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Patient-Derived iPSCs as a Model for Schizophrenia

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The advent of somatic cell reprogramming has provided a remarkable opportunity for neuropsychiatric research. Acquiring biological data on disorders of the central nervous system was previously restricted to studies on postmortem tissue and animal models of questionable validity. Now that neurons can be formed in a dish starting from patient fibroblasts, it is possible to generate cell culture models that may capture the biology of psychiatric disorders. For genetically complex and heterogeneous disorders like schizophrenia (SCZ), this means that the genetic background of a patient may be captured without necessarily knowing exactly which genetic variants are contributing to that person's illness.

A few studies have examined patient-derived induced pluripotent stem cells (iPSCs) that have been differentiated into neural progenitor cells (NPCs), and further into mature neurons. Brennand et al. [1] contributed the first SCZ iPSC study, which suggested that there were connectivity impairments in the four patient samples utilized. They also carried out gene expression analysis that implicated many pathways previously associated with SCZ. Highlighting the importance of using the disease-relevant cell type as a model, it was shown that gene expression of *NRG1*, a top hit in their screen, was only aberrant in patient-derived iPSCs, and no difference from controls was discernable in fibroblasts, iPSCs, or NPCs. A later study on NPCs derived from the same patients gave further details on gene expression profiles that implicated cytoskeletal remodeling and oxidative stress pathways [2].

These studies were done using a differentiation protocol that directs iPSCs to a neural fate, but not specifically toward a particular neural subtype. One later study uses SCZ as a proof-of-principle disorder for modeling hippocampal neurogenesis, and used iPSCs derived from the same patients as in the two previously described [3]. Here, the authors sought to direct differentiation toward neurons expressing a marker found in the dentate gyrus (DG), one of only two known areas of neurogenesis in the adult brain. They observed impaired production of DG neurons, and deficits in neuronal function and DG-associated gene expression, hinting at a possible basis for the cognitive impairments associated with SCZ. Directed differentiation methods have been described to preferentially generate excitatory cortical neurons [4] and GABAergic neurons [5], both of which have been implicated in SCZ, and which could yield valuable information if employed with SCZ iPSCs.

Focusing on specific cell types, however, has already generated conflicting results. A study that used the same four patient iPSCs found, using a protocol that did not direct differentiation toward any specific neural subtype, that SCZ iPSCs tended to produce more dopaminergic neurons and secreted more dopamine into the cell culture media [6], while another study that used three other patient lines, which were directed toward a dopaminergic fate, found the opposite [7]. The authors give a few potential explanations for discrepancies, all of which are issues inherent to the field of iPSC neuron generation. First, with small sample sizes, it is always difficult to generalize to entire patient population. Second, patients are selected using different criteria in different studies: while Hook et al. used a more heterogeneous set of patient lines, Robicsek et al. [6] selected patients with a specific diagnostic and medication profile. The fact that patient lines come with their own set of clinical data makes iPSCs both attractive, in that biological data can then be correlated with clinical data, and challenging, as the availability and quality of clinical data can vary widely from patient to patient. Combined with the small sample sizes that tend to come with the territory in stem cell research, this can make for slow progress. Finally, Robicsek et al. [7] note that although SCZ has been linked to increased midbrain dopaminergic activity, it has also been linked to decreased dopaminergic activity in the prefrontal cortex. Thus, it is possible that the different differentiation methods gave rise to neural populations representative of different parts of the brain.

As we continue to gain insight into the many ways different neural subtypes may play a role in SCZ physiology, another known aspect of SCZ to keep in mind is patient age at onset. Brennand et al. [2] found that their 6-week-old neurons had gene expression profiles most similar to first trimester fetal brain tissue when compared to profiles in the Allen BrainSpan Atlas. Other studies have also indicated that the timeline for differentiation of iPSC-derived neuronal cultures approximately mirrors the timeline for fetal brain development [4,5]. However, SCZ typically manifests clinically around 18-25 years of age. While the findings on early iPSC-derived neural cultures are intriguing and important, since prenatal stress and neurodevelopmental deficits have been implicated in SCZ, it is also important to consider that the changes that occur later in life, in the setting of environmental stressors and hormonal changes, may not be captured by neurons that are a few weeks or months old.

Interestingly, all SCZ iPSC studies that looked at mitochondrial function and reactive oxygen species (ROS) found that patient cell lines had an increased level of mitochondrial dysfunction and ROS, signs typical of aging [2,7,8]. Individuals with SCZ are disproportionately likely to show indications of more rapid aging, such as early heart and metabolic problems, and have a shorter average life expectancy, even when accounting for a higher suicide rate. It is possible that the telltale signs of cellular aging that have already been observed may provide biological insight into these clinical observations, and there may already be methods to enhance the "aged" phenotype observed in these early neuronal cultures. For example, expression of *NGN2* has been shown to rapidly differentiate iPSCs to neurons on a much faster time scale than traditional neural induction and differentiation methods [9]. Miller et al. reported an "aged" iPSC-derived neuron model of Parkinson's disease by expressing progerin, a protein associated with progeria [10]. These rapid-aging models may bring forth another useful phenotype from SCZ patient-derived cell lines.

Modeling SCZ at a cellular level is only beginning, and many questions remain. What sort of cell type-specific effects will be observed? Will there be different outcomes based on the neural induction and differentiation methods used? How much of those effects depends on the clinical phenotype of the subjects? To what extent will iPSC-derived neuronal cultures, which so far best model fetal development, explain a disorder that typically presents in early adulthood? Will methods that "age" cell cultures help? With the necessarily small number of patients from whom cell lines have been derived thus far, we have a long way to go, but as the list of patient lines becomes longer and more diverse, and as more groups approach the study of SCZ from different angles, a more complete picture of SCZ biology can emerge.

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