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Selective repression of Notch pathway target gene transcription

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ABSTRACT

The Notch signaling pathway regulates metazoan development, in part, by directly controlling the transcription of target genes. For a given cellular context, however, only subsets of the known target genes are transcribed when the pathway is activated. Thus, there are context-dependent mechanisms that selectively maintain repression of target gene transcription when the Notch pathway is activated. This review focuses on molecular mechanisms that have been recently reported to mediate selective repression of Notch pathway target gene transcription. These mechanisms are essential for generating the complex spatial and temporal expression patterns of Notch target genes during development.

Introduction

The Notch signaling pathway is necessary for regulating many cellular processes in metazoan development, including progenitor proliferation, cell-fate specification and cell death (Gazave et al., 2009; Richards and Degnan, 2009). This regulation involves a direct control of gene transcription that is coordinated by the DNA binding transcription factor CSL (CBF-1/RBPJκ/Suppressor of Hairless/LAG-1). A summary of the canonical model by which the Notch signaling pathway regulates gene transcription is provided in Fig. 1. In brief, when the Notch pathway is not active, target gene transcription is blocked by protein co-repressor complexes assembled on CSL (Kopan and Ilagan, 2009; Lai, 2002). Activation of target gene transcription involves the conversion of CSL from a co-repressor to a co-activator, and this conversion requires activation of the Notch pathway. Membrane-bound DSL (Delta/Serrate/LAG-2) proteins expressed by adjacent cells are the canonical ligands that activate the Notch receptors. These ligands bind to the Notch extracellular domain (NECD) and induce a proteolytic cleavage of the Notch receptor that releases the NECD-ligand complex. Endocytic trafficking of the NECD-ligand complex in the ligand-expressing cell is crucial for proper activation of the Notch pathway in the receptor-expressing cell (Le Borgne et al., 2005). Following cleavage of the NECD, the Notch intracellular domain (NICD) is proteolytically released and transported into the nucleus. In the nucleus, NICD forms a complex with CSL and displaces the co-repressor proteins bound to CSL. Mastermind (MAM)/Mastermind-like (MAML)/LAG-3 is the canonical transcription co-activator protein that binds the CSL/NICD complex. CSL/NICD/MAM complexes enhance target gene expression, in part, by recruiting other co-activators and chromatin remodeling enzymes (Kopan and Ilagan, 2009). This ensemble of co-activators bound to CSL/NICD is referred to as the "Notch transcription complex."

Recent proteomic approaches have expanded the number of genes that are direct targets of the Notch transcription complexes (Hamidi et al., 2011; Margolin et al., 2009; Palomero et al., 2006). In any given cellular context, however, only a subset of target genes is transcribed when the pathway is activated. In the *C.elegans* embryo, for example, different members of the *ref-1* family of basic-helix-loop-helix (bHLH) repressor genes are activated in partially overlapping patterns within the AB and EMS cell lineages (Neves and Priess, 2005). Alternatively, in *Drosophila melanogaster*, Notch signaling drives expression of individual genes of the *Enhancer of split Complex* (*E(spl)-C*) in spatially and temporally distinct patterns within the developing embryonic and larval tissues (Cooper et al., 2000; de Celis et al., 1996; Maeder et al., 2009; Nellesen et al., 1999; Wech et al., 1999). Also, murine *Hes5* and *Hes1* show reciprocal expression patterns in the developing midbrain, hindbrain, isthmus and optic vesicles (Hatakeyama et al., 2004). Additional examples of differential expression patterns for Notch target genes in vertebrate development are reported in the kidney (Chen and Al-Awqati, 2005; Leimeister et al., 2003; Piscione et al., 2004), intestine (Schroder and Gossler, 2002), heart (Fischer and Gessler, 2003), as well as embryonic stem cells (Meier-Stiegen et al., 2010).

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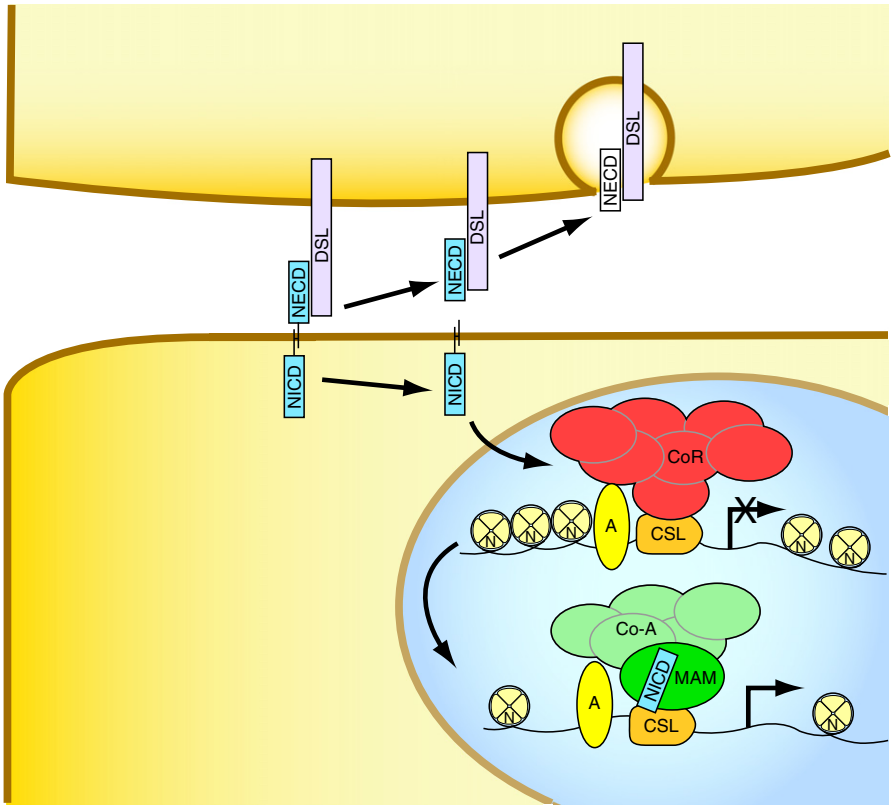

Fig. 1. Summary of the canonical Notch signaling pathway. DSL (Delta/Serrate/LAG2) ligand binding to the Notch extraceullular domain (NECD) induces proteolytic cleavage that releases the NECD-ligand complex, which is subsequently endocytosed by the ligand-expressing cell. The remaining membrane-bound Notch protein is proteolytically cleaved to release the Notch intracellular domain (NICD). In the absence of NICD, the DNA binding transcription factor CSL (CBF-1/RBPJκ/Suppressor of Hairless/LAG1) blocks transcription of pathway target genes by recruiting co-repressor (CoR) protein complexes. When the Notch pathway is activated, NICD translocates to the nucleus and forms a complex with CSL, which displaces the co-repressor proteins bound to CSL. The CSL/NICD complex recruits co-activator protein Mastermind (MAM) and the CSL/NICD/MAM complex serves as a scaffold for other transcription co-activators. Chromatin and nucleosome (N) remodeling enzymes are important components of both co-activator and co-repressor complexes recruited by CSL. Strong activation of gene expression requires synergistic interactions with local transcription factor activator proteins (A) also bound to the target gene cis-regulatory modules.

Selective activation of Notch pathway target gene transcription

Since all canonical Notch pathway target gene transcription is coordinated by a single CSL protein orthologue, a fundamental question is how the Notch pathway differentially activates transcription in a context-dependent manner? Combinatorial interactions between Notch transcription complexes and tissue-specific (or local) transcription factor activators bound to target gene cis-regulatory elements are an effective mechanism to selectively activate transcription (reviewed in Barolo and Posakony, 2002). These combinatorial interactions restrict target gene transcription to those cells that have both the specific local activators expressed and the Notch pathway activated. In the absence of local activators, Notch signaling is either insufficient to activate target gene expression or only induces weak expression levels (Barolo and Posakony, 2002). A well established example of this combinatorial regulation is the synergistic and physical interaction between basic-helix-loop-helix (bHLH) proteins and Notch transcription complexes that activate the expression of specific target genes in *Drosophila* and *Xenopus* neurogenic territories (Castro et al., 2005; Cave et al., 2005, 2009; Cooper et al., 2000; Lamar and Kintner, 2005; Singson et al., 1994). In other cellular contexts, Notch transcription complexes can synergistically and physically interact with other types of local transcription factors to activate transcription of different target genes (Blokzijl et al., 2003; Gustafsson et al., 2005; Hayashi and Kume, 2008; Itoh et al., 2004; Kitamura et al., 2007; Maekawa et al., 2008; Neves et al., 2007; Sakamoto et al., 2008; Sun et al., 2005; Takizawa et al., 2003; Tang et al., 2010).

For organisms that express multiple Notch receptor paralogues, the incorporation of different NICD paralogues into Notch transcription complexes increases the combinatorial complexity with local activators. Mammals, for example, express four Notch receptor paralogues and, in aortic smooth muscle cells, phosphorylated-SMAD2/3 transcription factors physically interact with Notch4-ICD, but not with either Notch1-ICD or and Notch2-ICD (Tang et al., 2010). These differential interactions with local activators are important for establishing target gene preferences for NICD paralogues (Ong et al., 2006).

Although combinatorial interactions between Notch transcription complexes and local activators are likely the predominant mechanism by which Notch target gene transcription is selectively activated, alternative mechanisms have been also reported. Transcription of the mammalian *Hes1* or *Hey2* canonical Notch target genes is activated by Notch-independent mechanisms in some developmental contexts (Curry et al., 2006; Doetzlhofer et al., 2009; Leimeister et al., 2000; Sanalkumar et al., 2010; Stockhausen et al., 2005; Timmerman et al., 2004; Wall et al., 2009). This Notch-independent activation of *Hes1* and *Hey2* transcription requires the activity of other signaling pathways, but how these other pathways abrogate repression mediated by CSL/co-repressor without the assistance of the Notch pathway is unclear. In the developing pancreas and spinal cord, CSL-mediated repression of *Elastase1* and *Neurogenenin2*, respectively, is alleviated by physical interactions between PTF1 protein complex and CSL (Beres et al., 2006; Henke et al., 2009). The PTF1 complex binds the genomic DNA adjacent to CSL and displaces the co-repressors bound to CSL to activate gene transcription. Notch signaling is dispensable for this mechanism since the PTF1 complex excludes NICD from binding to