



Significance of the dynamic expression of Pax6 and Dlx2 in the postnatal periventricular zone cells

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A commentary on

Dynamic expression of the pro-dopaminergic transcription factors Pax6 and Dlx2 during postnatal olfactory bulb neurogenesis

by Chevigny, A., Core, N., Follert, P., Wild, S., Bosio, A., Yoshikawa, K., Cremer, H., and Beclin, C. (2012). *Front. Cell. Neurosci.* 6:6. doi: 10.3389/fncel.2012.00006

The discovery of neurogenesis in the adult subventricular zone (SVZ) and the capability of these neuronal progenitors to migrate a long distance have an immense effect on the basic neurobiology as well as regenerative medicine. Neuronal progenitors are heterogeneous in terms of molecular expression, which suggests that these cells are already programmed to form specific cell types in the target area, the olfactory bulb (OB; Merkle et al., 2007). Transcription factors (TFs) are by far the most important groups of molecules that play a decisive role in the fate specification of these neuroblasts and their differentiation into different interneuron subtypes in the OB.

Pax6, a paired homeobox gene and Dlx2, a distal-less homeobox gene, are the two most extensively studied TFs related to the specification of the adult SVZ neuroblasts. Both these TFs are involved in the progenitor proliferation as well as specification of the OB dopaminergic neurons (Kohwi et al., 2005; Brill et al., 2008). Differential expressions of these two TFs in the adult SVZ and in the rostral migratory stream (RMS) have been previously reported by different groups (Hack et al., 2005; Kohwi et al., 2005; Brill et al., 2008). Chevigny et al. (2012) have further added to the existing knowledge about the spatio-temporal expression of these TFs in the SVZ and the RMS and discussed the significance of this dynamic expression in specifying dopaminergic cell population in the OB. For precise targeting of the progenitors in the SVZ and for lineage

tracing of these cells, they electroporated GFP construct in the newborn (P1) mouse SVZ (or periventricular zone, PVZ, as the authors termed in the article). They show that majority of the GFP-electroporated cells in the dorsal PVZ cells co-express Pax6, but Pax6 expression reduce drastically in the GFP-electroporated lateral PVZ cells. In contrast, Dlx2 is expressed only in the electroporated cells in the lateral PVZ and not in the dorsal PVZ.

The mutually exclusive expression pattern of Pax6 and Dlx2 in the neonatal pups is in parallel with what is observed during embryonic development (Toresson et al., 2000). During forebrain development, both cortical (pallial) and subcortical (subpallial) progenitors are generated in the ventricular zone (VZ) and migrate to their proper destinations. Expression of TFs in a defined dorso-ventral domain along the VZ determines generation and fate specification of cortical and subcortical neurons. Pax6 is expressed in the pallial progenitors and at a low level in the dorsal lateral ganglionic eminence (Stoykova et al., 1996; Toresson et al., 2000). Dlx2, on the other hand, is expressed in the subpallial VZ (Toresson et al., 2000; Long et al., 2007) and regulate generation of the OB interneurons (Long et al., 2007). In the newborn mice, the dorsal and lateral PVZ appear to be structurally equivalent and molecularly reminiscent of the developing forebrain pallial and subpallial VZ respectively.

In the article by Chevigny et al. (2012), the time course study revealed that in the RMS, the Pax6 expression predominantly remain restricted within the GFP+ cells from the dorsal PVZ. The spatio-temporal identity of Pax6 expression is maintained along the dorso-lateral and rostral-caudal axes at all-time post-electroporation. This is, however, not true with Dlx2 expression pattern. The authors observed that although in the PVZ, the expression of Dlx2 is restricted within the lateral progenitors; it is upregulated in

the dorsal PVZ-generated cells at the level of RMS and OB. This observation was further substantiated by microarray analysis of gene expression using FACS-sorted GFP+ RMS cells originated from the dorsal PVZ. On the contrary, they did not comment on the level of Pax6 expression in this cell population. These dorsal PVZ-derived cells co-express both Dlx2 and Pax6 in the RMS as evident from immunohistochemistry. It is possible that such ectopic Dlx2 expression may be indirectly regulated by the level of Pax6 expression in these cells. Indeed, during forebrain development, the dorso-ventral boundary of gene expression in the VZ is severely affected in *sey/sey* (small eye phenotype due to mutation in Pax6 gene) mutant mice where Dlx2 was found to be expressed ectopically in cortical progenitors (Toresson et al., 2000). Thus, an induction of Dlx2 expression appears to be a secondary effect of the inhibition (either complete or partial) of Pax6 expression.

Previous study has shown that there is heterogeneity in the number of Pax6 expressing cells along the rostro-caudal axis of the RMS (Hack et al., 2005). Least number of Pax6+ cells was observed along the SVZ lining the lateral ventricle, which then gradually increased rostrally and reached at its maximum around the central part of the RMS and then further reduced when the cells reached the OB. Microarray analysis performed by Chevigny et al. (2012) showed that Dlx2 expression level reaches its maximum after 4 days of electroporation when the GFP+ dorsal PVZ-derived cells are in the RMS. Here, two important questions pertaining to Dlx2 expression remain to be answered: (1) is this increase uniform along the entire RMS or exhibit any rostro-caudal difference, and (2) at a single cell level, does upregulation of Dlx2 associated with partial downregulation of Pax6? Previous study by Brill et al. (2008) showed that although Dlx2 and Pax6 proteins can physically interact, they are regulated independently. They also

showed that Dlx2 regulates dopaminergic cell fate through a pax6-dependent manner. Therefore, the level of each protein may be a crucial factor deciding the cell fate into dopaminergic lineage.

The new findings by Chevigny et al. (2012) emphasizes on the plasticity in molecular expression in the PVZ-derived cells along their migratory route, the RMS, and the importance of such combinatorial expression pattern of TFs in determining the cell fate. Similar analysis of other TFs will allow generation of a detailed dynamic expression profile of these genes and decipher their role in fate choice of the progenitors.

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