Regulation of Cell Differentiation by Notch Signaling: Lessons from Comparative Analysis of RBP-J-deficient mice and Mint-deficient Mice

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Notch signaling controls cell fate decisions through local cell-cell interactions. Ligand-binding of Notch receptors induces proteolytic cleavages of Notch receptors and releases Notch intracellular domain (NICD) from membranes. Released NICD migrates into the nucleus and form a complex with DNA-binding protein RBP-J to transactivate target genes, thereby controlling cell differentiation processes.

We previously identified Mint as a suppressor of Notch signaling because Mint competes with NICD for RBP-J-binding, recruits transcriptional co-repressors, and suppresses RBP-J-mediated transcription. Mint-deficient embryos die as early as E12.5, displaying abnormalities in heart and pancreas, whose development critically require regulation by Notch signaling. Importantly, Mint deficiency increases marginal zone B cells and decreases follicular B cells in spleen, whereas inactivation of Notch signaling displays the opposite phenotype, strongly suggesting that Mint suppresses Notch signaling.

To further explore Mint function in regulation of Notch signaling, we analyzed Mint deficiency in two systems: Early T cell development in thymi and neurogenesis in developing cerebral cortices. During T cell development, Mint deficiency enhances generation of early T progenitors (ETPs) to the contrary of the effects by deficiency of Notch signaling. Unexpectedly, Mint deficiency blocks differentiation of ETPs into more mature T cells through induction of Nrarp, one of the Notch target genes, suggesting existence of a novel step controlled by Notch signaling during T cell development. In developing cerebral cortices, Mint deficiency impairs differentiation of neuronal progenitor cells into postmitotic neurons, while RBP-J deficiency results in the opposing phenotype. Taken together, these results indicate that Mint negatively regulates the mammalian Notch signaling in a wide variety of developmental processes such as lymphogenesis and neurogensis.

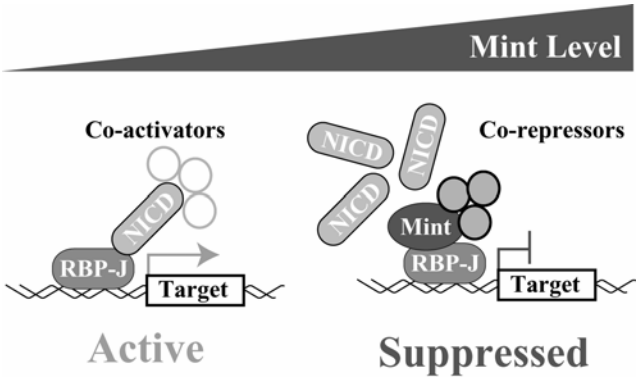

Fig. 1 Negative regulation of the Notch/RBP-J signaling by Mint.

Category	Biological Processes
Lymphogenesis	
B cells	MZB *vs* FoB cell fate decision
T cells	ETP production and differentiation αβT *vs* γδT cell fate decision
Neurogenesis	Cortical NPC differentiation
Pancreogenesis	Endocrine *vs* exocrine cell fate decision
Cardiogenesis	Septal development

Table. 1 Biological processes in which Mint has been shown to suppress the Notch/RBP-J signaling.