glucose) fuel shortage and a reduction in α-KG, which promotes the stabilization of Hif-1α and results in the secretion of Vegfa by starved photoreceptors to promote neovascularization in these mice.

A notable future molecular direction for the work could stem from the fact that Ffar1 also activates phospholipase C in the pancreas and increases intracellular calcium concentrations through the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2)[9]. There is a light-dependent increase of PIP2 in photoreceptors[10,11], and further studies are warranted to examine whether Ffar1 activates the hydrolysis of PIP2 in photoreceptors.

The authors of this study also found increased concentrations of VEGFA in vitreous from people with subretinal neovascularization and RAP, as compared to those in healthy controls, which is consistent with the *Vldlr*$^{-/-}$ mouse model. The study raises several important clinical questions. Does the function of retinal VLDLR or GLUT1 decline in aging and thus contribute to the development of AMD, or does aging increase the expression of FFAR1? What are the downstream effectors of FFAR1? From a clinical standpoint, the neovascularization of AMD is localized to the macular region, whereas *Vldlr* deletion in mice presumably occurs throughout the retina. Presumably, the fatty acid–uptake defect is diffuse, but the clinical entity—RAP—is limited to the macula, so the predilection for neovascularization to occur in the macula remains a mystery.

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Patient iPSCs: a new discovery tool for Smith-Lemli-Opitz syndrome

Zhexing Wen, Hongjun Song & Guo-li Ming

A new study with patient stem cell–based modeling of Smith-Lemli-Opitz syndrome (SLOS) shows that the accumulation of a specific cholesterol precursor dysregulates the Wnt/β-catenin pathway, which in turn leads to precocious neural differentiation.

One major breakthrough in the modeling of human diseases over the past decade emerged from cellular-reprogramming technologies, which turn differentiated cells, such as human skin fibroblasts, into pluripotent cells known as induced pluripotent stem cells (iPSCs)[1]. Patient-derived iPSCs have the same mutations as the donor individual and thus provide a renewable source of previously inaccessible, disease-relevant human cell types. Consequently, iPSC technology has opened up new avenues for disease modeling and drug development in a genetically tractable and disease-relevant system[2]. The promise of these cells as a leading discovery tool is just beginning to be realized[3]. In this issue of *Nature Medicine*, Francis *et al.*[4] used patient-derived iPSCs to model neural deficits in SLOS, a rare autosomal-recessive, multiple-malformations and intellectual-disability syndrome.

SLOS is caused by a deficiency of 7-dehydrocholesterol reductase, encoded by *DHCR7* (ref. 5), an enzyme of mammalian sterol biosynthesis that converts 7-dehydrocholesterol (7DHC) to cholesterol. Altered sterol biosynthesis disrupts neurodevelopment and cognitive and behavioral functions. Although biochemical defects in SLOS have been identified, the pathophysiological mechanism that underlies the neurocognitive deficits is not well understood. In particular, it remains elusive whether the cholesterol deficiency or the accumulation of 7DHC is primarily responsible for disease pathogenesis. To address these questions, Francis and colleagues[4] generated iPSCs from five people with SLOS. By further differentiating iPSCs into neural progenitor cells (NPCs) with cholesterol-deficient neural-induction media, and by immunostaining them with the NPC markers SOX2 and PAX6 and the neuronal marker βIII-tubulin, they discovered a previously unrecognized defect in the self-renewal of SLOS-derived NPCs, in which rosette structures were poorly defined and displayed premature neuronal differentiation.

A key finding of this study is that the aberrant neuronal differentiation of NPCs in SLOS is caused by 7DHC accumulation, but not cholesterol deficiency[4]. The authors found that the treatment of normal human embryonic stem cells (hESCs) with a DHCR7 inhibitor causes substantial 7DHC accumulation and aberrant neural differentiation, similar to that observed in iPSCs derived from people with SLOS; by contrast, treatments with inhibitors targeting cholesterol-synthetic enzymes other than DHCR7, which causes cholesterol loss without DHC accumulation, have no effect on hESC differentiation. The authors analyzed multiple iPSC models of cholesterol-synthesis disorders to gain additional evidence for their model of DHC accumulation resulting in the observed defects. Their analyses included iPSCs from Niemann-Pick disease, type C1 (NPC1)—a disease in which there is decreased cholesterol bioavailability because of impaired intracellular cholesterol transport[6]—and lathosterolosis, in which the cholesterol precursor lathosterol accumulates, rather than 7DHC (ref. 7). Both models showed similar morphology and gene-expression patterns to those of normal hESCs under either cholesterol-replete or cholesterol-deficient conditions. Collectively, these experiments not only suggest that the aberrant differentiation of SLOS iPSCs is caused by DHC accumulation rather than being a general consequence of cholesterol loss, but also highlight the power of using human iPSCs from individuals affected by different diseases as a model system for the investigation of disease pathogenesis.

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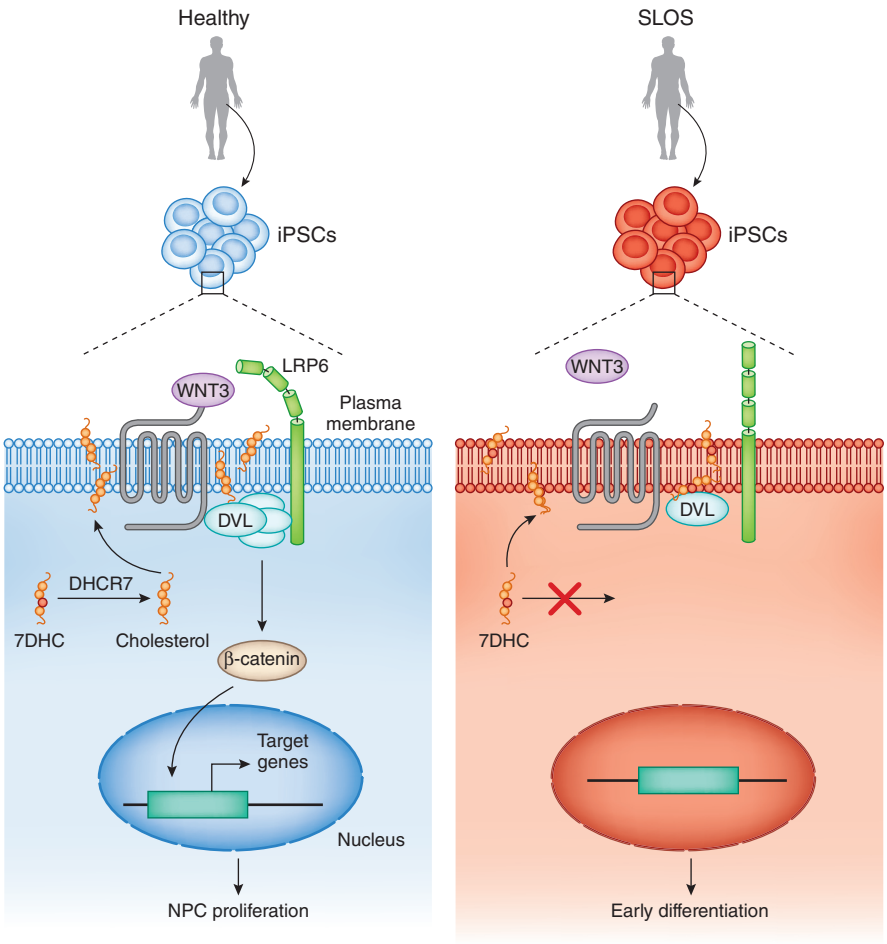

Figure 1 iPSCs from individuals with SLOS as a discovery tool for disease research. Francis *et al.*[4] find in the iPSC model that DHCR7 mutations lead to the accumulation of the specific cholesterol precursor 7DHC, which dysregulates the Wnt/β-catenin pathway and results in precocious neural differentiation. LRP6, low-density lipoprotein receptor-related protein 6.

Then, by comparing the gene-expression profiles of SLOS-derived iPSCs and controls, they identified that the Wnt/β-catenin–signaling pathway, which has a key role in embryonic development, neurogenesis and neuronal differentiation, was disrupted in SLOS iPSCs under cholesterol-deficient conditions. They postulated that 7DHC accumulation disrupts the scaffolding function of dishevelled (DVL), which coordinates the Wnt-signaling complex in a cholesterol-dependent manner, leading in turn to dysregulated Wnt/β-catenin activity (**Fig. 1**). This hypothesis was supported by surface plasmon resonance analysis, which showed that the DVL2-PDZ domain—a PSD95-DLG1-ZO1 domain that functions to anchor receptor proteins in the cell membrane to cytoskeletal components for signaling transduction—exhibits a 20-fold lower affinity for 7DHC-containing vesicles than for cholesterol-containing vesicles. Furthermore, the authors showed through imaging that the dynamic colocalization of DVL2 and the WNT receptor fizzled 7 (FZ7) in HeLa cells under WNT3A stimulation was greatly attenuated with 7DHC treatment, which suggests that 7DHC accumulation disrupts plasma-membrane binding and the scaffolding function of DVL, thus attenuating Wnt/β-catenin signaling. The dysregulation of the Wnt/β-catenin pathway is specific to SLOS, because it was not affected in lathosterolosis iPSCs. Importantly, the activation of β-catenin by either WNT3A or the GSK3β inhibitor CHIR99021 prevents the aberrant neural-differentiation phenotype in SLOS iPSCs. Thus, this study not only establishes the mechanistic link between DHCR7 mutation, Wnt/β-catenin dysregulation and aberrant neural differentiation, but also provides potential therapeutic targets for SLOS.

One drawback of using iPSCs to model human diseases in a dish is that this simple monolayer culture system lacks a physical, three-dimensional environment that recapitulates the intact central nervous system architecture. Mouse brain provides a complementary model system for validating human-relevant discoveries *in vivo*. Francis *et al.*[4] demonstrated that β-catenin activity is indeed decreased in the cerebral cortex of mice lacking *Dhcr7*, as compared to that in wild-type animals, and that the loss of DHCR7 leads to defects in neural progenitor proliferation and cortical-layer formation, which are consistent with and support findings in human iPSCs in culture.

This study provides an example of how human iPSCs can serve as a leading discovery tool to guide multi-model human-disease research, opening up a new avenue for the investigation of the biological mechanisms of other cholesterol-synthesis disorders and the identification of novel therapeutic targets. Given that the Wnt/β-catenin pathway is known to be involved in multiple processes during neuronal development[8], ranging from neuronal migration, axon guidance and synapse formation and plasticity to adult neurogenesis[9], it would be of interest in future studies to examine whether SLOS neurons have defects in these processes, and whether dysregulated Wnt signaling represents the underlying mechanism. This is particularly important because the link between the cellular phenotypes of NPCs *in vitro* and the cognitive and behavioral deficits in people with SLOS is still missing. Therefore, whether Wnt/β-catenin could serve as a therapeutic target in humans is still unclear. Substantial progress has been made in the targeted differentiation of human iPSCs into different types of cortical neurons, which has been applied in previous models of major psychiatric disorders to investigate synaptic defects[10]. In addition to the two-dimensional monolayer culture system, the recently developed three-dimensional cerebral organoid system[11] may provide an opportunity to model brain diseases in a system that is remarkably similar to human organogenesis *in vivo*. All these exciting advances in the iPSC field thus pave a new path for human-disease research, which will lead to a better understanding of the etiology and pathogenesis of diseases, and facilitate the development of novel drugs.

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