■ B-CELL DEVELOPMENT

Fringe benefits

Notch signalling, in addition to its well-known role in T-cell development, was recently found to be required for enabling immature B cells to become marginal zone (MZ) B cells — an innate-like population of mature B cells that resides in the spleen and is crucial for host defence against blood-borne bacteria. Specifically, Notch2 signalling induced by Delta-like ligand 1 (DLL1) drives the development of transitional 1 (T1) B cells into MZ B cells (via a MZ B-cell precursor) rather than into follicular B cells. However, it was unclear which cells in the spleen express DLL1 and how MZ B-cell development is regulated. Now, Guidos and colleagues show that DLL1 expression by vascular endothelial cells in the MZ and red pulp of the mouse spleen provides a niche to promote MZ B-cell development and that the DLL1–Notch2 interaction is positively regulated by the Fringe family glycosyltransferases.

Flow cytometry analysis of splenic B cells from Notch2 reporter mice indicated that the highest levels of Notch2 are present in MZ B-cell

precursors and MZ B cells. In addition, histological analysis of whole spleens revealed that DLL1 (as indicated by the expression of a LacZ reporter) was mainly observed in the red pulp vasculature, in particular in endothelial cells that interact closely with lymphocytes in the vessel lumen, and was the only Notch ligand to be highly expressed in the MZ. In contrast to previous predictions, expression of the DLL1–LacZ reporter was not detected in haematopoietic cells, including splenic dendritic cells. Experiments with chimeric mice confirmed that the expression of DLL1 by radioreistant stromal cells is required to support MZ B-cell development.

Next, the authors investigated whether Notch2-dependent MZ B-cell development was influenced by the Fringe enzymes Lunatic Fringe and Manic Fringe, which are thought to enhance interactions of Notch proteins with their ligands by modifying Notch glycosylation. Again, by generating various chimeric animals, they showed that deficiency of either Fringe

enzyme alone in transferred precursor cells compromised MZ B-cell development in mixed chimeras, but deficiency of both enzymes led to a more significant reduction in MZ B-cell development. This suggests that Lunatic Fringe and Manic Fringe function cooperatively to promote Notch2-mediated MZ B-cell development and that, in the absence of Fringe proteins, the DLL1–Notch2 interaction is inherently weak.

So, the authors propose that the vasculature of the red pulp provides a microenvironmental niche in which MZ B-cell precursors compete for limited amounts of DLL1, allowing some to mature into MZ B cells. Modification of Notch2 by the Fringe enzymes enhances this competition for DLL1 and thereby regulates the size of the MZ B-cell pool.

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ORIGINAL RESEARCH PAPER Tan, J. B. *et al.* Lunatic and Manic Fringe cooperatively enhance marginal zone B cell precursor competition for Delta-like 1 in splenic endothelial niches. *Immunity* **30**, 254–263 (2009)

FURTHER READING Allman, D. & Calamito, M. Instructing B cell fates on the fringe. *Immunity* **30**, 175–177 (2009)