PAX6: a transcriptional guardian for glutamatergic fate in the developing neocortex

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SIGNIFICANCE

- PAX6 protects glutamatergic fate in neocortical progenitors by suppressing regional morphogenetic actions
- Without PAX6, a subset of progenitors commit to multiple ectopic fates under the influences of surrounding morphogens in action

1. Summary

- PAX6 is a key transcription factor that regulates many aspects of neurogenesis in the neocortex including glutamatergic fate specification
- Previous studies reported neocortical progenitors commit to a GABAergic fate upon *Pax6* deletion (Stoykova *et al.*, 2000)
- We suggest this fate change is heterogenous in nature and region-specific depending on the morphogens in the milieu

2. Emergence of multiple ectopic fates caused by morphogens in the absence of PAX6

Methodology

Genes	p_val_adj	Log2FC	Genes	p_val_adj	Log2FC
<i>Fos</i>	3.42E-104	1.65	<i>Hes1</i>	1.64E-24	-0.69
<i>Meg3</i>	7.11E-37	1.44	<i>Meis2</i>	7.63E-30	-0.75
<i>Zic1</i>	5.80E-24	0.71	<i>Notch2</i>	3.92E-20	-0.81
<i>Hes6</i>	3.36E-07	0.51	<i>Nr2f1</i>	1.75E-23	-0.83
<i>Lhx2</i>	3.99E-16	0.48	<i>Cbx3</i>	4.44E-16	-0.92
<i>Gadd45g</i>	1.00E+00	0.47	<i>Ptn</i>	2.87E-43	-1.04
<i>Ascl1</i>	1.21E-01	0.37	<i>Hes5</i>	6.00E-121	-2.45

Genes	p_val_adj	Log2FC	Genes	p_val_adj	Log2FC
<i>Tubb3</i>	0.00E+00	8.06	<i>Cdkn1c</i>	3.25E-109	3.11
<i>Dlx6os1</i>	0.00E+00	7.71	<i>Zic1</i>	7.01E-56	2.84
<i>Meg3</i>	0.00E+00	6.78	<i>Crabp1</i>	6.25E-53	2.83
<i>Sp9</i>	0.00E+00	6.48	<i>Nrp2</i>	5.32E-143	2.76
<i>Dlx2</i>	0.00E+00	6.48	<i>Socs2</i>	1.09E-124	2.41
<i>Dlx1</i>	0.00E+00	6.40	<i>Mfap4</i>	2.42E-89	2.32
<i>Nrxn3</i>	0.00E+00	6.20	<i>Lhx2</i>	2.23E-129	2.16
<i>Dcx</i>	0.00E+00	5.55	<i>Nhlh2</i>	2.07E-76	2.14
<i>Arx</i>	0.00E+00	3.92	<i>Nhlh1</i>	4.07E-101	2.11
<i>Ccnd2</i>	0.00E+00	3.49	<i>Prdm13</i>	3.28E-107	1.88
<i>Gad2</i>	4.52E-241	3.20	<i>Lhx9</i>	4.34E-85	1.86
<i>Etv1</i>	1.84E-107	2.89	<i>Id2</i>	2.24E-46	1.68
<i>Sp8</i>	3.30E-154	2.82	<i>Emx2</i>	8.82E-71	1.63
<i>Gadd45g</i>	5.74E-142	2.66	<i>Sema6d</i>	4.71E-42	1.60

- At E13.5, a population of APs upregulated signaling-related genes such as *Zic1* (for WNT signaling) and *Ascl1* (for SHH), and downregulated *Hes1*, *Notch2* and *Hes5* (for NOTCH)
- At E14.5, a GABAergic population and another distinct ectopic fate (i.e. the population X) emerged at the expense of the diminished BP population

- A subset of GABAergic cells eventually became post-mitotic GABAergic neurons enriched with *Tubb3*, *Gad2*, *Ccnd2* (for SHH signaling) and *Etv1* (for FGF)
- Population X upregulated genes *Crabp1* (for RA signaling); *Zic1* (for WNT); and *Id2* (for BMP), in addition to those for the hippocampus (*Nrp2*, *Lhx2/9*) and the caudal neocortex (*Crabp1*, *Nhlh1/2*) fates

3. Reduced GABAergic genes expression upon SHH signaling attenuation using BMP4

Methodology

Data are mean ± SEM (N = 3 embryos from 3 females from 3 independent experiments); * p ≤ 0.05)