Journal Club

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Ptf1a Is a Molecular Determinant for Both Glutamatergic and GABAergic Neurons in the Hindbrain

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Review of Yamada et al. (http://www.jneurosci.org/cgi/content/full/27/41/10924)

The *pancreas transcription factor 1a* (*Ptf1a*) gene encodes a bHLH (basic helix-loop-helix) transcription factor that has been shown to be required for the specification and formation of the pancreas, as well as for the generation of Purkinje cells (PCs) and interneurons in the cerebellum (Hoshino et al., 2005) and specification of dorsal interneurons in the spinal cord (Glasgow et al., 2005). Mutations in human and mouse *PTF1A* cause permanent neonatal diabetes mellitus associated with pancreatic and cerebellar agenesis (Hoshino et al., 2005). In the absence of *Ptf1a*, progenitor cells required for the generation of GABAergic PCs and interneurons of the cerebellum, as well as GABAergic interneurons of the spinal cord, adopt a glutamatergic phenotype (Glasgow et al., 2005; Pascual et al., 2007). Moreover, in the dorsal telencephalon, electroporation of *Ptf1a* produces ectopic GABA-expressing neurons with morphology and migratory behavior similar to GABAergic neurons of the cerebral cortex (Hoshino et al., 2005). Together, these studies identify *Ptf1a* as a crucial molecular determinant of GABAergic neuronal fate.

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In the developing cerebellar anlage, recent cell fate-mapping studies have demonstrated that *Ptf1a*-expressing progenitor cells originate from the dorsal rhombomere 1 (r1) ventricular zone to produce cerebellar GABAergic cells, including PCs and interneurons, whereas *Math1*-expressing progenitor cells originate from the r1 rhombic lip to produce glutamatergic granule cell precursors in the cerebellar external granule layer (Hoshino et al., 2005; Wang et al., 2005). In contrast, precerebellar nuclei, consisting of mossy fiber (MF) neurons and climbing fiber (CF) neurons, are generated from the dorsal regions of multiple hindbrain rhombomeres (Wingate, 2001). A key finding of the recent study by Yamada et al. (2007) is that *Ptf1a* is required for the generation of glutamatergic CF neurons in the precerebellar inferior olivary nucleus (ION), suggesting that although the *Ptf1a* lineage gives rise to GABAergic neurons within the cerebellum and dorsal spinal cord, *Ptf1a*-expressing progenitors also contribute to glutamatergic neurons of the hindbrain. This surprising result indicates that *Ptf1a* is not simply a molecular switch determining GABAergic versus glutamatergic neuronal subtype fate, as was previously understood, but rather that it functions in a region-specific manner to specify neuronal fates.

To demonstrate that *Ptf1a*-expressing hindbrain progenitors give rise to glutamatergic CF neurons, Yamada et al. (2007) first generated a genetic fate map of hindbrain *Ptf1a*-expressing progenitor cells in mice engineered to express β-galactosidase (β-gal) in these cells [$Ptf1a^{cre/+}$;Floxed *LacZ* reporter mice (R26R)]. β-gal-positive CF neurons were found in the ventrally located ION. Strikingly, these neurons were also glutaminase positive, whereas the small population of GABA-positive CF neurons within the ION was β-gal negative. Thus, GABA-positive neurons in the ION are not derived from the *Ptf1a* lineage [Yamada et al. (2007), their Fig. 1*T*,*U* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F1)]. To investigate whether MF neurons also derive from the *Ptf1a* lineage, the authors performed retrograde labeling of MF and CF neurons by injecting Fluorogold into the cerebellar hemisphere and vermis of adult $Ptf1a^{cre/+}$; *R26R* mice [Yamada et al. (2007), their Fig. 2*A* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F2)]. Only CF neurons in the ION were Fluorogold negative and β-gal positive; Fluorogold-positive MF neurons throughout the hindbrain were not β-gal positive [Yamada et al. (2007), their Fig. 2*B–P* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F2)], confirming that CF but not MF neurons, are derived from *Ptf1a*-expressing progenitor cells.

Studies in mice have shown that both CF and MF neurons are specified within the dorsal caudal hindbrain region around embryonic day 10.5 (E10.5)–

E11.5. Following specification, these neurons follow a tangential and/or circumferential migration to occupy their final position (Wingate, 2001). The caudal hindbrain is divided into subregions defined along the dorsoventral axis by nonoverlapping expression patterns of transcription factors, including *Lmx1a*, *Math1*, and *Ngn1*. Yamada et al. (2007) show that Ptf1a protein is expressed in the caudal hindbrain between the dorsal and ventral Ngn1 domains at E11.5 [Yamada et al. (2007), their Fig. 3*A–I* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F3)]. To examine the migration of dorsal *Ptf1a*-lineage cells toward the ION, the authors followed the movement of β-gal-positive cells in *Ptf1a*$^{cre/+}$*;R26R* mice from E11.5 to E16.5 [Yamada et al. (2007), their Fig. 4*A–L* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F4)]. They showed that at early embryonic stages, Brn3a, a marker of CF neurons, was colocalized with β-gal within the path of CF neuronal migration [Yamada et al. (2007), their Fig. 4*O*,*Q*,*M* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F4)]. At later stages, colocalization was also observed within the ventral ION [Yamada et al. (2007), their Figs. 4*S*,*U* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F4), 5*K*,*M* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F5)], further confirming that ION neurons originate in the dorsal *Ptf1a* domain.

Finally, to demonstrate that Ptf1a is required for the specification of CF neurons, the authors analyzed the development of the ION in *Ptf1a* null mice (*Ptf1a*$^{cre/cre}$;R26R). Neither β-gal nor Brn3a expression was observed in the ventromedial region of the caudal hindbrain, including the ION, in mutants at E18.5 [Yamada et al. (2007), their Fig. 5*E–N* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F5)], indicating a requirement for Ptf1a in the development of CF neurons of the ION. No significant difference was seen in BrdU incorporation rates in the dorsal *Ptf1a*-expressing proliferative hindbrain in younger *Ptf1a*-null mice at E10–E11.5, leading the authors to conclude that progenitors are still generated from the Ptf1a domain in the absence of Ptf1a function. In contrast, no ventrally migrating β-gal-positive cells were observed in E13–E16.5 *Ptf1a* null mutants [Yamada et al. (2007), their Figs. 4*F*,*H–V* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F4), 6*A–D* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F6)]. Interestingly, at E13, Brn3a- and β-gal-positive cells accumulated in lateral regions of the mutant hindbrain [Yamada et al. (2007), their Fig. 4*N*,*W*,*X* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F4)]. At E18.5, β-gal-positive cells were observed ectopically in pontine nuclei in *Ptf1a*-null embryos [Yamada et al. (2007), Fig. 7*A–H* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F7)]; a subset of these cells also expressed *Mhb2/Barhl1* (a marker for MF neurons) [Yamada et al. (2007), their Fig. 7*J* (http://www.jneurosci.org/cgi/content/full/27/41/10924/F7)]. Collectively, these remarkable experiments indicate that inactivation of *Ptf1a* results in a change in fate from hindbrain glutamatergic ION CF into pontine MF neurons.

These findings complement another recent study demonstrating that in the absence of *Ptf1a* function, cerebellar *Ptf1a*-expressing progenitors in r1 adopt a more dorsal (*Math1*-expressing) fate of cerebellar granule cells (Pascual et al., 2007). Together, it seems likely that the MF neurons seen by Yamada et al. (2007) in *Ptf1a* null mice are derived from an expanded *Math1*-expressing domain within the developing dorsal r1. This hypothesis is testable through further fate-mapping experiments to examine *Math1*-positive lineages (Wang et al., 2005) in *Ptf1a* null mice.

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