Abstract View

PAX6 REGULATES NEURONAL FATES BY CONTROLLING THE EXPRESSION OF WNT ANTAGONISTS IN THE DEVELOPING SPINAL CORD

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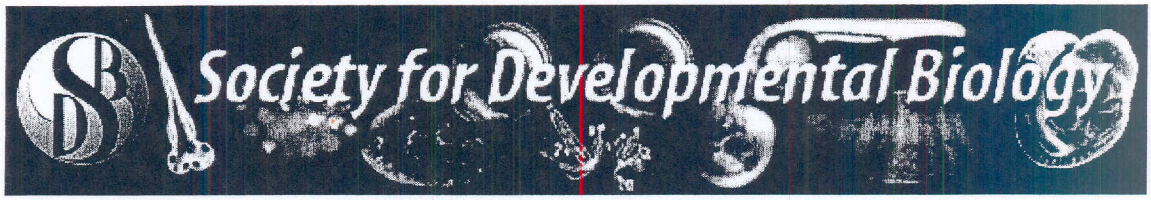
Pax6 plays a central role in cell fate specification in the developing CNS. However, little is known about the downstream mechanisms mediating Pax6 function. Here, we provide evidence that Pax6 controls cell fates by regulating Wnt signaling in the developing spinal cord (SC).

Although many Wnt ligands are expressed widely in both the dorsal and ventral SC, the mechanisms that control local responses to these signals are unclear. Here, we focused on the role of secreted sFRP Wnt antagonists during SC neurogenesis in mouse and chick models. We report that the expression of both *sFRP1* and *sFRP2* is altered in *Pax6* mutant embryos, suggesting aberrant Wnt signaling. As Wnt signaling is required for the proliferation and specification of some dorsal cell types, we analyzed dorsal interneuron development in *Pax6* mutants using cell-type specific markers. Strikingly, we found that Lbx1, a transcription factor normally restricted to a subset of dorsal interneurons, is up regulated specifically in the V2 domain in *Pax6* mutants.

To test whether sFRPs function to repress Lbx1 fates, we transfected full-length *sFRP* cDNAs into the neural tube of developing chick embryos using in ovo electroporation (EP). EP of either sFRP1 or sFRP2 inhibited Lbx1. We also found that ectopic Lbx1 expression was induced by co-EP of Mash1 and Gsh1, both of which are expressed in dorsal Lbx1 progenitors. Notably, sFRP2, but not sFRP1, inhibited Lbx1 induction in this assay. Furthermore, in both the wild type and *Pax6* mutants, Lbx1 cells are generated from Mash1+ progenitors, suggesting a role for Mash1 in Lbx1 induction. Consistent with this, ectopic Lbx1 expression in the V2 domain was significantly reduced in $Mash1^{-/-}$; $Pax6^{-/-}$ double mutants. Our data suggests that loss of *sFRP2* expression in $Pax6^{-/-}$ mutants leads to up-regulation of Wnt signaling in ventral SC, which, in co-operation with Mash1, results in the generation of ectopic Lbx1. Thus, Pax6 regulates cell fates in the SC by controlling Wnt signaling via sFRP2.

Supported by NJCSCR and NIH.

Citation: K. Misra, E. Kuang, S. Li, M.P. Matise. PAX6 REGULATES NEURONAL FATES BY CONTROLLING THE EXPRESSION OF WNT ANTAGONISTS IN THE DEVELOPING SPINAL CORD Program No. 145.20. *2005 Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience, 2005. Online.



Society for Developmental Biology

64th Annual Meeting

Abstract Receipt/Confirmation

Control Number: 644

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2. Presenting/First Author Status

Membership:	
Status:	Faculty
Platform Presentation:	
Best Poster Competition (Student/Postdoc)?	
Invited Speaker?	

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3. Theme Selection

Platform Theme:	
Poster Theme:	18. Cell Fate Specification
Elsevier License Agreement Acceptance:	Yes

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4. Abstract

Pax6 Controls Cell Fates in the Developing Spinal Cord by Regulating Wnt Signaling

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Pax6 is a homeodomain containing transcription factor that has been shown to play a central role in cell fate specification in the developing CNS. However, little is known about the downstream mechanisms mediating Pax6 activity. Here, we provide evidence that Pax6 influences cell fates by regulating Wnt signaling in the developing SC. We show that Lbx1, a transcription factor normally restricted to dorsal interneurons, is up regulated specifically in the V2 domain in Pax6 mutants. These mutants also exhibit down regulation of sFRP1&2 in the ventral SC. The sFRP genes encode secreted frizzled related proteins that function as antagonists of Wnt signaling. To test whether these factors normally function to repress Lbx1 fates ventrally, we transfected full-length sFRP cDNAs into the neural tube of developing chick embryos. Over expression of both sFRP1&2 inhibited Lbx1. To further explore the mechanisms regulating normal Lbx1 induction, we developed an assay in which co-electroporating Mash1 and Gsh1. sFRP2 could elicit ectopic Lbx1 expression, but not sFRP1 was able to inhibit Lbx1 induction by these factors. Strikingly, in both the wild type and Pax6 mutants, Lbx1 cells are generated from Mash1+ progenitors, suggesting a possible role for Mash1 in Lbx1 induction. Consistent with this, ectopic Lbx1 expression in the V2 domain was significantly reduced in Mash1-/-; Pax6-/- double mutants. We conclude that Pax6 regulates cell fates in the SC by controlling Wnt signaling via sFRP's. Our data suggests that loss of sFRP expression in Pax6-/- mutants leads to up-regulation of Wnt signaling, which, in co-operation with Mash1 results in up- regulation of Lbx1.