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 disease in which there is decreased cholesterol bioavailability because of impaired intracellular cholesterol transport\(^5\)—and lathosterolosis, in which the cholesterol precursor lathosterol accumulates, rather than \(7\text{DHC}\) (ref. 7). Both \(7\text{DHC}\) accumulation and aberrant \(\text{DHC}\) 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 \(7\text{DHC}\) (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 \(\text{DHC}\) 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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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 disheveled (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 vitro. Francis et al. 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, ranging from neuronal migration, axon guidance and synaptic formation and plasticity to adult neurogenesis, 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. In addition to the two-dimensional monolayer culture system, the recently developed three-dimensional cerebral organoid system 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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