How Can We Study Disorders of the Brain Using Teeny Tiny Skin Cells?

By Chloe Welch

Did you know that every year millions of people are afflicted by brain disorders and some might not even know they have one? These range from common, recurring headaches to developmental disabilities such as autism spectrum disorder [1, 2]. Currently, 1 in 10 individuals in the United States are impacted by neurodevelopmental disorders (NDDs). In addition to affecting 2 to 3 percent of the United States population, there are also large financial costs associated with NDDs with a lifetime cost of up to $1 million per individual diagnosed [3].

Jordan's Syndrome is the name recently given to a rare neurological disorder characterized by delayed motor skill and speech development, an enlarged head size, and distinct facial features such as a long face and widely-spaced eyes [4, 5]. When mutations occur in the gene implicated in Jordan's Syndrome, we see consequences such as disruption in developmental processes [1]. In many cases, these genetic mutations occur during gamete (egg or sperm) formation in one of the parents of an afflicted individual or they occur within the embryo during the very early stages of development [1]. Currently, there are limited treatment options and no known cure for Jordan's Syndrome.

What if the answer we're looking for could potentially lie in front of us? Or right on us, for that matter? What if the answer could be in cells—the smallest and most basic unit of life?

Mounting research suggests that cells—specifically those found on our skin—provide promising possibilities for a wide range of disease treatment. These skin cells are called fibroblasts, and are flat, spindle-shaped cells that are found in our connective tissue [6]. Fibroblasts produce proteins like collagen, which give organs like our skin its elasticity and help tissues retain their structural integrity [6, 7].

Unlike many other types of cells we have, skin cells aren't as fragile and are easy to grow in laboratory conditions. Thus, they are a valuable tool in biology research to understand human disease and development [8].

You might be wondering, how can cells from our skin be a relevant tool to study disorders of the brain? Jordan's Syndrome is caused by a rare variation in a gene that is thought to be involved in the normal development and function of neurons—the primary cell type found in the brain [3]. The fibroblasts in the skin of an individual diagnosed with Jordan's Syndrome will carry this same mutation. So, by studying fibroblasts derived from individuals diagnosed with Jordan's Syndrome, we might be able to learn about how this gene impacts the structure, function, and development of neurons.

Still wondering how a skin cell can tell us anything about neuron development? Well, it turns out that fibroblasts can be "re-programmed" to become induced pluripotent stem cells (iPSCs)—specific stem cells that have the ability to form pretty much any cell type from a brain cell to a liver cell [8]. We can think of iPSCs as blank tiles in the game of Scrabble. Just as the blank tiles can be any letter, iPSCs can be induced to form any cell type chosen by the scientist, including neurons.

iPSCs can tell us a great deal about disease pathophysiology—in this case, how a genetic change actually impairs brain development. Skin cell samples from human patients are much easier to obtain than brain tissue samples, and because these fibroblasts carry the genetic mutation of interest, the iPSCs will too. Once the fibroblasts are obtained, we can use established methods to differentiate them into neurons **(Figure 1).** We can then observe when and how the neurodevelopmental process goes awry. Understanding how the mutation influences neuronal properties is currently the primary point of investigation for Jordan's Syndrome research.

Another relevant and promising technique for Jordan's Syndrome patients is gene editing. Gene editing allows scientists to change the genetic code by either "cutting" the DNA to completely remove a gene, or by making edits to the sequence of a gene[9]. Some applications of gene-editing are used in regenerative medicine, a process that involves replacing damaged cells to restore their normal function [10]. A potential treatment could start with using gene-editing to repair DNA in fibroblasts from Jordan's Syndrome patients.

Using patient-derived fibroblasts provides a great advantage because patient-specific disease models can be generated and iPSC-derived tissues will be genetically identical to the patient. For regenerative therapy, this is critical because it would prevent rejection by the patient's immune system, which is key if we're talking potential treatment for human disease.

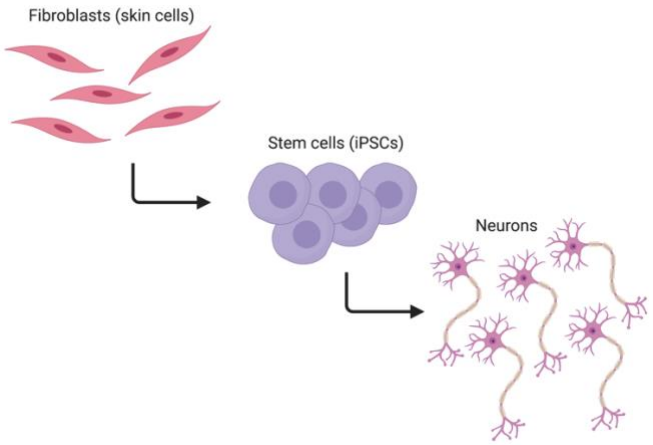

FIGURE 1. We can take patient-derived fibroblasts and re-program them into iPSCs. These iPSCs can then be differentiated into neurons using tools and techniques in regenerative medicine.

How does this all fit together? We can use iPSC-derived cells to study Jordan's Syndrome at a deeper level and assess the consequences of the genetic disruption on neurons in the brain. Patient-derived fibroblasts are re-programmed to assume properties of iPSCs and differentiated into neurons. We can examine how the genetic mutation impairs neuron development. Hopefully, we can eventually also use patient-derived iPSCs to repair the specific mutation, then introduce gene-corrected neurons from those iPSCs into Jordan's syndrome patients as a regenerative therapy. This work presents a promising avenue of cell replacement therapy.

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