Biochemical and Biophysical Research Communications 390 (2009) 1114–1120

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

SOX1 links the function of neural patterning and Notch signalling in the ventral spinal cord during the neuron-glial fate switch

Nicholas Genethliou [a,b], Elena Panayiotou [a,b], Helen Panayi [a], Michael Orford [a], Richard Mean [a], George Lapathitis [a], Herman Gill [a], Sahir Raoof [a], Rita De Gasperi [c], Gregory Elder [c], Nicoletta Kessaris [d], William D. Richardson [d], Stavros Malas [a,b,*]

[a] The Cyprus Institute of Neurology and Genetics, Airport Avenue, No. 6, Agios Dometios, 2370 Nicosia, Cyprus
[b] Department of Biological Sciences, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus
[c] James J. Peters VA Medical Center, Research and Development (3F22), 130 West Kingsbridge Road, Bronx, NY 10468, USA
[d] Wolfson Institute for Biomedical Research and Research Department of Cell and Developmental Biology, University College London, Gower Street, London WC1E 6BT, UK

ARTICLE INFO

Article history:
Received 25 August 2009
Available online 31 August 2009

Keywords:
Sox1
Pax6
Nkx2.2
Hes1
Oligodendrocytes
Astrocytes
Notch signalling

ABSTRACT

During neural development the transition from neurogenesis to gliogenesis, known as the neuron-glial (N/G) fate switch, requires the coordinated function of patterning factors, pro-glial factors and Notch signalling. How this process is coordinated in the embryonic spinal cord is poorly understood. Here, we demonstrate that during the N/G fate switch in the ventral spinal cord (vSC) SOX1 links the function of neural patterning and Notch signalling. We show that, SOX1 expression in the vSC is regulated by PAX6, NKX2.2 and Notch signalling in a domain-specific manner. We further show that SOX1 regulates the expression of Hes1 and that loss of Sox1 leads to enhanced production of oligodendrocyte precursors from the pMN. Finally, we show that Notch signalling functions upstream of SOX1 during this fate switch and is independently required for the acquisition of the glial fate *per se* by regulating Nuclear Factor I A expression in a PAX6/SOX1/HES1/HES5-independent manner. These data integrate functional roles of neural patterning factors, Notch signalling and SOX1 during gliogenesis.

Introduction

During embryonic development spinal cord (SC) neuro-epithelial progenitors (NEPs) are located in the ventricular zone (VZ). The VZ of the vSC is organised into five progenitor domains known as p3-pMN-p2-p1-p0. NEPs in each domain express different sets of homedomain (HD) transcription factors [1] and first produce neurons and then switch to producing glial cells. This N/G fate switch starts around embryonic day 12 (e12) and progresses in a ventral-to-dorsal direction [2]. At this stage NEPs transform to radial glial (RG) cells [3] and begin to express several Sox genes [4,5] and pro-astrocytic factors [6] while the expression of the Notch effectors HES1 and HES5 changes dynamically [7,8]. How the expression and function of this new set of RG-specific genes is regulated is not well understood.

One domain where glia specification has been extensively studied is the pMN progenitor domain. This domain first produces motor neurons (MNs) and then switches to generating oligodendrocyte precursors (OLPs) together and some astrocyte precursors (ASPs) [9–12]. It is the major source of spinal Oligodendrocytes (OL) but the interplay between different factors expressed in the pMN during OL specification is not well understood. The HD factor PAX6 has been proposed to block OL specification from the pMN [7] and is selectively expressed only in a subset of ASPs [13,14]. However, PAX6 target genes that potentially mediate this function are not known.

Another mechanism that affects glial cell specification is Notch signalling [15]. In the forebrain Notch signalling is sufficient to induce the NEP to RG transformation [16]. In the spinal cord reduced Notch signalling leads to enhanced production of pMN-derived OLPs while ASPs specification is severely reduced [17]. However, the molecular basis of this phenotype has not been convincingly resolved [4].

Here we have studied the function and genetic regulation of the high mobility group (HMG) transcription factor SOX1. We show that SOX1 links the function of neural patterning and Notch signalling specifically during gliogenesis. We further show that Notch signalling is genetically required to initiate the N/G fate switch *per se* independent of its role to regulate progenitor identities or Sox1 expression.

* Corresponding author. Address: The Cyprus Institute of Neurology and Genetics, Developmental and Functional Genetics Group, Airport Avenue, No. 6, Agios Dometios, 2370 Nicosia, Cyprus. Fax: +357 22 392641.
E-mail address: smalas@cing.ac.cy (S. Malas).

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doi:10.1016/j.bbrc.2009.08.154

Materials and methods

Transgenic mice. Mutant lines used were: Sox1^{KO} [18–19], Pax6 (Small eye; Sey) [20], Nkx2.2^{KO} [21] and PS-1^{KO} [22]. One new transgenic line was generated using Bacterial Artificial Chromosome (BAC) transgenesis that expresses nuclear GFP (GFPn) driven by Sox1 promoter/enhancer sequences. The Sox1^{-GFPn} allele was generated using the BAC clone RP23-118F24 modified using genetic recombination to replace the Sox1 ORF (single exon). Genotyping was performed by PCR or by scoring embryonic morphology (e.g. the Sey/Sey embryos). All procedures were performed in accordance with a licence issued by the Chief of Veterinary Services of the Republic of Cyprus.

Tissue histology. For in situ hybridization (ISH) embryos were fixed overnight in 4% (w/v) paraformaldehyde (PFA) in 0.1 M phosphate buffer (PB), cryo-protected overnight in 20% (w/v) sucrose in PB and sectioned on a cryostat (14 μm) as described [23–24]. The following probes were used: Sox3, Sox6, Sox8 and Sox9 (from Michael Wegner), Pax6 (from Peter Gruss), Hes1, Dll1, Dll3, Jagged1 (from Ryoichiro Kageyama) Sox10, PDGFRα and Fgfr3. All probes were transcribed from mouse cDNAs except the Sox10 probe which was from rat. The rest of the probes were generated by PCR amplification of mouse cDNA. Images were captured using an Olympus microscope (Olympus SZX12) and digital camera (Olympus DP70). For immunohistochemistry embryos were fixed in MEMFA (0.1 M MOPS, 2 mM EGTA, 1 mM $MgSO_4$, 3.7% formaldehyde). Sections were cut on a cryostat (10–12 μm). Antibodies used were against the following: GFP (Invitrogen), SHH, NKX2.2, PAX3 (Developmental Studies Hybridoma Bank), OLIG2, NGN2 and SOX1 (Santa Cruz), PAX6, GLAST and GFAP (Chemicon), SOX1 (generated against the peptide AGGRHPHAHPAHPHPHHPHAHPHNPQP raised in guinea pig), SOX10 (from Michael Wegner), GSH2 (from Kenneth Campell), MASH1 (from François Guillemot) and S100β (Sigma). Images were captured on a TCSL confocal microscope (Leica, Germany). Serial sections from equivalently-staged embryos at forelimb level were used for cell counting. The quantitative results were analysed by two-tailed distribution, homoscedastic Student's *t*-test. The graphed results are shown as means ± SEM (standard error of the mean).

Results

To monitor SOX1 expression in the embryonic spinal cord we used antibody staining, in situ hybridization and a reporter BAC transgenic line that faithfully expresses nuclear GFP driven by Sox1 promoter/enhancer sequences, denoted Sox1^{-GFPn} (Suppl. Fig. 1). In the VZ during neurogenesis at e9.5, Sox1^{-GFPn} expression was uniform in all regions of the VZ but was excluded from the floor plate (FP), roof plate (RP) and a region ventral to the RP (Suppl. Fig. 2A–C; data not shown). However, between late e11.0 and e12.0, when NEPs transform to RG, this uniform expression resolved into three expression domains: a ventral SOX1-negative expressing NKX2.2, an intermediate SOX1^{high} expressing GLAST and a dorsal SOX1^{low} expressing GSH2 (Suppl. Fig. 2D–F). MASH1^{+} OLPs [7] appeared in the pMN precisely when Sox1^{-GFPn} expression was extinguished (Suppl. Fig. 2G–L). The repression of Sox1^{-GFPn} expression from the p3 domain coincided with reported boundary changes in the expression of NKX2.2, OLIG2 and PAX6 [25–26]. Importantly, at around e11.0 just before OLPs begin to be specified Sox1^{-GFPn} and PAX6 expression in the VZ precisely matched each other in the entire spinal cord (Suppl. Fig. 3M–O). After e12.5, when OL begin to migrate out of the pMN domain, Sox1^{-GFPn} was switched of from migrating OLIG2^{+} OLPs (Suppl. Fig. 4A, C, and D). All PAX3^{+} progenitors that generate dorsal OLPs at e15.5 [27], also switch off Sox1 at this stage (Suppl. Fig. 4B) and by this stage Sox1 is expressed in progenitors of white matter (WM) ventral astrocytes types 1 and 2 (VA1/2) that also express PAX6 [14] (Suppl. Fig. 4G–J). These data show that the expression of Sox1 changes from being uniform during neurogenesis to becoming domain-specific during gliogenesis. Importantly, during OL and AS specification we find that Sox1 and PAX6 expression precisely match in uncommitted RG and in differentiated glial lineages. To our knowledge no other transcription factor reported to date shows such a temporal pattern of expression.

The precise co-expression between Sox1/PAX6 on the one hand and the mutually exclusive expression between Sox1/NKX2.2 on the other, prompted us to investigate if Sox1 expression was regulated by these two HD factors. We thus monitored Sox1^{-GFPn} expression in embryos that lacked either PAX6 or NKX2.2 function. In Pax6-mutant embryos at e10.5 Sox1^{-GFPn} expression was completely lost in all VZ progenitors except for a few cells dorsal to the pMN. The latter represent a particular subclass of p2-progenitors (SM-submitted) (Fig. 1A and B). At e12.5 the expression of Sox1^{-GFPn} was restored in the dorsal (PAX3^{+}) domain but in the vSC (p0-pMN), Sox1^{-GFPn} expression was still totally abolished. Several other SoxB, SoxD and SoxE genes analysed were expressed normally in Pax6- (and Sox1-) mutant embryos (Suppl. Fig. 5), so the requirement for PAX6 appears specific to the regulation of Sox1. In Nkx2.2$^{-/-}$ embryos at e12.5, both Sox1^{-GFPn} and OLIG2 expression expanded ventrally, but not to the same extent; while OLIG2 expanded through the entire prospective p3 domain [28], Sox1^{-GFPn} expression expanded less far so that the ventral-most cells were Sox1^{-}/OLIG2^{+} (Fig. 1E and F). Unlike Sox1, PAX6 expression did not expand ventrally in Nkx2.2$^{-/-}$ spinal cord (Fig. 1G and H) [13].

These data suggest that PAX6 is specifically required for the maintenance of Sox1 expression in RG residing in the pMN-p0 domains, independent of its ability to repress NKX2.2. Conversely, NKX2.2 suppresses Sox1 in the ventral pMN (vpMN) and possibly in some p3 progenitors, in a PAX6-independent manner. NKX2.9, a close relative of NKX2.2 that is co-expressed with NKX2.2 in the vSC during neurogenesis, is down-regulated before e12.5 [13], therefore the repression of Sox1 is NKX2.2-dependent.

The precise correlation between PAX6 and Sox1 expression during gliogenesis, particularly the fact that neither gene is expressed in OLPs suggested that SOX1, like PAX6 [7], might control the production of OLPs in this domain. Consistent with such a function, we noted a significantly higher number of MASH1/OLIG2^{+} cells in the VZ at e11.5 (Fig. 2A, B and O). At e12.5 the number of pre-migratory SOX10^{+} pMN-derived OLPs was also significantly higher in mutant embryos (Fig. 2C, D and O). A similar result was obtained for migrating Sox10^{+} and PDGFRα^{+} OLPs at e13.5 and e14.5 (Fig. 2E–J and O; data not shown). At e13.5, we consistently observed that OLIG2^{+} progenitors in the VZ were depleted in mutant embryos and, conversely, the number of migratory OLIG2^{+} OLPs was significantly increased (Fig. 2K and L; data not shown). While OLP numbers increased at early stages of development, the number of MBP^{+} OLs at e15.5 and e18.5 was normal (Fig. 2M and N; not shown). This is not surprising since the number of OLs can adjust irrespective if there is delayed [4,29] or enhanced [5] production of OLPs. These data suggest that SOX1, functioning downstream of PAX6, is normally required to control the normal production of OLs from the pMN. The fact that at the peak of ventral OL specification, between e12.5 and 13.5, Sox1 (and PAX6), are normally expressed only in a subset of pMN progenitors, (Suppl. Figs. 2 and 3) is consistent with such a role.

As mentioned earlier, loss of Notch signalling also leads to overproduction of OLPs from the pMN but the molecular basis of this phenotype has not been convincingly established [17]. We thus asked if SOX1 regulates any components of Notch signalling. The expression of all Notch receptors (Notch1–3) and Notch ligands was normal in both Sox1- and Sey/Sey embryos (Suppl. Fig. 6).

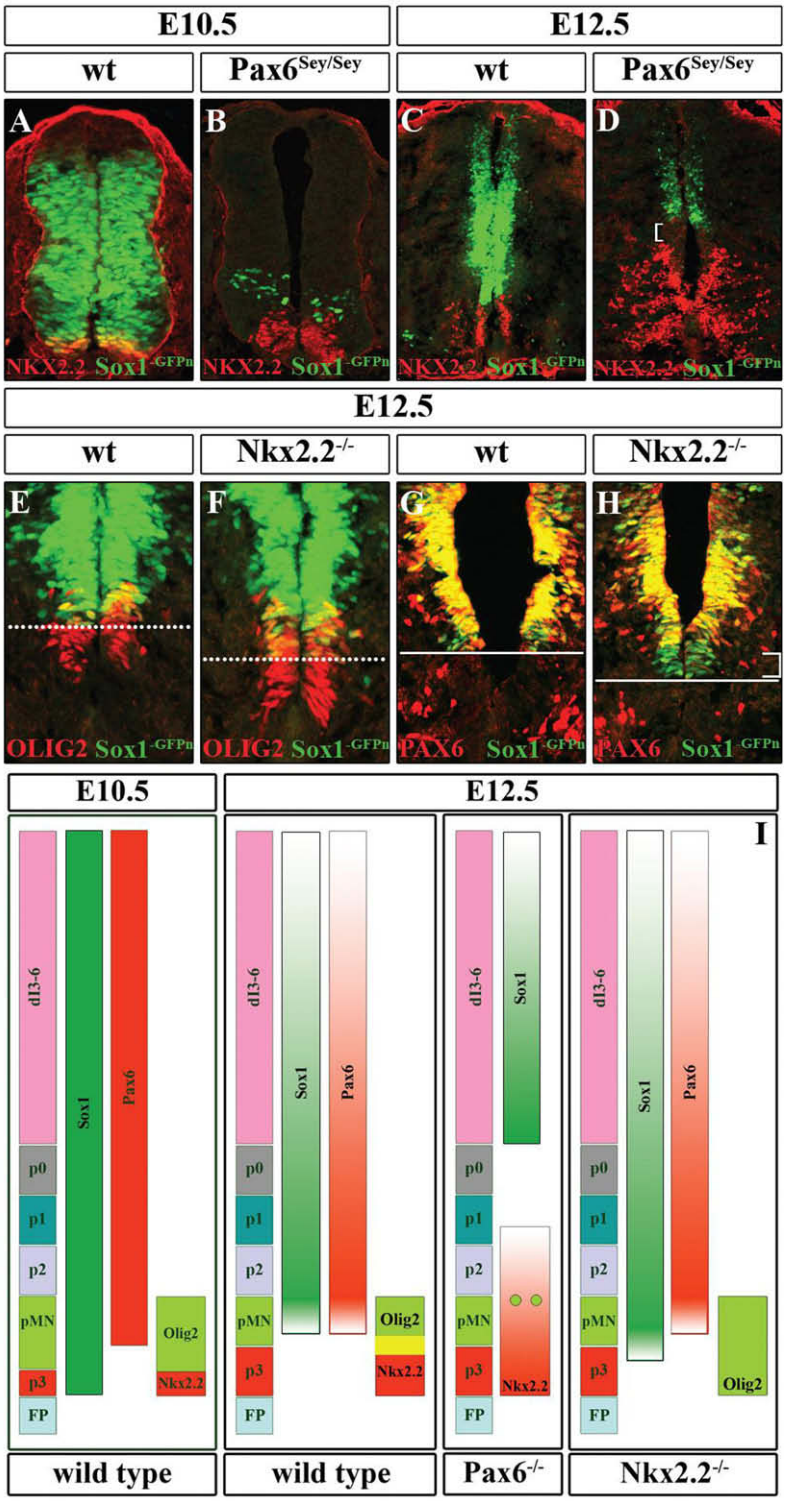

Fig. 1. Genetic requirement for PAX6 and NKX2.2 to regulate Sox1^{-GFPn} in the vSC (A and B) shows Sox1^{-GFPn} expression at e10.5 in wt and Pax6-mutant embryos. GFPn^{+} in B represent a subclass of p2-progenitors. (C and D) Shows Sox1^{-GFPn} expression in wt and Pax6-mutant embryos relative to NKX2.2. Note that NKX2.2 expression does not expand in the vSC as far as the Sox1-negative domain (brackets in D). In Nkx2.2$^{-/-}$ embryos Sox1^{-GFPn} expands ventrally (E and F) beyond the PAX6^{+} domain (G and H). Lines indicate the ventral limit of Sox1^{-GFPn} expression. (I) Diagrammatic representation of the temporal and spatial changes in the expression of the markers analyzed. Progenitor domains are represented as single coloured boxes. Dorsal progenitors (dI3–6) are shown as a single box. Fating colour bars represent diminishing expression. The precise ventral expansion of Sox1^{-GFPn} in Nkx2.2$^{-/-}$ is tentative and may not reach the p3 domain.

However, the expression of the Notch effector HES1, a factor with specific anti-oligogenic function [8] was specifically reduced in both Sox1- and Pax6-mutant embryos only at e12.5, when OLPs start to be specified (Compare Fig. 3A–C, G and H). These data suggest that SOX1 regulates the expression of HES1 only during gliogenesis in the entire spinal cord while PAX6 regulates the expression of HES1 only where PAX6 is required to regulate Sox1, that is in the vSC. This PAX6 → SOX1 → Hes1 regulatory cas-

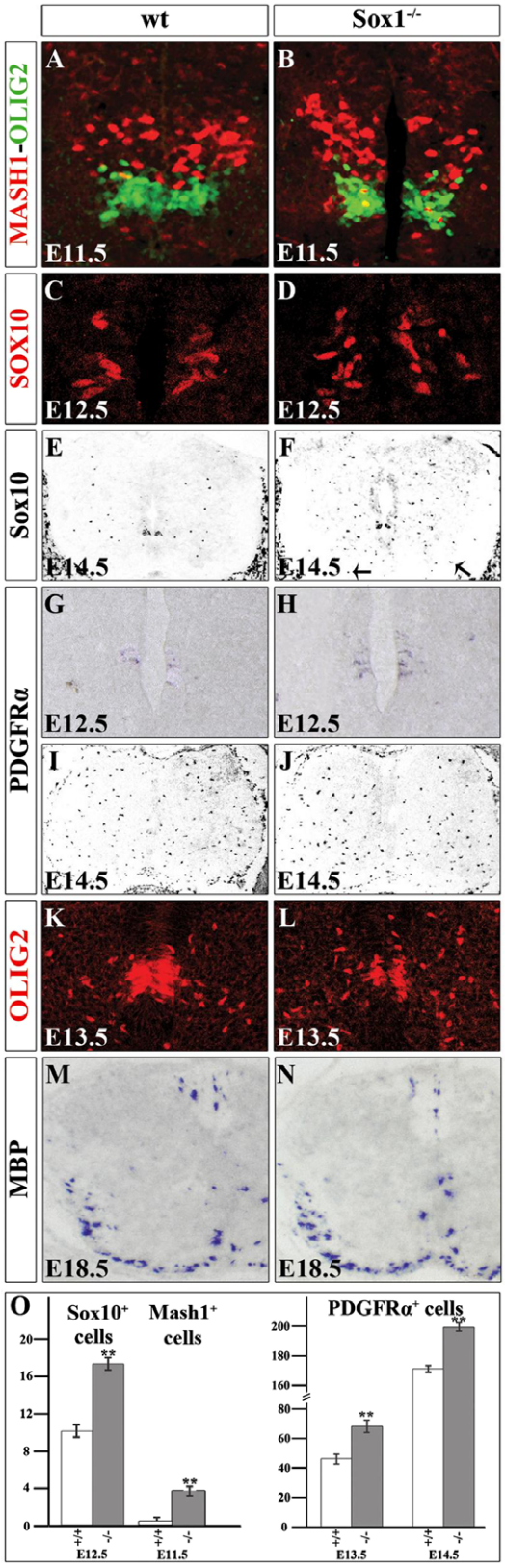

Fig. 2. Oligodendrocyte development in Sox1$^{-/-}$ embryonic spinal cord (A and B) Show pre-migratory MASH1/OLIG2^{+} at e11.5 and (C and D) show SOX10^{+} OLPs. (E and F) and (G-J) show post-migratory Sox10^{+} and Pdgfrα^{+} OLPs. Note the rapid depletion of Olig2^{+} progenitors in Sox1$^{-/-}$ embryos (K and L). White matter MBP^{+} OL appear normally distributed (M and N). (O) Pre-migrating (Sox10^{+}; or MASH1^{+}/OLIG2^{+}) and post-migrating (Pdgfrα) pMN-derived OLPs show statistically significant increase in mutant spinal cords (40 sections of 3 pairs of embryos). Statistical significance is indicated above respective bars ($^{**}P \leqslant 0.001$).

cade is stage-specific and establishes a link between the function of neural patterning and that of Notch signalling during OL specification.

Since Hes1 expression is modulated by Notch signalling [30] and SOX1 (this study), we asked whether Sox1 itself is under control of Notch, by examining Presenilin-1 (PS-1) mutant embryos, in which Notch signalling is attenuated [31]. In PS-1$^{-/-}$ embryos at e12.5 SOX1 expression was lost in the vSC (Fig. 4A–B) while the expression of Pax6, Sox2 and Sox9 was not affected (Fig. 4C–H). Thus SOX1 not only is responsible for maintaining HES1 expression in RG, but it is also a target of Notch signalling in a manner that does not involve deregulation of PAX6 or loss of progenitor identities as evidenced by the normal expression of Pax6/Sox2/Sox9/Hes5.

Loss of Notch signalling also leads to greatly reduced AS specification and loss of SOX9 was proposed to mediate this effect [17]. Since we found that Sox1 lies downstream of Notch and that Hes1 lies downstream of SOX1, we investigated the regulatory relationship between Notch, SOX1 and the expression of Nuclear Factor I A (NFIA), a key pro-astrocytic factor required for the induction of a generic program of AS specification [6]. In Sox1- and Pax6-mutant embryos AS specification was normal (Suppl. Fig. 7). However, in PS-1-mutant embryos HES1 expression was drastically reduced in all domains of the VZ at e12.5 whereas HES5 expression was not affected (Suppl. Fig. 8A–D). Likewise, the expression of NFIA was strongly reduced and the expression of its downstream target GLAST was also reduced in extent (Suppl. Fig. 8E–H). By e13.5 the expression of Fgfr3, which marks ASPs [32], was almost abolished (Suppl. Fig. 8I–J). On the other hand, OLIG2 expression was normal both in vSC and in migrating OLPs (Suppl. Fig. 8K and L; not shown).

These data reveal a specific requirement for Notch signalling to initiate a pro-astrocytic program of specification in the entire spinal cord by regulating NFIA in a manner that does not affect SOX9 expression and which is not caused by depletion of progenitors as Pax6/Sox2/Sox9/Hes5 expression was normal. Overall, our data identify several converging pathways functioning upstream and downstream of SOX1 during glial specification that couple the function of neural patterning factors with that of Notch signalling and SOX1 (Suppl. Fig. 9).

Discussion

We have shown that the transcription factor SOX1 has a dynamic pattern of expression in RG progenitors. In the pMN domain, the main site of OL specification, this expression pattern depends on PAX6 and NKX2.2. We also report that Sox1 is not expressed in OLPs but only in a subset of ASPs that also express PAX6. We found that loss of Sox1 did not affect generic aspects of AS specification but led to a significant increase in the production of OLPs derived from pMN, suggesting that SOX1 is likely to antagonize OL specification in Olig2^{+} pMN progenitors. Given that all pMN progenitors express OLIG2 and both ASs and OLs are likely to be produced at the same time from Olig2^{+} progenitors [12–14], there must be a mechanism that instructs pMN progenitors to make this binary fate choice. SOX1 is a strong candidate for this function.

We showed that loss of PAX6 led to loss of Sox1 in the entire vSC (pMN-p0) at e12.5. In these embryos NKX2.2 does not expand in all vSC progenitors suggesting that it is the loss PAX6 and not the ectopic expression of NKX2.2 that caused the repression of Sox1. In the vSC PAX6 has multiple independent functions. First, it regulates AS subtype identity by regulating Slit1 expression in the VZ [13–14]. Second, in the pMN-p0 domains it represses the expression of Sulf1, coding for an enzyme believed to be responsible for the sudden accumulation of Sonic Hedgehog in the p3 domain during the N/G switch [13,33]. Neither SOX1 nor the Wnt inhibitor

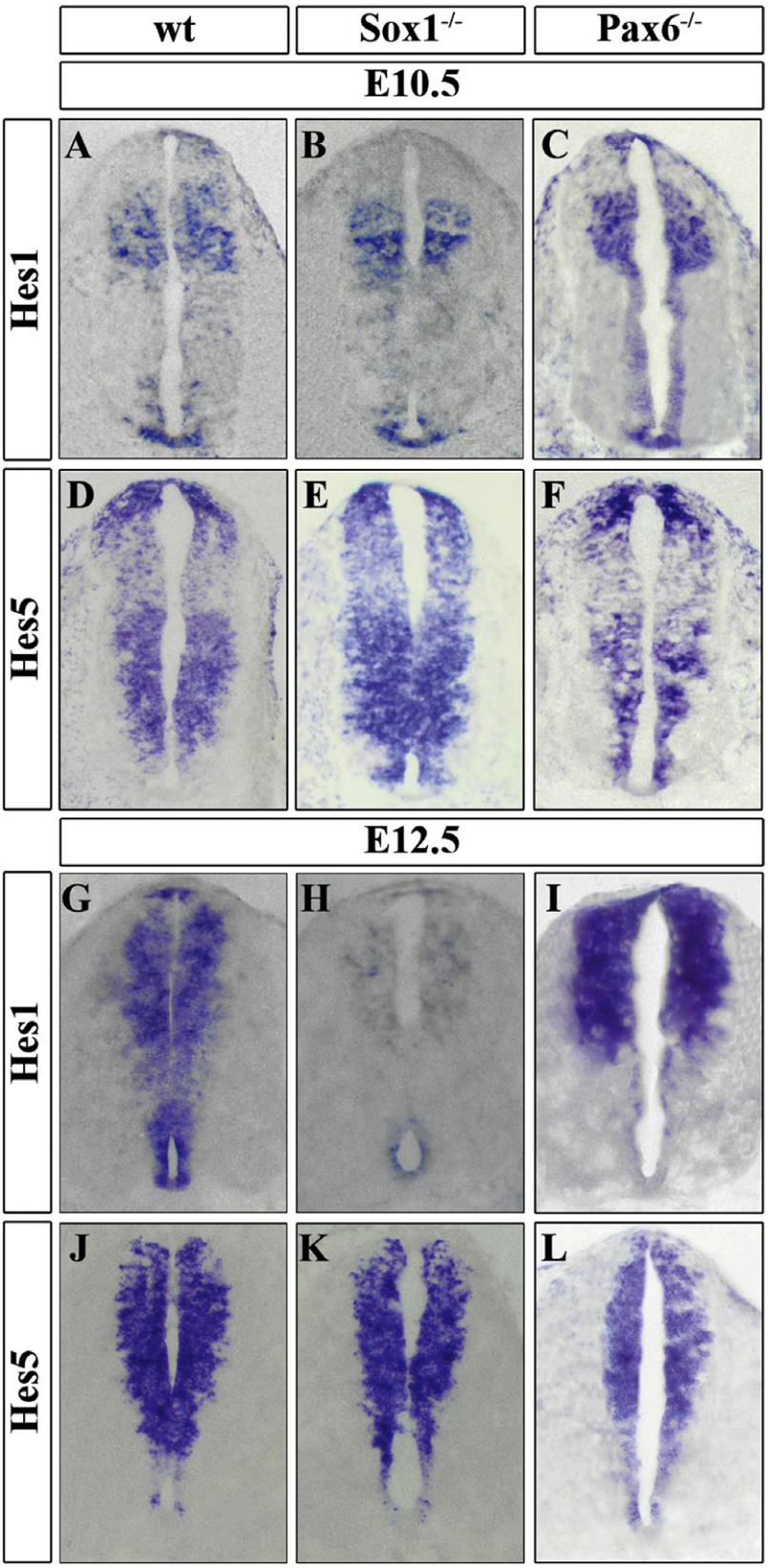

Fig. 3. Expression of Hes1 and Hes5 in Pax6 and Sox1-mutant embryos (A–F) Hes1 and Hes5 expression was normal at e10.5 in both genetic backgrounds. At e12.5 Hes1 expression is reduced in the vSC of Pax6-mutants but in Sox1$^{-/-}$ embryos the reduction extends to all regions of the spinal cord (G–I) while some reduction in Hes5 expression in the vSC is noted in Pax6-mutant embryos (J–L).

SFRP2, also a target of PAX6 in the pMN-p0 domains [34], mediate any of these functions of PAX6 (SM; unpublished data). Thus the PAX6→SOX1 cascade must have a distinct function. Loss of PAX6 led to an increase in OLIG1^{+} OLPs [7] and likewise loss of SOX1

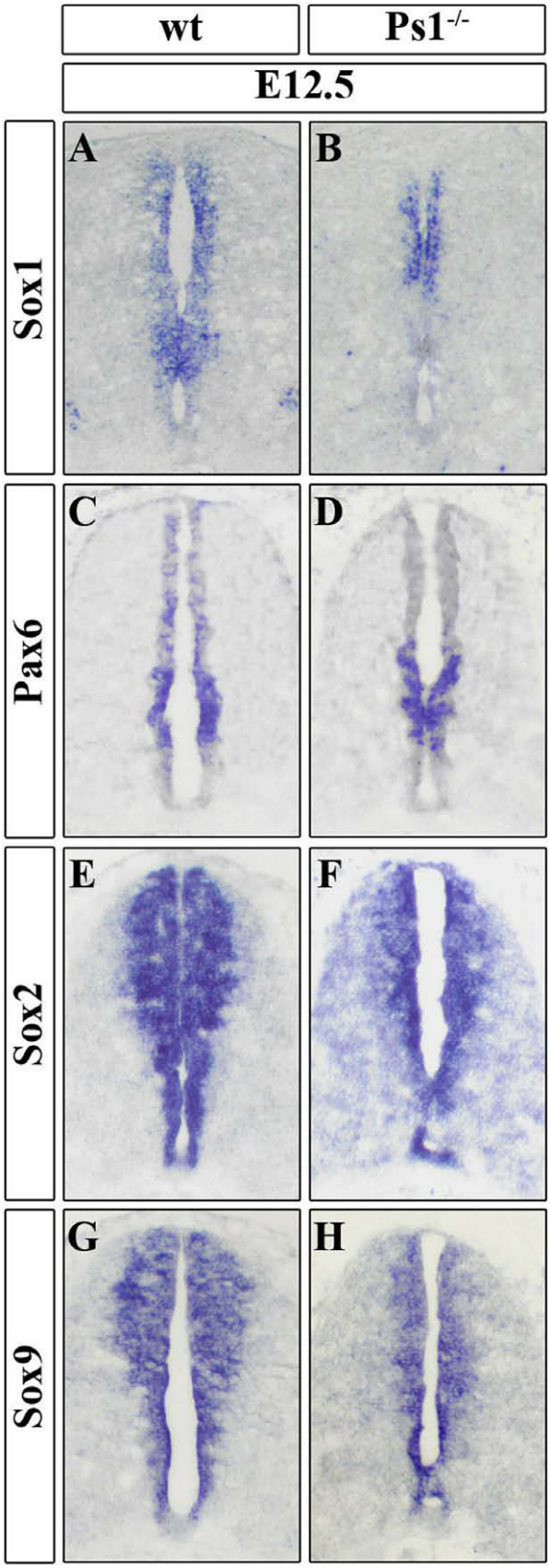

Fig. 4. Genetic requirement for Notch signalling to maintain Sox1 expression in the vSC Analysis of Sox1 expression in PS-1$^{-/-}$ at e12.5 shows strong reduction of Sox1 expression in the vSC (A and B). The precise limits of the Sox1-negative domain were not determined but they most likely include the p0-pMN domain. Pax6, Sox2 and Sox9 expression were not affected (E–J).

leads to an increase in OLs (this study). HES1 has also been proposed to have anti-oligogenic properties [8]. Therefore the PAX6 → SOX1 → HES1 regulatory cascade that we have uncovered could be a key anti-oligogenic component operating in the pMN.

Our studies suggest that Notch signalling, that also has an anti-oligogenic function [17], is also required to maintain SOX1 expression in the vSC and that SOX1 itself is required to maintain the expression of HES1 [8]. Therefore our data not only link the function of a HD factor with Notch signalling but establish that SOX1 is a mediator of Notch signalling during gliogenesis and specifically regulates anti-oligogenic components of this pathway. A functional SOX1 binding site has been reported to exist on the Hes1 promoter next to an RBP/J binding site pointing to a direct function of SOX1 [35]. This requirement must be stage-specific since at e10.5 we could not detect any changes in Hes1 expression in Sox1 nulls.

Another unresolved issue from previous studies was to determine if Notch signalling is required to initiate a generic program of glial specification. We provide genetic evidence that Notch signalling, independent from its function to regulate Sox1, is required to initiate the expression of NFIA [6]. We find that attenuation of Notch signalling leads to severe reduction of NFIA and severe reduction of ASPs. A previous study suggested that Notch signalling regulates astro-gliogenesis by regulating Sox9 expression at e14.5 [17]. However, we find that Sox9 expression at e12.5 is normal in PS-1-mutant embryos, while NFIA expression is strongly reduced. Therefore our work provides direct genetic evidence of an early requirement for Notch signalling to initiate astro-gliogenesis, independent of its function to maintain progenitor identities or SOX1 expression. Furthermore, we propose that Notch most likely regulates NFIA in a HES1/5-independent manner based on the expression of HES genes in Sox1-, Pax6- and PS-1-mutant embryos (see model; Suppl. Fig. 9). An early requirement for Notch to initiate NFIA expression has recently been reported using an *in vitro* model [36].

Acknowledgments

We thank Johan Ericson, Anastasia Stoykova and Austin Smith for the mice and Michael Wegner for antibodies and plasmids. This work was supported by the European Union (SM) and the UK Medical Research Council and the Wellcome Trust (WDR and NK).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2009.08.154.

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