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MAML1-Dependent Notch-Responsive Genes Exhibit Differing Cofactor Requirements for Transcriptional Activation

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Abstract

Mastermind proteins are required for transcription of Notch target genes, yet the molecular basis for mastermind function remains incompletely understood. Previous work has shown that Notch can induce transcriptional responses by binding to promoters but more often by binding to enhancers, with HES4 and DTX1 as representative mammalian examples of promoter and enhancer responsiveness, respectively. Here, we show that mastermind dependence of the Notch response at these loci is differentially encoded in Jurkat T-cell acute lymphoblastic leukemia (T-ALL) cells. Knockout of Mastermind-like 1 (MAML1) eliminates Notch-responsive activation of both these genes, and reduced target gene expression is accompanied by a decrease in H3K27 acetylation, consistent with the importance of MAML1 for p300 activity. Add-back of MAML1 variants in knockout cells identifies residues 151 to 350 of MAML1 as essential for expression of either Notch-responsive gene. Fusion of the Notch-binding region of MAML1 to the histone acetyltransferase (HAT) domain of p300 rescues expression of HES4 but not DTX1, suggesting that an additional activity of MAML1 is needed for gene induction at a distance. Together, these studies establish the functional importance of the MAML1 region from residues 151 to 350 for Notch-dependent transcriptional induction and reveal differential requirements for MAML1-dependent recruitment activities at different Notch-responsive loci, highlighting the molecular complexity of Notch-stimulated transcription.