IJAE
Vol. 120, n. 1 (Supplement): 98, 2015
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Zinc-finger and helix-loop-helix transcription factors regulate Purkinje neuron neurogenesis and cerebellar corticogenesis

Laura Croci[1], Aurora Badaloni[1], Davide Gaudesi[1], Richard Hawkes[2], Søren Warming[3], Ottavio Cremona[4], G. Giacomo Consalez[4]

[1] Ospedale San Raffaele, IRCCS, Milano, Italy - [2] University of Calgary, Calgary, Canada - [3] Genentech, South San Francisco, USA - [4] Università Vita-Salute San Rafffaele, Milano, Italy

Many regulatory genes have been pinpointed as orchestrators of cerebellar development, from the onset of neurogenesis to the patterning of the adult cerebellar cortex, with a special reference to the development of cerebellar Purkinje cells (PCs). PCs provide the sole output from cerebellar cortical circuits, where each PC integrates myriads of presynaptic inputs, both inhibitory and excitatory. In the murine cerebellar primordium PCs are generated from a pool of ventricular zone progenitors facing the fourth ventricle between embryonic day (E) 10.5 and 13.5. This progenitor pool expands in the ventricular zone (VZ) through symmetric cell division until E10.5, when a gradual switch to asymmetric cell division occurs, regulated by Notch1 (Lutolf et al., 2002) and its interactor (Masserdotti et al., 2010), the Zn-finger TF Zfp423 (Alcaraz et al., 2006; Warming et al., 2006; Croci et al., submitted). Zfp423 was recently implicated in Joubert syndrome and cerebellar vermis hypoplasia (Chaki et al., 2012). Allelic mutations of *Zfp423* produce distinct alterations in PC development (Croci et al., submitted). PCs arise from a pool of progenitors positive for the basic-helix-loop-helix transcription factors (TFs) neurogenin (Ngn) 1 and 2 (Zordan et al., 2008; Lundell et al., 2009). Ngn2 regulates cell cycle progression and dendritic arbor generation in PC precursors (Florio et al., 2012). PCs also express HLH transcription factors of the Olf/EBF family. In *Ebf2* -/- mutants, PC migration and survival are affected (Croci et al., 2006). Neonatal PC death is due to local downregulation of *Igf1* gene expression (Croci et al., 2011). Finally, EBF2 regulates cortical patterning in the adult cerebellum, regulating its subdivision into alternate parasagittal stripes of distinct PC subtypes. Indeed, EBF2 is required to repress the zebrin II+ phenotype in postnatal PCs (Croci et al., 2006; Chung et al., 2008).

References

Alcaraz et al. (2006). Zfp423 controls proliferation and differentiation of neural precursors in cerebellar vermis formation. Proc Natl Acad Sci U S A 103:19424-19429.

Chaki et al. (2012). Exome capture reveals ZNF423 and CEP164 mutations, linking renal ciliopathies to DNA damage response signaling. Cell 150:533-548.

Chung et al. (2008). Purkinje cell subtype specification in the cerebellar cortex: Ebf2 acts to repress the Zebrin II-positive Purkinje cell phenotype. Neuroscience 153:721-732.

Croci et al. (2011). Local insulin-like growth factor I expression is essential for Purkinje neuron survival at birth. Cell Death Differ 18:48-59.

Croci et al. (submitted). Domain-specific regulation of cerebellar neurogenesis by Zfp423, a gene implicated in Joubert Syndrome and cerebellar vermis hypoplasia.

Croci et al. (2006). A key role for the HLH transcription factor EBF2COE2,O/E-3 in Purkinje neuron migration and cerebellar cortical topography. Development 133:2719-2729.

Florio et al. (2012). Neurogenin 2 regulates progenitor cell-cycle progression and Purkinje cell dendritogenesis in cerebellar development. Development 139:2308-2320.

Lundell et al. (2009). Neurogenin1 expression in cell lineages of the cerebellar cortex in embryonic and postnatal mice. Dev Dyn 238:3310-3325.

Lutolf et al. (2002). Notch1 is required for neuronal and glial differentiation in the cerebellum. Development 129:373-385.

Masserdotti et al. (2010). ZFP423 coordinates Notch and bone morphogenetic protein signaling, selectively up-regulating Hes5 gene expression. J Biol Chem 285:30814-30824.

Warming et al. (2006). Zfp423 is required for normal cerebellar development. Mol Cell Biol 26:6913-6922.

Zordan et al. (2008). Comparative analysis of proneural gene expression in the embryonic cerebellum. Dev Dyn 237:1726-1735.

Keywords

Cerebellar organogenesis; cerebellar neurogenesis; cerebellar cortical patterning; cell death; development; Purkinje neurons.