Oxysterols Drive Dopaminergic Neurogenesis from Stem Cells

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Stem cell therapy for Parkinson’s disease requires effective production of dopaminergic neurons. In this issue of Cell Stem Cell, Sacchetti et al. (2009) report an unexpected role of liver X receptors and their ligand, oxysterols, in regulating dopaminergic neurogenesis.
supplemented with Shh, Fgf8, GDNF, and BDNF, and yet the efficiency of these conditions for dopaminergic neuron generation remains low (Gale and Li, 2008; Kim and de Vellis, 2009). Treatment with oxysterols during neuronal differentiation of human ESCs markedly increases the production of TH+ neurons, along with concurrent reduction in the numbers of astrocytes, neural progenitors, and proliferative cells (Figure 1). These TH+ neurons appear to have acquired many hallmarks of dopaminergic neurons, including depolarization-induced release of dopamine, and seem to be metabolically normal with respect to cellular lipid and cholesterol homeostasis. One challenge that must be overcome prior to wide application of stem cell-based cell replacement therapy is the ability to generate desired cell types in large quantities that are also of high quality and sufficient purity so as to minimize contamination of undesired cells, especially proliferating progenitors that may cause tumorigenesis after transplantation. Oxysterols enhance dopaminergic neuronal differentiation, promote cell-cycle exit, and decrease gliogenesis of stem cells and thus kill multiple birds with one stone. The majority of identified nuclear receptors are known to be expressed in the embryonic and adult brain, and yet few have been investigated as to their potential roles in regulating neurogenesis and development, with the exception of retinoic acid receptor. The identification of novel functions of LXRs in neurogenesis, distinct from their classic roles in lipid homeostasis, opens doors for studying other nuclear receptors in neural development. This study also illustrates a prime example of how discoveries in basic developmental biology can be highly instructive for improving practical schemes of therapeutic stem cell applications. Several important issues, however, remain to be addressed by future studies. First, the mechanism responsible for the impact of oxysterol/LXRs on cell-cycle dynamics of dopaminergic neural progenitors remains unclear. Activation of LXRs has been shown to suppress key cell-cycle genes in other cell types (Vedin et al., 2009). Identifying direct targets of LXRs through Chip-on-chip or Chip-seq technologies would yield insights into this issue. Given that Shh and retinoic acid signaling components exhibit altered expression in acute response to oxysterols or in LXR null mice (Dwyer et al., 2007; Volle et al., 2007), these pathways represent attractive candidates as potential LXR targets, and as converging points that may couple oxysterol signaling to known genetic programs for dopaminergic neuron specification. Second, LXR-mediated effects appear to be highly specific for the midbrain region, for the dopaminergic neuron subtype, and for a subset of dopaminergic specification genes. How is such specificity achieved? How is oxysterol/LXR signaling initiated and regulated in different biological contexts? From the perspective of disease and stem cell-based therapeutic interventions, screening for more potent LXR agonists and inducers of LXR expression is warranted, given the observed additive effects of oxysterols and overexpression of LXRβ on dopaminergic neurogenesis. Additional work is also needed to understand whether defective oxysterol/LXR signaling might be involved in predisposing PD patients for the onset of symptoms. Furthermore, it will be interesting to assay how oxysterol-like molecules might be used to augment dopaminergic neurogenesis from other stem cell populations, such as adult neural stem cells and PD patient-specific induced pluripotent stem cells. Success in these endeavors may offer meaningful advances for both preclinical and translational applications, as well as drug testing and in vitro disease modeling.

**REFERENCES**


**Figure 1. A Schematic Illustration of The role of Oxysterols in Promoting Dopaminergic Neurogenesis**

Dopaminergic neural progenitors undergo active cell-cycle progression in the ventral midbrain domain from the mouse embryonic stage E9 to E12 and then dopaminergic neuron fate determination and maturation from the stage E11 to E15 (A). Acting in the nuclei of the early progenitors in a presumably cell-autonomous manner, oxysterols (22-oxycholesterol depicted) activate LXRs and regulate target gene transcription to induce cell-cycle exit and dopamine neuron differentiation. Such effects of oxysterols are conserved during dopaminergic neurogenesis from human embryonic stem cells (B). Shh and Fgf8 induce neural progenitor cell competency for midbrain neuron specification. By inducing cell-cycle exit specifically toward neuronal fate, oxysterols then act in coordination with other factors and genetic programs to promote dopaminergic neuron differentiation from progenitor cells.