Supplemental Information

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Development and Evolution

of the Human Neocortex

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Extended Discussion

The OSVZ as a Site of Human Disease

The appreciation that OSVZ proliferation could be responsible for generating the majority of cortical neurons invites a re-interpretation of the mechanisms behind a wide range of neurodevelopmental diseases. Particularly relevant are those diseases that broadly affect neuronal number and brain size such as lissencephaly and microcephaly. Some of the genes shown to cause these disorders in humans have now been studied in model systems, and appear to be frequently involved in maintaining the proper structure and function of the mitotic spindle and centrosome. In the context of the mouse neocortex, these proteins tightly regulate RG divisions and neuronal migration (Wynshaw-Boris, 2007; Bond et al., 2002, 2005; Lizarraga et al., 2010; Buchman et al., 2010). However, in the context of the human neocortex, the function of these genes must also extend to oRG cells, since their mitotic somal translocation, division, and derivation from ventricular RG cells are likely to utilize related microtubule-based mechanisms. Pursuing a cell biological understanding of oRG cell behavior will be an exciting future direction that may reveal unexpected links to other neurodevelopmental disorders such as autism and schizophrenia.

A full understanding of OSVZ neurogenesis will also be critical for the proper generation of specific neuronal subtypes for cell replacement therapies, where potential differences between neurons derived from ventricular and outer subventricular regions may have to be recapitulated *in vitro*. Since OSVZ proliferation may be responsible for production of most neurons in the human neocortex, it is possible that derivation of neuron subtypes from human embryonic stem (hES) cells or induced pluripotent stem (iPS) cells could

require a transitional oRG-like progenitor state. Supporting this, recent studies have shown that neuroepithelial “rosette” structures resembling VZ progenitor cells can be derived *in vitro* from hES cells. In contrast to the rosettes derived from mouse ES cells that generate both deep and upper layer neurons in correct laminar positions, rosettes from hES cells only succeed in producing deep layer neurons (Eiraku et al., 2008). Although these observations could be a reflection of limitations in the time frame or conditions of culture, they may suggest that even *in vitro*, OSVZ progenitor cell identity is distinct and particularly important for generating upper layer neurons. An appreciation of the OSVZ in neurogenesis and an understanding of the regulators that control its development will be critical for deriving a full repertoire of human neurons for therapeutic ends.

Supplemental References

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