PRIMER

Setting the Stage for Notch: The *Drosophila* Su(H)-Hairless Repressor Complex

**Tilman Borggrefe**1, **Franz Oswald**2

1 Institute of Biochemistry, University of Giessen, Giessen, Germany, 2 Center for Internal Medicine, Department of Internal Medicine I, University Medical Center Ulm, Ulm, Germany

* Tilman.Borggrefe@biochemie.med.uni-giessen.de

**Abstract**

Notch signaling is iteratively used throughout development to maintain stem cell potential or in other instances allow differentiation. The central transcription factor in Notch signaling is CBF-1/RBP-J, Su(H), Lag-1 (CSL)—Su(H) in *Drosophila*—which functions as a molecular switch between transcriptional activation and repression. Su(H) represses transcription by forming a complex with the corepressor Hairless (H). The Su(H)-repressor complex not only competes with the Notch intracellular domain (NICD) but also configures the local chromatin landscape. In this issue, Yuan and colleagues determined the structure of the Su(H)/H complex, showing that a major conformational change within Su(H) explains why the binding of NICD and H is mutually exclusive.

Notch signaling is one of only a handful of highly conserved signal transduction pathways that translate extracellular cues into changes in gene expression. Upon ligand binding, the Notch receptor is proteolytically cleaved, resulting in the release of the Notch intracellular domain (NICD). NICD subsequently migrates into the nucleus and binds to the transcription factor CBF-1/RBP-J, Su(H), Lag-1 (CSL), which in *Drosophila melanogaster* is known as Suppressor of Hairless, or Su(H) (see also Fig 1). The activation of Notch target genes requires the recruitment of the coactivator complex, which is composed of transcription cofactors like mastermind (MAM) and the histone acetyltransferase (HAT) p300 [1,2]. Distinct positive histone marks, like H3K27ac and H3K4me3, characterize this transcriptionally active state (see Fig 1[right side: “ON”]). In the absence of a Notch signal, CSL recruits a corepressor complex containing histone deacetylases (HDACs) and H3K4 demethylases (KDMs) (see Fig 1[left side: “OFF”]; reviewed in [3]). Thus, the transcription factor CSL functions as a molecular switch by binding either to corepressors or coactivators. In this issue, Yuan et al. [4] unveil the structural and molecular details of the Su(H) corepressor complex in *Drosophila*. This is not only important for the Notch community but is also a pioneering example of how other central transcriptional switches in other evolutionary conserved signal transduction pathways may work. Interestingly, it is known that epigenetic modifiers such as HDACs and HATs as well as histone lysine demethylases (KDMs) and histone lysine methyltransferases (KMTs) contribute to the fine-tuning of the transcriptional switch by dynamically regulating the chromatin environment at
the core promoters and/or at enhancers. At the heart of this, there is a single transcription factor—or most likely an ensemble of several transcription factors—orchestrating the signaling output even before the ligand binds to its cognate receptor. Thus, understanding the molecular details of the key players in such switches—for example, the transcription factor Su(H) bound to its cofactor Hairless—is the eye-opener for designing mutants that allow for differentiation between activating and repressing mechanisms by changing individual amino acids. As an excellent example, this has been done in the study by Yuan et al. using the power of crystallography together with Drosophila genetics, which is particularly well-studied in regard to Notch signaling.

**The Notch Transcriptional Activator Complex**

In order to understand molecular mechanisms of biological processes, crystal structures are extremely insightful. Table 1 summarizes the structures that contain CSL-mediated transcription complexes. Historically, the mammalian transcription factor CSL (also known as recognition binding protein of Jκ [RBP-J or RBP-Jκ]) was discovered by Honjo and colleagues in the 1990s [5] and later was revealed to be the mammalian ortholog of Su(H) from Drosophila [6]. The original CSL-DNA complex structure showed that CSL is a distant relative of the Rel

---

**Lef, Lymphoid enhancer binding factor; MAM, Mastermind; NICD, Notch intracellular domain; NTD, N-terminal domain; PDB, protein data bank; RAM, RBP-J associated molecule; RBP-J, recognition binding protein of Jκ; RITA, RBPJ interacting and tubulin associated; SHARP, SMRT/HDAC1 associated repressor protein; Su(H), Suppressor of Hairless; TCF, T cell factor.**
homology–containing transcription factor family [7]. The structure clearly shows that CSL is composed of three domains: N-terminal domain (NTD), β-trefoil domain (BTD), and C-terminal domain (CTD) [7–9]. The NTD and BTD domains are involved in DNA binding. Subsequently, two landmark studies determined the structure of the Notch activator complex, comprising CSL, a small N-terminal peptide of MAM, and the RAM (RBP-J associated molecule) and ANK (ankyrin repeats) domains of NICD. Importantly, as depicted in Fig 2A and described in [10,11], the RAM domain of NICD interacts with the BTD of CSL, whereas MAM is sandwiched between the surface formed between the CTD and ANK. This macromolecular assembly is supported by experiments demonstrating that the ~70 amino acids of MAM seen in the structure are sufficient to block transcription of Notch target genes in a dominant-negative manner [12].

The CSL [Su(H)] Transcriptional Repressor Complex

Like the Notch locus itself, the Hairless (H) locus was discovered in 1923 by Bridges and Morgan as a haploinsufficient mutation in *Drosophila* (reviewed in [16]). The genetic interactions demonstrated that H antagonizes Notch signaling in a dose-dependent manner. Considering all the known interaction partners for CSL, H binds to Su(H) with the highest affinity (Kd = 2 nM) [4,17]. The Su(H)-interaction domain of H on its own is an unstructured random coil. After binding to the CTD of Su(H), H assumes a β-hairpin conformation (see Fig 2C and the manuscript in this issue [4]). Surprisingly, H interacts with specific side chains within the hydrophobic core of the Su(H)-CTD that are not exposed to the surface in the unbound structure of Su(H) [4]. The CTD of Su(H) is composed of a seven-stranded immunoglobulin (Ig) fold (two β-sheets composed of three and four β-strands). This Ig-fold shows dramatic conformational changes when bound to H. H is sandwiched between the two β-sheets that compose the CTD, which is a hitherto completely new and unique interaction mode for Ig-folds. The conformational changes within the CTD block the CTD–NICD interaction and explain why binding of NICD and H are mutually exclusive. Based on their structural data, Yuan and colleagues designed specific point mutations within the CTD of Su(H), which lost H binding capacity but still was able to bind to NICD. In *D. melanogaster* in vivo experiments, using

### Table 1. Available CSL complex structure data (protein data bank [PDB] database).

| PDB-ID | Complex | Species | Reference |
|-------|---------|---------|-----------|
| 1TTU  | CSL bound to DNA | *Caenorhabditis elegans* | [7] |
| 2FO1  | activator complex bound to DNA* | *C. elegans* | [10] |
| 2F8X  | activator complex bound to DNA* | *Homo sapiens* | [11] |
| 3BRD  | CSL-RAM bound to DNA | *C. elegans* | [8] |
| 3BRF  | CSL-RAM bound to DNA | *C. elegans* | [8] |
| 3BRG  | CSL bound to DNA | *Mus musculus* | [8] |
| 3NBN  | activator complex dimer bound to DNA | *H. sapiens* | [13] |
| 3V79  | activator complex bound to DNA* | *H. sapiens* | [14] |
| 3IAG  | CSL bound to DNA | *M. musculus* | [9] |
| 4J2X  | repressor complex bound to DNA** | *M. musculus, H. sapiens* | [15] |
| 5E24  | repressor complex bound to DNA*** | *Drosophila melanogaster* | [4] |

*(CSL/ANK/RAM/MAM),

*(CSL/ANK/MAM),

**(CSL/KyoT2),

***([Su(H]/H).
Notch-dependent wing and eye development as a readout, they could finally show that these Su(H) mutants have lost their corepressor activities but preserved their coactivator activity. These data highlight the importance of using Drosophila as a model system.

Considering the structure by Yuan et al. [4] in a broader context, the repressor structure also suggests that the on- and off-rates of the Su(H)/H corepressor complex are slow; this is in contrast to CSL/NICD/MAM coactivator. To date, a pulse of Notch signaling was mainly considered to be an interplay between receptor–ligand binding, posttranslational modifications of the NICD, and, ultimately, turnover of the coactivator complex [18]. Now, the rate of Su(H)-corepressors should be included in such considerations. Furthermore, the repressive mechanism at Notch target genes could also be a general theme used for other signaling pathways, like Wnt and Hedgehog signaling. For Hedgehog signaling, Gli is the central transcription factor, but the mechanisms of cofactor recruitment remain to be elucidated. For Wnt signaling, the central transcription factor is T cell factor (TCF)/Lymphoid enhancer binding factor (Lef),...
which in the absence of a Wnt signal binds promoters and recruits HDAC-containing corepressor complexes (reviewed in [19]).

The CSL-Repressor Complex Configures Chromatin for the Notch Response

Regarding the repressive mechanism mediated by the CSL-repressor complex, H recruits Groucho and an HDAC-containing C-terminal binding protein (CtBP) corepressor complex [20–22]. The same is true for the human CSL-repressor complex containing HDACs and CtBP [23] (reviewed in [24]). Surprisingly, there is no direct Hairless homolog in mammals, but the functional homolog suggested by us and others is SHARP (also known as Spen or MINT). SHARP directly binds CSL, and intriguingly, it also interacts with the CTD of CSL similarly to Hairless [25].

Biochemical experiments from several laboratories implicated not only HDACs but also H3K4 demethylases as direct CSL-associated factors both in *Drosophila* [26–28] and mammals [28,29]. Recently, we added the counteracting H3K4 methyltransferase KMT2D as a novel component of the CSL coregulator complex [30]. All of these chromatin modifications are not only directed by a single transcription factor but most likely by a set of few transcription factors. The created balance between positive and negative histone marks sets the stage for the incoming extracellular signal.

The structure-based point mutants described in [4] gives us insights into how precisely mutagenesis can be used to dissect function of pivotal transcription complexes. Clearly, the next big step in the field is to solve the structure of human CSL/SHARP corepressor complex. Since CSL has been shown to function as a tumor suppressor [31], it might be feasible to design therapeutics that disrupt CSL-corepressor interactions in order to weakly activate Notch signaling, which may be beneficial in some disease settings.

Genome-wide studies using anti-CSL and anti-NICD antibodies have been important to define bona fide Notch target genes [32–34] in cells. Further analysis suggests that CSL occupancy depends on the presence of an active Notch signal [35,36], questioning the whole concept of CSL-bound corepressors. On the other hand, there are reports showing that deletion of CSL leads to derepression of some Notch target genes, both in *Drosophila* [20,37,38] and mammals [39]. Certainly, CSL knockout followed by rescue with wildtype or mutant CSL will be key to addressing this open question, leading the way forward to dissect individual functions of this central transcription factor. It will also be interesting to dissect the chromatin landscape at Notch target genes in the presence or absence of CSL or of individual corepressors.

In mammals, the situation of the CSL corepressor—namely SHARP [40,41], KyoT2 [42], and RITA [43] complex—is more complex, and the molecular mechanisms need to be further elucidated in the future. Clearly, as a next step, the cocrystal structures of CSL/SHARP and CSL/RITA would be a big move forward. (Fig 2D). This will unravel the molecular mechanisms whether or not the RAM-type or Hairless-type of binding to transcription factor CSL is the predominant one or if alternative types of interactions do exist.

References

1. Oswald F, Tauber B, Dobner T, Bourteele S, Kostezka U, Adler G, et al. p300 acts as a transcriptional coactivator for mammalian Notch-1. Mol Cell Biol. 2001; 21(22):7761–74. PMID: 11604511.
2. Kurooka H, Honjo T. Functional interaction between the mouse notch1 intracellular region and histone acetyltransferases PCAF and GCN5. J Biol Chem. 2000; 275(22):17211–20. PMID: 10747963.
3. Borggreve T, Liefke R. Fine-tuning of the intracellular canonical Notch signaling pathway. Cell Cycle. 2012; 11(2):264–76. Epub 2012/01/10. doi: 10.4161/cc.11.2.18995 PMID: 22223095.
Nagel AC, Krejci A, Tenin G, Bravo-Patino A, Bray S, Maier D, et al. Hairless-mediated repression of
22.
12.
Maillard I, Weng AP, Carpenter AC, Rodriguez CG, Sai H, Xu L, et al. Mastermind critically regulates
19.
Borggrefe T, Lauth M, Zwijsen A, Huylebroeck D, Oswald F, Giaimo BD. The Notch intracellular domain
Morel V, Lecourtois M, Massiani O, Maier D, Preiss A, Schweisguth F. Transcriptional repression by
20.
21.
Barolo S, Stone T, Bang AG, Posakony JW. Default repression and Notch signaling: Hairless acts as
10.
13.
Arnett KL, Hass M, McArthur DG, Ilagan MX, Aster JC, Kopan R, et al. Structural and mechanistic
11.
Nam Y, Sliz P, Song L, Aster JC, Blacklow SC. Structural basis for cooperativity in recruitment of MAML
14.
Choi SH, Wales TE, Nam Y, O'Donovan DJ, Sliz P, Engen JR, et al. Conformational locking upon coop-
15.
Collins KJ, Yuan Z, Kovall RA. Structure and function of the CSL-KyoT2 corepressor complex: a nega-
16.
Hamaguchi Y, Yamamoto Y, Iwanari H, Maruyama S, Furukawa T, Matsunami N, et al. Biochemical and
17.
Maier D, Kurth P, Schulz A, Russell A, Yuan Z, Gruber K, et al. Structural and functional analysis of the
18.
Hein K, Mittler G, Cizelsky W, Kuhl M, Ferrante F, Liefke R, et al. Site-specific methylation of Notch1
19.
and immunological characterization of the DNA binding protein (RBP-J kappa) to mouse J kappa
10.
11.
Kovall RA, Hendrickson WA. Crystal structure of the nuclear effector of Notch signaling, CSL, bound to
DNA. EMBO J. 2004; 23(17):3441–51. Epub 2004/08/07. doi: 10.1093/emboj/ded288; PubMed Central PMC:
15297877; PubMed Central PMCID: PMC516623.
8. Friedmann DR, Wilson JJ, Kovall RA. RAM-induced allostery facilitates assembly of a notch pathway
active transcription complex. J Biol Chem. 2008; 283(21):14781–91. Epub 2008/04/03. doi: 10.1074/jbc.
M709501200 PMID: 18381292; PubMed Central PMCID: PMC2386923.
9. Friedmann DR, Kovall RA. Thermodynamic and structural insights into CSL-DNA complexes. Protein
Sci. 2010; 19(1):34–46. Epub 2009/10/30. doi: 10.1002/pro.280 PMID: 19866488; PubMed Central
PMCID: PMC2817837.
10. Wilson JJ, Kovall RA. Crystal structure of the CSL-Notch-Mastermind ternary complex bound to DNA.
Cell. 2006; 124(5):985–96. Epub 2006/03/15. doi: 10.1016/j.cell.2006.01.035 PMID: 16530045.
11. Nam Y, Sliz P, Song L, Aster JC, Blacklow SC. Structural basis for cooperativity in recruitment of MAML
coactivators to Notch transcription complexes. Cell. 2006; 124(5):973–83. Epub 2006/03/15. S0092-
8674(06)00122-X [pii] doi: 10.1016/j.cell.2005.12.037 PMID: 16530044.
12. Maillard I, Weng AP, Carpenter AC, Rodriguez CG, Sai H, Xu L, et al. Mastermind critically regulates
Notch-mediated lymphoid cell fate decisions. Blood. 2004; 104(6):1696–702. Epub 2004/06/10. doi:
10.1182/blood-2004-02-0514 2004-02-0514 [pii]. PMID:15187027.
13. Arnett KL, Hass M, McArthur DG, Iglan MX, Aster JC, Kopan R, et al. Structural and mechanistic
insights into cooperative assembly of dimeric Notch transcription complexes. Nat Struct Mol Biol. 2010;
17(11):1312–7. doi: 10.1038/nsmb.1938 PMID: 20972443; PubMed Central PMCID: PMC3024583.
14. Choi SH, Wales TE, Nam Y, O’Donovan DJ, Sliz P, Engen JR, et al. Conformational locking upon coop-
erative assembly of notch transcription complexes. Structure. 2012; 20(2):340–9. doi: 10.1016/j.str.
2011.12.011 PMID: 22325781; PubMed Central PMCID: PMC3285698.
15. Collins KJ, Yuan Z, Kovall RA. Structure and function of the CSL-KyoT2 corepressor complex: a nega-
tive regulator of Notch signaling. Structure. 2014; 22(1):70–81. doi: 10.1016/j.str.2013.10.010 PMID:
24290140; PubMed Central PMCID: PMC3947186.
16. Maier D. Hairless: the ignored antagonist of the Notch signalling pathway. Hereditas. 2006; 143
(2006):212–21. doi: 10.1111/j.2007.0018-0661.01971.x PMID: 17362357.
17. Maier D, Kurth P, Schulz A, Russell A, Yuan Z, Gruber K, et al. Structural and functional analysis of
the repressor complex in the Notch signalling pathway of Drosophila melanogaster. Mol Biol Cell. 2011;
22(17):3242–52. Epub 2011/07/09. doi: 10.1091/mbc.E11-05-0420 PMID: 21737682; PubMed Central
PMCID: PMC3164469.
18. Hein K, Mittler G, Cizelsky W, Kuhl M, Ferrante F, Liefke R, et al. Site-specific methylation of Notch1
controls the amplitude and duration of the Notch1 response. Sci Signal. 2015; 8(369):ra30. doi: 10.
1126/scisignal.2005892 PMID: 25805888.
19. Borggrefe T, Lauth M, Zwijsen A, Huylenbroeck D, Oswald F, Giavo BD. The Notch intracellular domain
integrates signals from Wnt, Hedgehog, TGFbeta/BMP and hypoxia pathways. Biochim Biophys Acta.
2016; 1863(2):1702. Epub 2015/11/10. doi: 10.1016/j.bbamcr.2015.11.020 PMID: 26592459.
20. Morel V, Lecourtois M, Massiani O, Maier D, Preiss A, Schweiguth F. Transcriptional repression by
suppressor of hairless involves the binding of a hairless-dCTBP complex in Drosophila. Curr Biol. 2001;
11(10):789–92. Epub 2001/05/30. PMID: 11378391.
21. Barolo S, Stone T, Bang AG, Posakony JW. Default repression and Notch signaling: Hairless acts as an
adaptor to recruit the corepressors Groucho and dCTBP to Suppressor of Hairless. Genes Dev. 2002;
16(15):1964–76. doi: 10.1101/gad.987402 PMID: 12154126; PubMed Central PMCID: PMC186408.
22. Nagel AC, Krejci A, Tenin G, Bravo-Patino A, Bray S, Maier D, et al. Hairless-mediated repression of
notch target genes requires the combined activity of Groucho and CtBP corepressors. Mol Cell Biol.
2005, 25(23):10433–41. doi: 10.1128/MCB.25.23.10433-10441.2005 PMID: 16287856; PubMed Central
PMCID: PMC1291231.
23. Oswald F, Winkler M, Cao Y, Astrahantseff K, Bourteele S, Knochel W, et al. RBP-Jκappa/SHARP recruits CtIP/CtBP corepressors to silence Notch target genes. Mol Cell Biol. 2005; 25(23):10379–90. PMID: 16287852.

24. Borggrefe T, Oswald F. The Notch signaling pathway: transcriptional regulation at Notch target genes. Cell Mol Life Sci. 2009; 66(10):1631–46. Epub 2009/01/24. doi:10.1007/s00018-009-8668-7 PMID: 19165418.

25. VanderWielen BD, Yuan Z, Friedmann DR, Koval RA. Transcriptional repression in the Notch pathway: thermodynamic characterization of CSL-MINT (Msx2-interacting nuclear target protein) complexes. J Biol Chem. 2011; 286(17):14892–902. Epub 2011/03/05. doi:10.1074/jbc.M110.118156 PMID: 21372128; PubMed Central PMCID: PMC3083192.

26. Moskvin YM, Kan TW, Goodfellow H, Bezstarosti K, Maeda RK, Pilyugin M, et al. Histone chaperones ASF1 and NAP1 differentially modulate removal of active histone marks by LID-RPD3 complexes during NOTCH silencing. Mol Cell. 2011; 35(6):782–93. Epub 2009/09/29. doi:10.1016/j.molcel.2009.07.020 PMID: 19782028.

27. Di Stefano L, Walker JA, Burgio G, Corona DF, Mulligan P, Naar AM, et al. Functional antagonism between histone H3K4 demethylases in vivo. Genes Dev. 2011; 25(1):17–28. Epub 2011/01/06. doi:10.1101/gad.1983711 PMID: 21205864; PubMed Central PMCID: PMC3012933.

28. Mulligan P, Yang F, Di Stefano L, Ji JY, Ouyang J, Nishikawa JL, et al. A SIRT1-LSD1 corepressor complex regulates Notch target gene expression and development. Mol Cell. 2011; 42(5):689–99. Epub 2011/05/21. doi:10.1016/j.molcel.2011.04.020 PMID: 21596603; PubMed Central PMCID: PMC3119599.

29. Liefke R, Oswald F, Alvarado C, Ferres-Marco D, Mittler G, Rodríguez P, et al. Histone demethylase KDM5A is an integral part of the core Notch-RBP-J repressor complex. Genes Dev. 2010; 24(6):590–601. Epub 2010/03/17. doi:10.1101/gad.563210 PMID: 20231516; PubMed Central PMCID: PMC2841336.

30. Oswald F, Rodríguez P, Giaino BD, Antonello ZA, Mira L, Mittler G, et al. A phospho-dependent mechanism involving NCoR and KMT2D controls a permissive chromatin state at Notch target genes. Nucleic Acids Res. 2016; 44(10):4703–20. doi: 10.1093/nar/gkw105 PMID: 26912830.

31. Kulic I, Robertson G, Chang L, Baker JH, Lockwood WW, Mok W, et al. Loss of the Notch effector RBPJ promotes tumorigenesis. J Exp Med. 2015; 212(1):37–52. doi:10.1084/jem.20121192 PMID: 25512468; PubMed Central PMCID: PMC4291530.

32. Skalska L, Stoijnic R, Li J, Fischer B, Cerda-Moya G, Sakai H, et al. Chromatin signatures at Notch-regulated enhancers reveal large-scale changes in H3K56ac upon activation. EMBO J. 2015; 34(14):1889–904. doi: 10.15252/embj.201489923 PMID: 26069324; PubMed Central PMCID: PMC4547894.

33. Wang H, Zou J, Zhao B, Johannsen E, Ashworth T, Wong H, et al. Genome-wide analysis reveals conserved and divergent features of Notch1/RBPJ binding in human and murine T-lymphoblastic leukemia cells. Proc Natl Acad Sci U S A. 2011; 108(36):14908–13. Epub 2011/07/09. doi:10.1073/pnas.1109023108 PMID: 21737748; PubMed Central PMCID: PMC3169118.

34. Geimer Le Lay AS, Oravecz A, Mastio J, Marchal P, Ebel C, et al. The tumor suppressor Ikaros shapes the repertoire of notch target genes in T cells. Sci Signal. 2014; 7(317):ra28. Epub 2014/03/20. doi: 10.1126/scisignal.2004545 PMID: 24643801.

35. Castel D, Mourikis P, Bartels SJ, Brinkman AB, Tajbakhsh S, Stunnenberg HG. Dynamic binding of RBPJ is determined by Notch signaling status. Genes Dev. 2013; 27(9):1059–71. Epub 2013/05/09. doi:10.1101/gad.211912.112 PMID: 23651858.

36. Krejci A, Bray S. Notch activation stimulates transient and selective binding of Su(H)/CSL to target enhancers. Genes Dev. 2007; 21(11):1322–7. Epub 2007/06/05. doi:10.1101/gad.424607 PMID: 17545467; PubMed Central PMCID: PMC1877745.

37. Furriols M, Bray S. Dissecting the mechanisms of suppressor of hairless function. Dev Biol. 2000; 227(2):520–32. doi:10.1006/dbio.2000.9923 PMID: 11071771.

38. Klein T, Seugnet L, Haenlin M, Martinez Arias A. Two different activities of Suppressor of Hairless during wing development in Drosophila. Development. 2000; 127(16):3553–66. PMID: 10903180.

39. Procopio MG, Laszlo C, Al Labban D, Kim DE, Bordignon P, Jo SH, et al. Combined CSL and p53 downregulation promotes cancer-associated fibroblast activation. Nat Cell Biol. 2015; 17(9):1193–204. doi:10.1038/ncb3228 PMID: 26302407; PubMed Central PMCID: PMC4694446.

40. Oswald F, Kostezka U, Astrahantseff K, Bourteele S, Dillinger K, Zechner U, et al. SHARP is a novel component of the Notch/RBP-Jκappa signalling pathway. Embo J. 2002; 21(20):5417–26. PMID: 12374742.
41. Kuroda K, Han H, Tani S, Tanigaki K, Tun T, Furukawa T, et al. Regulation of marginal zone B cell development by MINT, a suppressor of Notch/RBP-J signaling pathway. Immunity. 2003; 18(2):301–12. PMID: 12594956.

42. Taniguchi Y, Furukawa T, Tun T, Han H, Honjo T. LIM protein KyoT2 negatively regulates transcription by association with the RBP-J DNA-binding protein. Mol Cell Biol. 1998; 18(1):644–54. Epub 1998/01/07. PMID: 9418910; PubMed Central PMCID: PMC121531.

43. Wacker SA, Alvarado C, von Wichert G, Knippschild U, Wiedenmann J, Clauss K, et al. RITA, a novel modulator of Notch signalling, acts via nuclear export of RBP-J. EMBO J. 2011; 30(1):43–56. Epub 2010/11/26. doi:10.1038/emboj.2010.289 PMID: 21102556; PubMed Central PMCID: PMC3020113.