SC1/PRDM4 recruits PRMT5 to control the timing of neural precursor differentiation in developing neural stem cells

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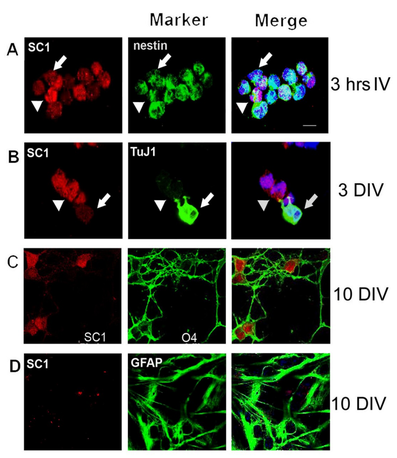
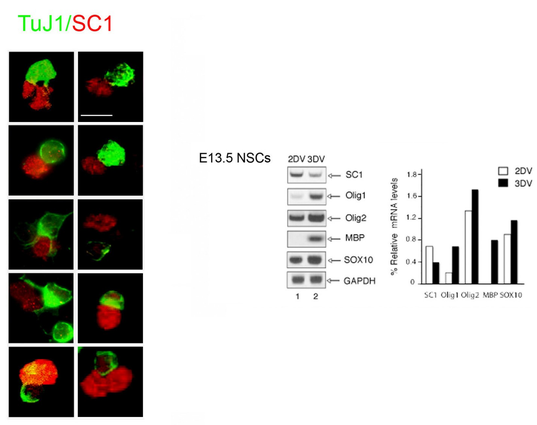
Introduction

During cortical development, neural stem cells (NSCs) switch from proliferative to neuron-generating asymmetric divisions. Here we investigated the role of Schwann cell factor 1 (SC1/PRDM4), a transcriptional repressor highly expressed in the developing nervous system, during NSCs development. We found that SC1 protein levels were down-regulated in newly differentiating neurons, while remaining high in undifferentiated NSCs, suggesting an asymmetric inheritance of SC1. Knockdown of SC1 in the NSCs led to precocious differentiation of neurons and its overexpression led to an increase in Nestin-expressing precursors. We found that SC1, through its amino-terminus, recruits the chromatin modifier PRMT5, a histone arginine methyltransferase that catalyses histone H4R3 symmetric dimethylation (H4R3me2s). Mutations disrupting SC1/PRMT5 interaction resulted in loss of SC1-mediated increase in undifferentiated neural precursor cells. Our data demonstrate that SC1 and PRMT5 are components of an epigenetic regulatory complex that provides an epigenetic signature of a "stem-like" cellular state in the NSCs and which may be asymmetrically inherited during neurogenic divisions.

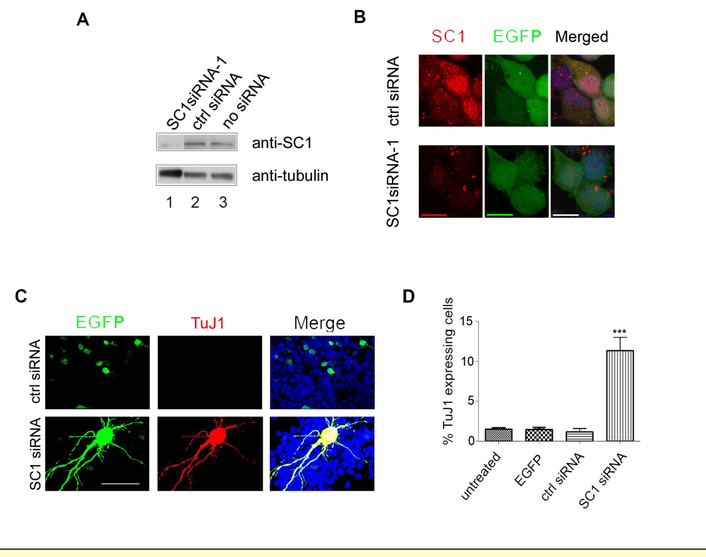
1. SC1/PRDM4 expression in the NSCs is dynamic



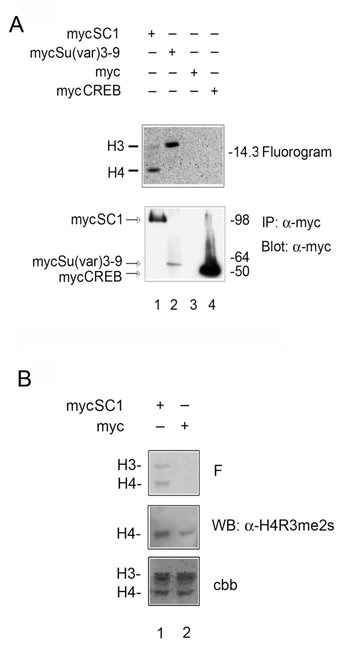
2. SC1/PRDM4 is down-regulated at the onset of neurogenesis and gliogenesis



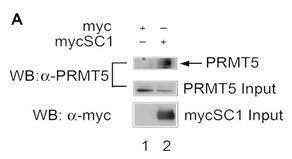
3. Knockdown of SC1/PRDM4 leads to precocious neurogenesis



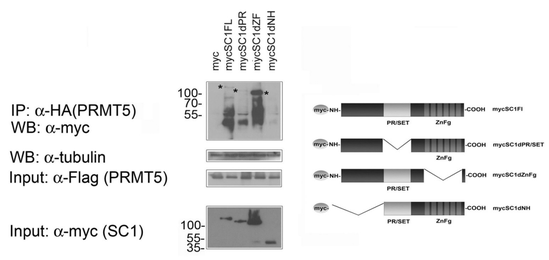
4. SC1/PRDM4 exhibits a histone methyltransferase activity and recruits protein arginine methyltransferase, PRMT5 to mediate symmetric H4R3 dimethylation



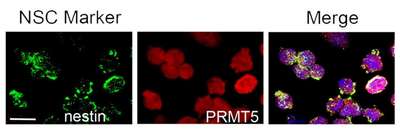
Co-IP of mycSC1 and endogenous PRMT5



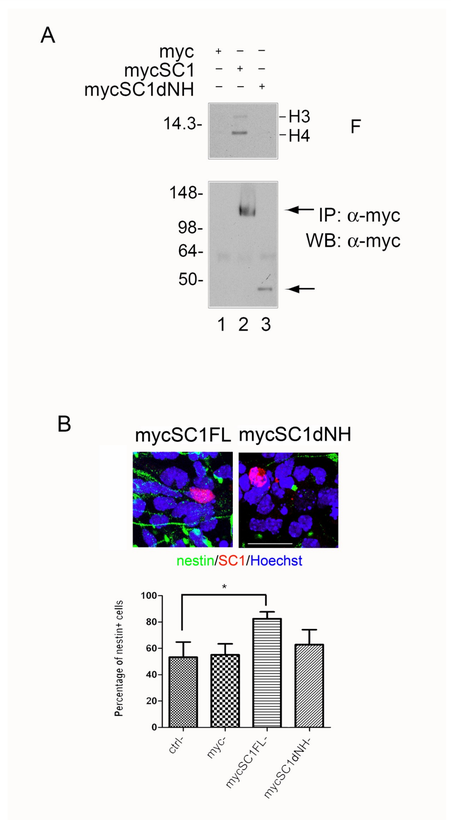
PRMT5 binds to the NH- and in part to PR/SET domains of SC1/PRDM4



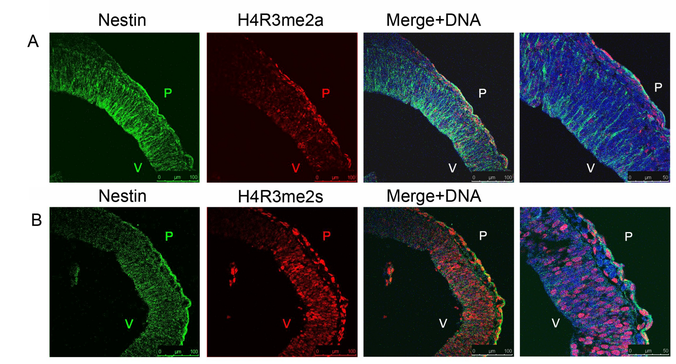
5. PRMT5 is expressed in the neural stem cells



6. SC1/PRDM4 and PRMT5 Interaction is necessary to mediate histone H4 methylation and maintain NSCs in an undifferentiated cellular state



6. Symmetric H4R3 dimethylation is prevalent in the murine cortex at E10.5



Conclusions

1) SC1/PRDM4 expression is dynamic in the differentiating neural stem cells
2) SC1/PRDM4 is down-regulated at the onset of neurogenesis and gliogenesis
3) Knockdown of SC1/PRDM4 in neural stem cells leads to precocious neurogenesis
4) SC1/PRDM4, through its NH- and PR/SET domains, recruits PRMT5 to mediate histone H4R3 symmetric dimethylation
5) The complex of SC1/PRDM4 and PRMT5 is necessary to:
l) mediate histone H4 methylation,
m)maintain the undifferentiated cellular state of the NSCs
6) High levels of H4R3 symmetric dimethylation are found in the developing murine cortex at E10.5 during the proliferative stage of cortical development.

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