The Revolution of Personalized Medicine

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What if I told you that scientists are one step away from finding a therapeutic treatment for various diseases, including those that were once thought to be incurable? It seems a little far-fetched doesn't it? Well as unbelievable as it sounds, scientists have discovered techniques that will enable delivery of personalized treatment to patients suffering from a wide range of diseases. In the past few years, there has been a major breakthrough in the field of regenerative medicine, a field of translational medicine centered on the use of stem cells to regenerate tissues and organs. You've probably heard that stem cells have the ability to become any type of cell in the body. They regenerate damaged tissues and deliver therapeutic molecules. It's quite impressive! I'm sure you've asked yourself: how do stem cells become specialized cells? What properties allow them to deliver specific molecules? And, lastly, what are the benefits associated with the use of stem cells?

Let us begin our journey of personalized medicine by talking about induced pluripotent stem cells (iPSCs). These revolutionary cells can be generated from any mature cell found in the body, like a skin cell. iPSCs are called "induced" pluripotent stem cells because scientists "induce" these cells to become stem cells by adding a few key genes to them. The term "pluripotent" refers to their ability to create any cell type in the body. That means scientists can generate any type of cell from a patient's own cells! (Figure 1) Why is this important, you ask? Well, if docs were to use patient-derived iPSCs to create an organ to put back into the patient it would eliminate the risk that the patient's immune system would attack and destroy the transplanted cells (this is the biggest danger of organ transplantation). Therefore, iPSC-derived cells can survive long-term and provide the therapeutic benefits for which they were engineered .

But let's take a step back. During the beginning stages of human development, an embryo begins as a mass of pluripotent stem cells that require specific signals to become the different cell types needed to form an organism. The different signals provided to the immature cells allow certain genes to be turned on or off, depending on the tissue or organ the cell is destined to become. Just like in embryonic development, scientists can mimic the signals that dictate the fate of each cell *in vitro*, outside the human body. Using combinations of different molecules, scientists can now restrict the cell to become the specific cell they desire. For example, individuals suffering from Hemophilia A, a genetic deficiency in blood clotting, lack a single but critical protein known as Factor 8 that allows their blood to clot following an injury. If scientists can generate the cells specific to the organ or tissue responsible for expressing this protein, they can then genetically manipulate the cells and restore the body's own ability to produce Factor 8, and therefore eliminate the need for life-long treatment. That's right! Stem cells may be used to rescue Factor 8 and thus cure Hemophilia A! Unfortunately, the process is not as easy as it sounds.

Let's look at the molecular level of this disorder. Factor 8 is mainly released by endothelial and hepatocyte cells. Endothelial cells are the cells that line the interior of blood vessels, while hepatocyte cells are the main cells that make up the liver. Current research is focusing on generating endothelial and hepatocyte cells from patient-derived iPSCs to treat Hemophilia A. If iPSCs are successfully differentiated into endothelial and hepatocyte cells; these cells can be genetically manipulated to express Factor 8. How exactly does this work? Viruses! Harmless viruses are engineered to carry the gene responsible for making the protein of interest. The iPSCs or differentiated cells are then exposed to these viruses that maintain the ability to deliver the foreign DNA, where it integrates into the host's DNA, without causing harm (Figure 2). It might sound like a scary technique, but so far it is one of the most efficient ways of delivering specific molecules to our cells.

This research is being performed at the Institute of Regenerative Cures by scientist Dr. Ping Zhou and her team. They have demonstrated successful differentiation of iPSCs into endothelial and hepatocyte cells by exposing them to specific molecules that are needed to guide them down their appropriate cell lineage. The differentiated cells demonstrate markers specific to both cell types, confirming the identity of the desired cells. Even more exciting, Factor 8 was successfully expressed in these cells with the help of viruses carrying the Factor 8 gene. Expression of Factor 8 in these cells was at higher levels compared to non-virus exposed cells and human umbilical vein endothelial cells (HUVECs), which are obtained from biopsied tissue and represent normal biological levels of Factor 8.

The technique described above allows expression of Factor 8 *in vitro*, with hopes that once these cells are transplanted back into the patient, the cells will express and release the protein at levels comparable to those that are naturally present in a healthy individual (Figure 3). Although further research is needed to accomplish clinical trials, this practice has so far proven an attainable personalized gene therapy to cure Hemophilia A.