Coordinating neuronal differentiation with repression of the progenitor program: Role of the transcription factor MyT1

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ABSTRACT
The generation of neurons at the correct time and location in the developing nervous system requires a fine balance between gene expression programs that regulate differentiation and maintenance of neural stem cells. During vertebrate neurogenesis, cell fate commitment and differentiation of neural stem cells toward the neuronal lineage are regulated by the opposing activities of the proneural and Notch pathways. Neuronal differentiation is inhibited by high Notch signaling characteristic of neural stem/progenitor cells, and requires the repression of the Notch transcriptional program by mechanisms that are still poorly understood. In a recent study, we showed the zinc-finger transcription factor MyT1 promotes neurogenesis downstream the proneural factor Ascl1. MyT1 functions as a repressor of many Notch transcriptional target genes, linking the activation of a differentiation program by Ascl1 with the repression of the neuronal progenitor identity. Here we analyze our findings in light of the current knowledge in the field, and discuss the implications to our understanding of how MyT1 family members operate in vertebrate neurogenesis.

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In the developing vertebrate embryo, bHLH proneural factors such as Ascl1 are both required and sufficient to promote the cell fate commitment and differentiation of neural stem cells toward the neuronal lineage. Previous studies have shown that Ascl1 functions as a transcriptional activator during neurogenesis, activating a wide range of target genes with various biological activities, and associated with multiple components of the differentiation program. While promoting neurogenesis, proneural factors induce the expression of Notch ligands, resulting in activation of Notch signaling in neighboring progenitors via direct cell-cell interactions. Cleavage of the Notch intracellular domain (NICTD) upon Notch receptor activation results in its translocation to the nucleus, where it will associate with the sequence-specific transcription factor Rbpj and other co-activator proteins. This results in activation of Notch target genes, including the transcriptional repressors Hes1 and Hes5, which themselves repress proneural gene expression. Inhibition of Notch signaling is therefore a required event for the onset of neuronal differentiation. This can putatively be achieved by targeting the pathway at distinct levels, from the cell-surface receptor to its downstream program.

Myelin transcription factor (MyT1) is among the many transcriptional regulators encoded by Ascl1 target genes, identified by screenings in both embryonic and cellular models of neurogenesis. MyT1 was first identified in differentiating oligodendrocytes through its ability to bind to the promoter of Proteolipid protein (PLP) gene, one of the essential constituents of myelin. It is the founding member of a family that includes also MyT1Like (NZF1 or MyT1L) and MyT3 (NZF3 or St18), all characterized by the presence of several zinc-finger (ZF) domains with an unusual C2HC arrangement of the zinc ion-coordinating residues. A seminal study in Xenopus neurogenesis showed that MyT1 promotes neuronal differentiation in cooperation with proneural transcription factors, by counteracting the inhibitory activity of Notch signaling. However the molecular basis for this observation, namely the identity of MyT1 target genes, remained to be determined.

MyT1 expression in the mouse telencephalon, the most anterior region of the mouse embryonic brain, has suggested an important role in the development of...
the neuronal lineage. Both immunohistochemistry and in situ hybridization analyses of this brain region show that MyT1 starts to be expressed, both in the dorsal and the ventral domain, at the transition from radial glia (RG) neural stem cells to differentiating neurons, either directly (in the ventricular zone, VZ) or indirectly through the generation of intermediate progenitor cells (IPs) located in the subventricular zone (SVZ).1,14 The generation of germline MyT1 null mice has so far failed to provide insights into its role in the developing nervous system, most likely due to genetic redundancy with other MyT1 family members.15,16 As such, in our study we resorted to acute functional experiments by in utero electroporation of mouse embryos, complemented with functional assays in cultured neural stem/progenitor cells.1 Both gain- and loss-of-function approaches in telencephalon led us to conclude that MyT1 promotes neuronal differentiation, providing the first evidence for a neurogenic role of MyT1 in mammalian neurogenesis. In addition, and in line with the previous study in Xenopus,13 these results suggested that MyT1 does not activate neurogenesis on its own, but instead enhances the activity of the proneural factor by antagonizing the inhibition conferred by Notch signaling.

The characterization of the MyT1 transcriptional program in neural stem/progenitor cells in culture that we performed by combining genome-wide location analysis (by ChIP-seq) with transcriptional profiling upon MyT1 gain-of-function, provided us with two important clues on how MyT1 functions at molecular level. First, MyT1 binding occurs mostly at active regulatory regions in undifferentiated neural stem/progenitor cells, as assessed by histone modification profiles, and is associated with transcriptional repression. Second, the gene expression changes induced by MyT1 are to large extent similar to those obtained upon the pharmacological inhibition of the Notch pathway, with both pathways oppositely regulating many transcriptional targets. That both pathways converge on the regulation of direct common target genes was further shown by analysis of the genomic binding profile of Rbpj. We found that common target genes include important regulators of the progenitor program including Sox2, Id3, Olig1 and the canonical Notch target Hes1. Thus, MyT1 promotes neuronal differentiation by directly binding and repressing the expression of Notch transcriptional targets, some of which promote the maintenance of the progenitor program. In addition, direct repression of the Notch1 gene by MyT1 provides another mechanism to dampen the overall levels of Notch signaling. Thus, MyT1 activation by Ascl1 reveals how activation of neuronal differentiation is coordinated with repression of the progenitor program (Fig. 1). Other similar mechanisms that function to suppress the progenitor program have been identified. Notably, is the activation by proneural factors of the transcription factor Sox21, which counteracts the activity of Sox1–3 factors characteristic of progenitor cells,17 suggesting multiple mechanisms link the transcriptional networks that promote neural stem cell maintenance and differentiation.

In the absence of active Notch signaling and nuclear NICD, Rbpj recruits a protein complex with transcriptional repression activity. Such mechanism mediates repression of Notch target genes once differentiating neural stem cells leave the VZ and are subjected to decreased Notch signaling. Various studies indicate that distinct levels of Notch activity distinguish RG (high Notch) from IPs (low/no Notch). In line with this, inhibition of canonical Notch signaling with a pharmacological inhibitor, or loss-of-function of Rbpj (using a short-hairpin RNA or targeted Rbpj

![Figure 1. MyT1 promotes neuronal differentiation by counteracting the neural progenitor program.](image-url)
alleles) induces the conversion of RGs into IPs.\textsuperscript{18-21} This difference in Notch signaling between RGs and IPs could result exclusively from decreased input signaling from neighboring cells, as cells migrate away from the VZ. However, several studies have suggested that intrinsic differences in the ability of progenitors to respond to Notch activation may also play a role. Early IPs present in the VZ of the dorsal telencephalon are unresponsive to Notch signaling,\textsuperscript{18-20,22} and display lower Hes1 and Hes5 expression, as compared with RGs, despite of the presence of nuclear NICD in both cell types.\textsuperscript{18,19} Overall, these observations suggest that cell-autonomous mechanisms that block the response to Notch activation may precede the loss of input signaling from neighboring cells, a model that highlights the importance of MyT1 cell-autonomous inhibition of Notch transcriptional activity in differentiating cells (Fig. 2).

The canonical Notch target Hes1 intrinsically oscillates while promoting neural stem cell maintenance, while its sustained downregulation determines the onset of neuronal differentiation.\textsuperscript{8,23,24} We found in our study that MyT1 directly represses the expression of Hes1. On Hes1 proximal promoter, 3 MyT1 binding motifs are found interspersed and partially overlapping with 3 Rbpj binding motifs previously shown to mediate Notch activation.\textsuperscript{25-27} Strikingly, this particular cis-architecture of the Hes1 promoter is conserved in various vertebrate species including human, frog and fish. Our \textit{in vitro} binding assays confirmed that MyT1 recruitment to Hes1 promoter is dependent on the integrity of the 3 consensus binding sites. A pair of zinc-fingers (ZFs) is the minimal functional unit for the recognition of a MyT1 motif (AAGTT).\textsuperscript{13,28} MyT1 contains 3 pairs of ZFs, raising the possibility that one MyT1 molecule may recognize more than one motif at the Hes1 promoter.\textsuperscript{28} Structural modeling of MyT1 binding to Hes1 promoter demonstrates that the distance between the 2 ZF pairs at the C-terminal end is compatible with simultaneous binding to two motifs, suggesting that more than one consensus binding site may indeed interact with the same MyT1 molecule (Joel Mackay, personal communication). Our transcriptional assays revealed that MyT1 can very effectively abolish the activation of Hes1 promoter by the Notch pathway. Although this has not been fully demonstrated experimentally, the cis-architecture of the Hes1 promoter suggests MyT1 may hamper Rbpj binding, resulting in a very effective and quick mechanism to down-regulate Hes1. Despite extensive overlap of binding of MyT1 and Rbpj to regulatory regions identified by ChIP-seq, our \textit{in silico} analysis did not find evidence for a similar mechanism (based on overlapping sites) operating at other common target genes, reflecting the uniqueness of Hes1 in the gene regulatory network that controls neurogenesis.

Additional components to this gene regulatory network have been found, in particular the microRNA miR-9 which establishes with Hes1 a double negative feed-back loop. It was recently proposed that accumulating levels of miR-9, itself a target of the Notch pathway, contribute to dampen Hes1 oscillations.\textsuperscript{29} This and our work suggest that mechanisms operating at different levels negatively regulate Hes1 expression during differentiation.

**Figure 2.** MyT1 represses Notch signaling cell-autonomously at the onset of neuronal differentiation. Intermediate neuronal progenitors can be distinguished from neural stem cells by their attenuated response to Notch pathway activation. Despite the presence of nuclear NICD in both types of progenitors, expression of the canonical Notch targets Hes1 and Hes5 occurs exclusively in neural stem cells. These observations are consistent with the existence of cell-autonomous mechanisms that block Notch signaling, as the one defined by MyT1.
A striking parallel can be established between our findings and a more recent study that investigated the role of MyT1Like in the context of the so-called BAM factors, a cocktail of transcription factors (Brn2, Ascl1 and MyT1Like) used to reprogram somatic cells, such as mouse embryonic fibroblasts (MEFs), into induced neurons. A similar genomics approach, combining location analysis with transcriptional profiling, found MyT1Like to work as a transcriptional repressor of genes highly expressed in fibroblasts to facilitate neuronal reprogramming driven by Ascl1. Although the contribution of Notch signaling to the transcriptional program present in MEFs has not yet been established, repression of Hes1 gene is required for the reprogramming activity of MyT1Like, which binds to the same region of the Hes1 promoter recognized by MyT1, both in neural stem/progenitor cells and in MEFs. Thus, in addition to highlight similar molecular activities between MyT1 and MyT1Like, both studies reveal the importance of repressing the starting gene expression program to promote changes in cell identity, either during development or reprogramming.

Supporting a role for MyT1 and MyT1Like in repressing gene expression, previous studies found both factors in complexes that mediate transcriptional repression. MyT1 and MyT1Like have been shown to physically interact with Sin3B in a repressor complex that contains HDAC1 and, to a lesser extent, HDAC2. MyT1 also physically interacts with the LSD1 demethylase in a complex that contains CoREST. By contrast, other studies associated MyT1 family members with gene activation. These were however, based on transcriptional assays using artificial promoter constructs, or functional assays using MyT1 truncations containing ZF pairs fused to the VP16 activator domain. Crucially, the latest strategy missed the central domain that in MyT1 and MyT1Like has been shown to mediate the interaction with HDACs- and LSD1-containing complexes. We found in our study that MyT1-mediated repression of target gene expression is associated with increased recruitment of the histone demethylase LSD1 to its target sites. The MyT1-LSD1 complex was shown to promote transcriptional repression via demethylation of H3K4me2 sites in a neuroblastoma cell line. Future experiments should investigate if changes in chromatin landscape expected to be triggered upon LSD1 recruitment affect Rbpj affinity and dwell time at MyT1/Rbpj common targets. Alternatively, these changes may interfere selectively with the recruitment of NICD or other coactivators by Rbpj, as shown with other transcription factors that counteract the Notch transcriptional program in different cellular contexts. Although our analysis clearly links MyT1 activity with repression of gene expression on a genome-wide level, we cannot exclude that MyT1 may promote gene activation at particular target genes, or when expressed in a different cellular context.

The broad MyT1 expression has since long suggested a pan-neuronal function in neurogenesis. In mouse embryo, expression of MyT1 transcript during the neurogenic period is seen in both peripheral and central nervous system regions, starting with the appearance of the earliest-born neurons within the neural epithelium and neural crest at E9.5 stage of development. In the developing brain and spinal cord, the onset of MyT1 expression is consistent with that observed in the telencephalon, with few scattered cells in the VZ expressing MyT1, and highest transcript level occurring in the SVZ. MyT1 expression is maintained, albeit to lower levels, in differentiated neurons in the mantle layer. Given the conserved function of Notch pathway across neuronal lineages, it is plausible that MyT1 function and its interaction with the Notch pathway are also conserved in different neurogenic regions. It is also possible that, in some progenitor domains, MyT1 expression may be induced downstream proneural factors other than Ascl1 (Fig. 1). In the dorsal telencephalon, where neurogenesis is mostly controlled by proneural factors of the Neurog family, examination of publically available data suggests MyT1 may be directly activated by Neurog2. ChIP-seq binding profile reveals Neurog2 binding to the MyT1 locus, whereas gain-of-function of this transcription factor in the dorsal telencephalon increases MyT1 expression. This would be reminiscent of the regulation of MyT1 by X-NGNRI in Xenopus embryos.

The high sequence homology displayed by MyT1 family members within the ZF domains (all of which recognize the AAGTT DNA binding motif) predicts they may be functionally interchangeable. Genetic redundancy has, in fact, been invoked to explain the relatively mild phenotype of MyT1 null embryos in the developing pancreas, where MyT1Like and MyT3 are ectopically expressed upon MyT1 ablation. Moreover, all MyT1 family members have neurogenic
potential when ectopically expressed in mouse embryonic teratocarcinoma P19 cells cultured in differentiating conditions. MyT1Like and MyT3 may therefore be expected to regulate gene expression in a similar manner to the one reported in our study for MyT1. In fact, we have shown in our study that MyT1Like and MyT3 can both counteract Notch activation of Hes1 promoter in transcriptional assays. However, although all 3 factors are widely expressed in neurogenic regions throughout the mouse developing nervous system, their expression onset occurs at distinct stages of the neuronal lineage. While MyT3 expression starts in SVZ progenitors but is spatially and temporally more restricted than that of MyT1, MyT1Like starts to be expressed only in post-mitotic precursors and remains throughout life. MyT1 is therefore expected to play the most prominent role at the beginning of differentiation, but its post-mitotic expression suggests additional functions besides the one uncovered in our study. In addition to control the early step of neuronal commitment, several reports have highlighted a role for Notch activation in dendritic growth and branching, axon guidance and migration of post-mitotic neurons. It is therefore tempting to speculate that post-mitotic expression of MyT1 family members may reflect the need to suppress Notch activity at later stages. Knocking-down MyT1Like expression in the embryonic mouse cerebral cortex inhibits neurogenesis, although how this factor acts in post-mitotic cells in this brain region, remains to be investigated. Strikingly, knock-down of MyT1Like in primary hippocampal neurons in culture, results in the derepression of many MyT1Like targets including Notch related genes, resulting in loss of neuronal function. These observations suggest a common theme among MyT1 family members in these different cellular contexts, although further work will be required to fully demonstrate this idea.

MyT1 expression has also been well documented in differentiating oligodendrocytes and in endocrine progenitors and differentiated islet cells in the pancreas. Both germline and pancreas-specific MyT1 null embryos have been generated, containing islet cells that abnormally co-express multiple hormones. Interestingly, some parallels can be made with the gene regulatory network that controls neurogenesis. MyT1 is induced downstream Neurog3, and both proneural and MyT1 pathways function also here in synergy to promote endocrine islet cell differentiation. It is possible that this relies in the ability of MyT1 to repress Notch target genes, considering the importance of Notch signaling and the timing of Hes1 expression in this developmental context. Ironically, given its postulated function in regulating the PLP gene transcription, the role of MyT1 in differentiating oligodendrocytes remains elusive.

Concluding remarks

The expression pattern of MyT1 and related transcription factors during neurogenesis has since long indicated an important regulatory role in the neuronal lineage. However, since its identification more than two decades ago, very little advances have been made toward understanding such function. We have recently shown that MyT1 promotes neurogenesis downstream proneural factors, by repressing the transcription of Notch pathway target genes. Particularly relevant was the regulation of Hes1 by MyT1, given the pivotal role this transcription factor plays at the onset of differentiation. Many questions however, remain to be addressed. How much of our findings can be extrapolated to other developmental contexts where MyT1 plays a regulatory role, and to other members of the MyT1 family? Addressing them will benefit from strategies aimed at conditionally deleting multiple members of the family in space and time.

Disclosure of potential conflicts of interest

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