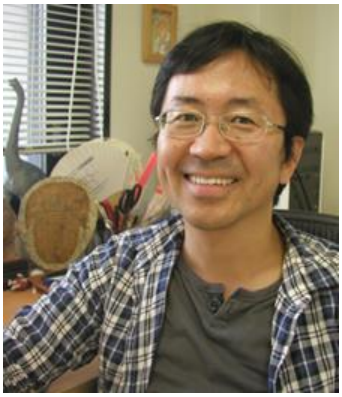
Principal Investigator: Kenji Matsuno

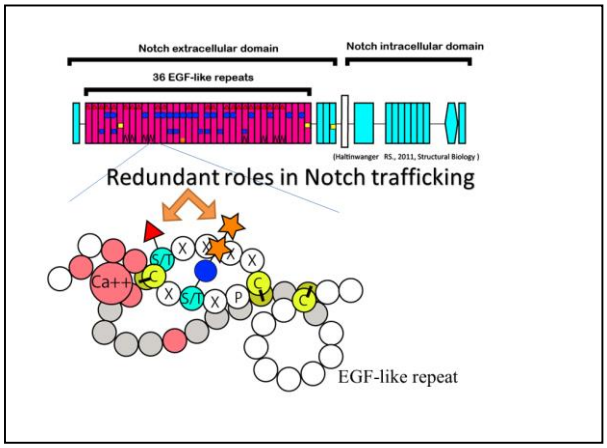
Grant Title: Functional interactions among glycan modification on EGF-like repeats of Notch

Abstruct



Notch is a transmembrane receptor that mediates cell-cell interactions and controls various cell-fate specifications in metazoans. The extracellular domain of Notch contains multiple epidermal growth factor (EGF)-like repeats. At least five different glycans are found in distinct sites within these EGF-like repeats. The function of these individual glycans in Notch signaling has been investigated, primarily by disrupting their individual glycosyltransferases. However, we are just beginning to understand the potential functional interactions between these glycans. Monosaccharide *O*-fucose and *O*-glucose trisaccharide (*O*-glucose-xylose-xylose) are added to many of the Notch EGF-like repeats. The goal of this study was to explore the functional interplay between these two *O*-glycans.

To address this, we analyzed the phenotypes of *Drosophila* mutants that affect the monosaccharide *O*-fucose and *O*-glucose trisaccharide modifications on Notch EGF-like repeats. In *Drosophila*, Shams adds a xylose specifically to the monosaccharide *O*-glucose. We here reports that loss of terminal dixylose of *O*-glucose-linked saccharides had little effect on Notch signaling. However, our analyses of double mutants of *shams* and other genes required for glycan modifications revealed that both the monosaccharide *O*-glucose and the terminal dixylose of *O*-glucose-linked saccharides function redundantly with the monosaccharide *O*-fucose in Notch activation and trafficking. The terminal dixylose of *O*-glucose-linked saccharides and the monosaccharide *O*-glucose were required in distinct Notch-trafficking processes: Notch transport from the apical plasma membrane to adherence junctions, and Notch export from the endoplasmic reticulum, respectively. Therefore, the monosaccharide *O*-glucose and terminal dixylose of *O*-glucose-linked saccharides have distinct activities in Notch trafficking, although the lack of these activities is compensated for by the presence of monosaccharide *O*-fucose.



Given that various glycans attached to a protein motif may have redundant functions, our results suggest that these potential redundancies may lead to a serious underestimation of glycan functions.