation by JAG1 ligand is largely preserved in the absence of EOGT. Notch signaling is important for vascular development, and mice lacking EOGT were defective in vascular development in retina. The retina phenotype in EOGT-deficient mice was similar to that in retinas lacking DLL4, and distinct from that observed in retinas lacking JAG1, consistent with the different effects of DLL4 and JAG1 observed in cell culture experiments.

Future Perspective

Our mouse and cell models will be used to identify additional biological functions for the O-GlcNAc glycans on Notch receptors, and to determine how these glycans regulate Notch signaling during development. The results will provide molecular insights into Adams-Oliver syndrome, whose pathological mechanisms are largely unknown.



Differential effect of EOGT and Fringe on Notch-ligand interaction

	DLL ligand	JAG ligand
EOGT	↑↑	→
Fringe	↑↑	↓↓

Publication

Shogo Sawaguchi, Shweta Varshney, Mitsutaka Ogawa, Yuta Sakaidani, Hirokazu Yagi, Kyosuke Takeshita, Toyoaki Murohara, Koichi Kato, Subha Sundaram, Pamela Stanley and Tetsuya Okajima. O-GlcNAc on NOTCH1 EGF Repeats Regulates Ligand-Induced Notch Signaling and Vascular Development in Mammals. Elife *in press*

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