

## Regulation of Notch-Fringe Interactions During Lymphocyte Development: How Sweet it Is!

Fringe glycosyltransferases enhance Notch sensitivity to Delta-like (DL) Notch ligands and inhibit activation by Jagged ligands<sup>1</sup>. We have previously shown that developmentally stage-specific expression of Lunatic Fringe (Lfng) regulates T cell progenitor access to intrathymic niches that support Notch1-dependent phases of T cell development<sup>2,3</sup>. More recently, we have shown that Lfng and Manic Fringe (Mfng) co-operatively enhance Notch2 activation by DL-1 to promote marginal zone B cell generation in the spleen. Thus, Notch-Fringe interactions regulate competition for limiting DL ligands in multiple lymphoid organ niches, providing a general mechanism to homeostatically regulate the development of specific lymphocyte populations. Recently, we have used Notch ligand Fc fusion proteins, OP9 stromal cell lines, and mice lacking Lfng or Manic Fringe (Mfng) to determine how different Fringes modulate sensitivity of Notch receptors to DL versus Jagged ligands during T cell development. We will show multiple lines of evidence suggesting that DL-4 and not DL-1 is the intrathymic ligand that drives T cell development. In contrast, Jagged-1 is poorly expressed in the thymus, and hematopoietic stem cells (HSCs) are unresponsive to Jagged-1 (since they generate B cells but no T cells on OP9-Jag1). We then evaluated how loss of Lfng, Mfng, or both Fringes affects HSC generation of T, B and myeloid progeny in response to DL-1, DL-4 and Jagged-1 *in vitro*. Our data reveal that Lfng and Mfng co-operatively enhance the strength of Notch1 activation by DL ligands and suppress responsiveness to Jagged-1. Collectively, these findings suggest that Lfng and Mfng prevent HSCs from inappropriately responding to Jagged-1 outside the thymus while also ensuring that they respond robustly to intrathymic DL-4 to undergo T cell commitment.

### References:

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3. Visan, I., Tan, J.B., Yuan, J.S., Harper, J.A., Koch, U. & Guidos, C.J. Regulation of T lymphopoiesis by Notch1 and Lunatic fringe-mediated competition for intrathymic niches. *Nat Immunol* **7**, 634-643 (2006).