Human oligodendrocyte fate is promoted by SOX10 overexpression

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Abstract

Remyelination is the process of restoring myelin sheaths and neuronal functional deficits caused by myelin loss (Franklin et al., 2008, Nat. Rev. Neurosci.). Differentiation of oligodendrocyte progenitors is considered a rate-limiting step in remyelination. Our genomic studies revealed that transcription factors (TFs) ASCL1, SOX10, NKX2-2, PRRX1, and POU2F1 were upregulated during human oligodendrocyte differentiation in vitro (Sim et al., 2011, Nat Biotech). We hypothesized that enforced expression of these TFs in human oligodendrocyte progenitors (OPCs) will induce oligodendrocyte differentiation. CD140a-sorted OPCs were isolated from human fetal brains and infected with individual lentivirus to express each TF. Four days after infection, O4+ oligodendrocyte and GFAP+ astrocyte differentiation was assessed by immunofluorescence. Among the TFs tested, only SOX10 significantly increased oligodendrocyte differentiation relative to the control (174±10%, n=4 fetal samples, p<0.05). However, oligodendrocyte maturation, assayed by oligodendrocyte marker ASCL1, SOX10, NKX2-2, PRRX1, and POU2F1 was upregulated during human oligodendrocyte progenitor stage. In summary, while several transcription factors can influence OPC differentiation, only SOX10 was capable of inducing oligodendrocyte differentiation and might be a promising therapeutic target.

Background

Remyelination in demyelinating diseases

Critical transcription factors responsible for induction of oligodendrocyte fate from OPCs

Experimental Design

Results

1. Can OL-lineage transcription factors induce oligodendrocyte progenitor cells?

- OPCs are significantly more abundant in overexpression of ASCL1

2. Can OL-lineage transcription factors promote oligodendrocyte differentiation and maturation?

- There are significantly more O4+ oligodendrocyte cells only following SOX10 overexpression.
- There are no significant differences observed in oligodendrocyte morphology following transcription factor infection.

3. Can OL-lineage transcription factors influence astrocyte differentiation?

- Over expression of ASCL1(B), NKX2-2(C), PRRX1(B) and SOX10 (F) significantly reduced astrocyte differentiation.

Conclusion

- SOX10 over expression promotes oligodendrocyte differentiation in human OPCs.
- Over expression of ASCL1, NKX2-2, PRRX1 and SOX10 inhibits astrocyte differentiation in human OPCs.
- ASCL1, NKX2-2 and PRRX1 might function to maintain cells in the progenitor stage.
- SOX 10 might be a key regulator in oligodendrocyte differentiation and serves as target in therapeutical remyelination.

References


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