Bacterial protein can help convert stem cells into neurons

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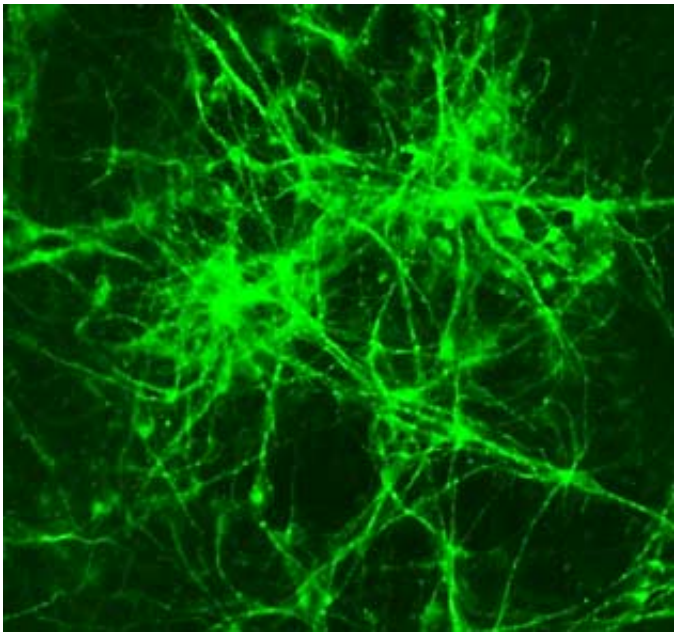

Functional neurons derived from pluripotent P19 cells by a sequential treatment of Skp and Nz. Credit: Shin Lab/Yonsei University

As the recipe book for turning stem cells into other types of cells keeps growing larger, the search for the perfect, therapeutically relevant blend of differentiation factors is revealing some interesting biology. A study published November 19 in *Chemistry & Biology*, for example, found that a protein in *E. coli* bacteria combined with small molecules can act synergistically to push pluripotent cells into functional neurons.

The research began when Sungkyunkwan University scientists in Korea made a serendipitous discovery that Sox2—one of the four Yamanaka factors that affect a stem cell's ability to remain a stem cell or differentiate—can bind to a bacterial chaperone protein, Skp. They then tested what would happen if Skp was introduced into stem cells and found that it could initiate differentiation. This led to the hypothesis that Skp could be combined with other techniques to make differentiation more efficient.

"Although there has been considerable research in this field, there is still a bottleneck in being able to produce a high number of stem cells efficiently," says study co-author Kyeong Kyu Kim, of the Sungkyunkwan University School of Medicine. "This problem can be solved, but we need to look for new ways to guide stem cell differentiation and then understand the molecular mechanisms underlying improved protocols."

Injae Shin of Yonsei University and Kim say that the differentiation of pluripotent stem cells can be conceived as two simple steps: first, a stem cell decides to no longer be a stem cell and begins to differentiate; second, the cell decides what kind of cell it wants to be. In their protocol to induce neuron differentiation, the bacterial protein Skp acts in the first step by binding to Sox2 and inhibiting its function. The small chemicals neurodazine (Nz) and neurodazole (Nzl) then act in the second step by telling the stem cell to become a neuron.

By influencing both steps, more functional neurons can be produced per batch of stem cells and at a faster rate if using either protein or small molecules alone. "The synergy thus mainly arises from combining suppression of stemness by protein and directing lineage-specific commitment by chemical inducers," Shin says. "Hence this process stands as an example of rationally designed cell differentiation to achieve a high level of lineage commitment efficiency."

One weakness of the protocol is that there are safety concerns around using bacterial proteins such as Skp in a therapeutic setting. However, using this protein is advantageous compared to introducing genetic elements because protein cannot cause any genetic alteration or instability, which are the major concerns of using virus-mediated gene delivery to the stem cells. The authors hope that this study can encourage others to develop similar approaches based on small molecule mimics of the first stage of stemness suppression.

They are now working on using similar combinatorial approaches to explore how to make differentiation more efficient in other cell types, particularly those in the heart.

More information: *Chemistry & Biology*, Halder et al.: "Combining Suppression of Stemness with Lineage-Specific Induction Leads to Conversion of Pluripotent Cells into Functional Neurons" dx.doi.org/10.1016/j.chembiol.2015.10.008

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