Modulation of epigenetic marks at cell-context dependent Notch target genes

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Notch proteins are transmembrane receptors which influence cell fate decisions, differentiation, proliferation and apoptosis in many developmental systems including neurogenesis and myogenesis. After ligand binding and activation, the Notch intracellular domain (NIC) is cleaved from the cytoplasmic membrane and translocates into the nucleus to act as a transcription factor. NIC binds to DNA via the adapter protein RBP-J (also termed CBF-1) and converts the transcriptional repressor RBP-J into a transcriptional activator. Recently we have shown that Notch signaling regulates expression of genes playing key roles in cell differentiation, cell cycle control and apoptosis in a highly context dependent manner. Epigenetic events like histone modification, DNA methylation and chromatin remodeling are tightly involved in the control of gene expression. To investigate the role of chromatin modifications for cell-context dependent activation of direct Notch target genes, we analysed the chromatin modifications present at the regulatory regions of genes that we identified to be regulated in embryonic stem cells (ESC) by activated Notch using public databases. We found that the promoter regions of Notch target genes are marked by an enrichment of H3K4me3 and bivalent domains (H3K4me3 and H3K27me3). We further screened the regulatory regions of the Notch1 target genes Hes5, Sox9 and Myf5 for potential RBP-J binding sites and analysed the modifications and their changes upon Notch activation in ESC and mesodermal cells. After activation of Notch signaling for 4 h, H3K4me3 and H3K4me2 marks at the regulatory regions of Notch target genes, Hes5 and Sox9 in ESC and Myf5 in mesodermal cells, were increased, suggesting that Notch signaling may lead to remodeling at the regulatory regions of its target genes. In addition, we tested the effect of LSD-1 (Lysine specific demethylase 1), a histone modifying enzyme that controls gene repression, on the expression of Notch target genes. After inhibition of LSD-1 by PCPA, Notch induced gene expression of the target genes Hes5, Hey1, Id4 and Pax6 was increased in ESC, further indicating an important role for histone modifications in the regulation of Notch target gene activation.