Tuning of neocortical astrogenesis rates by Emx2 in neural stem cells

Generation of astrocytes within the murine developing cerebral cortex mainly takes place during the first postnatal week, after neurongenesis and prior to the bulk of oligogenesis. This process involves a great variety of highly complex regulatory mechanisms. Astrocytic outputs depend on two primary factors: progressive commitment of multipotent precursors to astroglial fates and proper tuning of proliferation of astrocyte-committed progenitors. To date, several regulatory mechanisms have been identified for the former process, while very little is known about modulation of astroblast proliferation (reviewed in Mallamaci, 2013). Intriguingly, astrogenic rates remain very low during the whole neurogenenic phase, although the mouse cortex is already able to generate astrocytes at E14.5–E15.5, thanks to specific chromatin reconfiguration (Fan et al., 2005). Poor proliferation of astroblasts may contribute to this effect (Seuntjens et al., 2009). Among different factors modulating astrocyte-committed proliferation, the Egf-receptor (EgfR) and the secreted ligand Fgf9 both specifically promote it (Viti et al., 2003; Lum et al., 2009). Emx2, a pleiotropic hub (Gangemi et al., 2006) controlling a variety of neurodevelopmental processes, is highly expressed in the early neurogenenic pallium, while it fades out together with neurongenesis ending. This temporal progression is possibly linked to the progressive decline of Wnt signals supporting Emx2 expression (Theil et al, 2002) and late arousal of Fgf8 (http://developingmouse.brain-map.org/) antagonizing it (Garel et al., 2003). In a previous in vitro study (Brancaccio et al., 2010), we reported that Emx2 overexpression in neural stem cells (NSCs) leads to a reduction of their astrocytic outputs, due to unknown mechanisms. In the paper highlighted here (Falcone et al., 2014), we showed that this phenomenon occurs also in vivo and dissected its cellular and molecular mechanisms.

At the beginning of our study, we verified that the decrease of the ultimate glial output of NSCs induced by Emx2 overexpression takes place also in vivo and it is due to a shrinkage of the proliferating astrogenic pool. We injected a plasmid expressing Emx2 into the lateral ventricular cavity of P0 pups and electroporated it into the cortex. The analysis of P4 mice electro- transported Emx2 both specifically promote it (Viti et al., 2003; Lum et al., 2009). Emx2, a pleiotropic hub (Gangemi et al., 2006) controlling a variety of neurodevelopmental processes, is highly expressed in the early neurogenenic pallium, while it fades out together with neurongenesis ending. This temporal progression is possibly linked to the progressive decline of Wnt signals supporting Emx2 expression (Theil et al, 2002) and late arousal of Fgf8 (http://developingmouse.brain-map.org/) antagonizing it (Garel et al., 2003). In a previous in vitro study (Brancaccio et al., 2010), we reported that Emx2 overexpression in neural stem cells (NSCs) leads to a reduction of their astrocytic outputs, due to unknown mechanisms. In the paper highlighted here (Falcone et al., 2014), we showed that this phenomenon occurs also in vivo and dissected its cellular and molecular mechanisms.

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Figure 1 Altered astrocytogenesis upon Emx2 manipulation in vivo.

(A) Distribution of S100β+ astrocytes and S100β Ki67+ astroglial proliferating progenitors in the posterior parietal cortex of P4 pups electroporated at P0 with a control (NC) and, alternatively, a constitutive Emx2 expressor plasmid (Emx2-GOF). (B) Distribution of S100β+ astrocytes and S100β Ki67+ astroglial proliferating progenitors in the posterior parietal cortex of E17.5 embryos heterozygous for an Emx2-null allele and their littermate wild type controls.

Figure 2 Epistatic relationships among Emx2 and mediators of its antiastrogenic activity.

The question mark highlights a hypothetical regulatory branch accounting for the divergent effects exerted by Emx2 overexpression on Fgf9 mRNA levels in control conditions and upon Bmp signalling inhibition.