which are translated from the same mRNA, but from differential starting codons. To investigate this issue, it would be necessary to generate mice carrying a mutation in the alternative start codon preventing FOXP1C translation. It would be also interesting to determine which co-factors interact with or activate FOXP1 in NSCs in order to repress JAG1 and promote NSC differentiation. In our study, we observed that overexpression of FOXP1 leads to increased neuronal differentiation. Therefore, ectopic expression of FOXP1 in NSCs improves the capacity of NSCs to generate neurons, potentially increasing the regenerative capacity of transplanted NSCs upon brain damage. In the future, it would be relevant to investigate whether transplantation of FOXP1-overexpressing NSCs upon HI could induce a more efficient generation of neurons when compared to regular NSCs, and if this could lead to increased improvements in functional and anatomical impairments after HI, compared to regular NSC treatment.

A second study by Konopka and colleagues has tackled the question as to whether FOXP1 plays a role in the neocortex during postnatal development in mice, as this stage is relevant for ASD (Usui et al., 2017). To this end, they generated a transgenic mouse model carrying a mutation in the alternative start codon preventing FOXP1C translation. In this study, the authors have investigated whether the expression of relevant target genes is affected in sumoylation-deficient FOXP1 mutants during embryonic to postnatal development. By generation of a sumoylation-deficient mutant of FOXP1 (K63R), it was demonstrated that FOXP1 sumoylation is necessary to promote neurite outgrowth of mouse and human cortical neurons in vitro, and neuronal migration in mouse embryonic cortex in vivo. Sumoylation of FOXP1 was also found to prevent the interaction of FOXP1 with members of the nucleosome remodeling deactylase (NURD) chromatin remodeling complex, including histone deactylases (HDAC) 1/2 and metastasis associated proteins (MTA) 1/2. However, while sumoylated-FOXP1 was shown to promote neurite outgrowth and neuronal migration, it remains unclear whether either this sumoylation is such, or the association of FOXP1 with the NuRD complex, is directly required for FOXP1-mediated transcriptional regulation. Rocca et al. (2017) also provide evidence that FOXP1 can be sumoylated in rat cells (in this case the sumoylated residue is K670) and that this modification promotes dendritic outgrowth in embryonic rat cortical neurons. The authors suggest that sumoylation of FOXP1 enhances binding of the transcriptional co-repressor C-terminal-binding protein 1 (CTBP1). In this study, it was also shown that sumoylation at K670 is required for FOXP1-mediated transcriptional repression of the simian virus (SV40) promoter in human embryonic kidney cells (HEK293T), implicating that this modification could be important in regulating the transcriptional targets of FOXP1 (Rocca et al., 2017) (Figure 1). Taken together, these observations indicate that FOXP1 requires sumoylation to interact with CTBP1, thereby repressing transcription of its target genes. However, it remains unclear whether FOXP1 is a relevant gene in the mouse neocortex during postnatal development. To this end, we compared the results of our study with the results obtained by Konopka’s group: we overlapped the genes associated with ASD and those differentially regulated by FOXP1 found by Usui et al. (2017) and targeted by FOXP1 overexpression. From our study, we identified 13 genes that are regulated by FOXP1. Among these three ASD-associated genes (Cttnbp2, Pcdh15 and Cdhr10), besides Foxp1 itself, that were downregulated both in NSCs upon FOXP1A knockdown in our dataset and in the cortex at postnatal day 9(P9) upon
Figure 1 Schematic model illustrating the role of forkhead box protein P1 (FOXP1) in neurogenesis.

Figure 2 Overlap between autism-spectrum diseases (ASD)-associated genes and genes regulated by forkhead box protein P1 (FOXP1).