Bypassing stem cells, scientists make neurons directly from human skin

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Researchers have come up with a recipe for making functional neurons directly from human skin cells, including those taken from patients with Alzheimer's disease. The new method may offer a critical short cut for generating neurons for replacement therapies of the future, according to research published in the August 5th issue of the journal *Cell*, a Cell Press publication. Already, the converted neurons are beginning to yield insights into what goes wrong in the Alzheimer's brain and how diseased neurons might respond to treatment.

In earlier approaches to generate neurons from skin cells, those adult cells first had to be returned to an embryonic stem cell state. Those cells, called induced pluripotent stem (iPS) cells, are hard to come by – less than one percent of cells are typically reprogrammed successfully. In addition, the entire process is time-consuming, requiring months to coax cells into iPS cells and then stimulate them to become neurons.

"iPS cells are exciting given the limits on cloning and embryonic stem cells, but it is still a roundabout and lengthy process if the goal is to take patient cells or normal cells and use them as replacement cells," said Asa Abeliovich of Columbia University, senior author of this study.

Not only are there efficiency issues, there is also an increasing concern about the stability of iPS cells, he said. Their ability to grow and produce any cell type makes them a cancer risk. Moreover, the cells may have limited use as models for understanding disease states because the processes used to derive them "may erase or overwhelm" the natural

biology of the cells.

To get around these potential pitfalls, Abeliovich's team started with known transcriptional regulators and, through a process of trial and error, identified a cocktail of factors that could turn human skin cells into neurons. While the process was not initially very efficient, they refined the protocol, ultimately converting about 50 percent of the cells.

"It is a huge leap over the iPS-based process," he said. It is also more efficient than a similar method recently developed by another group.

When studied in a dish, the neurons derived from healthy skin cells could fire and receive signals, just like normal neurons. What's more, when placed into the brains of developing mice, the converted cells were able to connect up to the existing circuitry. "They really are neurons," Abeliovich said.

The method can also produce neurons from the skin cells of patients with a rare familial form of Alzheimer's disease (AD). The AD neurons superficially looked normal, but upon closer inspection, Abeliovich's team saw abnormalities in the processing of amyloid precursor protein, the source for the amyloid plaques that riddle the brains of those with Alzheimer's disease. The neurons also showed more general differences in the way proteins inside the cell move around.

Abeliovich says that to really understand what goes wrong in Alzheimer's disease it will be important to look at what is happening in living human neurons. Earlier studies have been limited to exploring the consequences of the Alzheimer's mutations in tumor cells, skin cells or in mouse models of the disease.

Potentially the most exciting use of these Alzheimer's neurons will be for testing new drug candidates. Abeliovich notes that when the cells were

treated with one existing candidate drug that reduces beta amyloid production, the protein 'trafficking' problem actually worsened, raising caution about that particular treatment. Going forward, his group plans to study neurons derived from skin cells from patients with the more common, sporadic forms of Alzheimer's disease.

"Sporadic disease accounts for 99 percent of cases and no one really knows if it is similar or different from the simpler genetic forms," Abeliovich said. "It's not a done deal that we'll be able to come up with answers, but at least we can now ask the question. In that sense, this is the tip of the iceberg."

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