Cells forged from human skin show promise in treating multiple sclerosis, myelin disorders

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A study out today in the journal *Cell Stem Cell* shows that human brain cells created by reprogramming skin cells are highly effective in treating myelin disorders, a family of diseases that includes multiple sclerosis and rare childhood disorders called pediatric leukodystrophies.

The study is the first successful attempt to employ human induced pluripotent stem cells (hiPSC) to produce a population of cells that are critical to neural signaling in the brain. In this instance, the researchers utilized cells crafted from human skin and transplanted them into animal models of myelin disease.

"This study strongly supports the utility of hiPSCs as a feasible and effective source of cells to treat myelin disorders," said University of Rochester Medical Center (URMC) neurologist Steven Goldman, M.D., Ph.D., lead author of the study. "In fact, it appears that cells derived from this source are at least as effective as those created using embryonic or tissue-specific stem cells."

The discovery opens the door to potential new treatments using hiPSC-derived cells for a range of neurological diseases characterized by the loss of a specific cell population in the central nervous system called myelin. Like the insulation found on electrical wires, myelin is a fatty tissue that ensheathes the connections between nerve cells and ensures the crisp transmission of signals from one cell to another. When myelin

tissue is damaged, communication between cells can be disrupted or even lost.

The most common myelin disorder is multiple sclerosis, a condition in which the body's own immune system attacks and destroys myelin. The loss of myelin is also the hallmark of a family of serious and often fatal diseases known as pediatric leukodystrophies. While individually very rare, collectively several thousand children are born in the U.S. with some form of leukodystrophy every year.

The source of the myelin cells in the brain and spinal cord is cell type called the oligodendrocyte. Oligodendrocytes are, in turn, the offspring of another cell called the oligodendrocyte progenitor cell, or OPC. Myelin disorders have long been considered a potential target for cell-based therapies. Scientists have theorized that if healthy OPCs could be successfully transplanted into the diseased or injured brain, then these cells might be able to produce new oligodendrocytes capable of restoring lost myelin, thereby reversing the damage caused by these diseases.

However, several obstacles have thwarted scientists. One of the key challenges is that OPCs are a mature cell in the central nervous system and appear late in development.

"Compared to neurons, which are among the first cells formed in human development, there are more stages and many more steps required to create glial cells such as OPCs," said Goldman. "This process requires that we understand the basic biology and the normal development of these cells and then reproduce this precise sequence in the lab."

Another challenge has been identifying the ideal source of these cells. Much of the research in the field has focused on cells derived from tissue-specific and embryonic stem cells. While research using these cells has yielded critical insight into the biology of stem cells, these

sources are not considered ideal to meet demand once stem cell-based therapies become more common.

The discovery in 2007 that human skin cells could be "reprogrammed" to the point where they returned to a biological state equivalent of an embryonic stem cell, called induced pluripotent stem cells, represented a new path forward for scientists. Because these cells – created by using the recipient's own skin – would be a genetic match, the likelihood of rejection upon transplantation is significantly diminished. These cells also promised an abundant source of material from which to fashion the cells necessary for therapies.

Goldman's team was the first to successfully master the complex process of using hiPSCs to create OPCs. This process proved time consuming. It took Goldman's lab four years to establish the exact chemical signaling required to reprogram, produce, and ultimately purify OPCs in sufficient quantities for transplantation and each preparation required almost six months to go from skin cell to a transplantable population of myelin-producing cells.

Once they succeeded in identifying and purifying OPCs from hiPSCs, they then assessed the ability of the cells to make new myelin when transplanted into mice with a hereditary leukodystrophy that rendered them genetically incapable of producing myelin.

They found that the OPCs spread throughout the brain and began to produce myelin. They observed that hiPSC-derived cells did this even more quickly, efficiently, and effectively than cells created using tissue-derived OPCs. The animals were also free of any tumors, a dangerous potential side effect of some stem cell therapies, and survived significantly longer than untreated mice.

"The new population of OPCs and oligodendrocytes was dense,

abundant, and complete," said Goldman. "In fact, the re-myelination process appeared more rapid and efficient than with other cell sources."

The next stage in evaluating these cells – clinical studies – may not be long in the offing. Goldman, along with a team of researchers and clinicians from Rochester, Syracuse, and Buffalo, are preparing to launch a clinical trial using OPCs to treat multiple sclerosis. This group, titled the Upstate MS Consortium, has been approved for funding by New York State Stem Cell Science (NYSTEM). While the consortia's initial study – the early stages of which are scheduled to begin in 2015 – will focus cells derived from tissue sources, Goldman anticipates that hiPSC-derived OPCs will eventually be included in this project.

Provided by University of Rochester Medical Center