nature REPORTS stem cells
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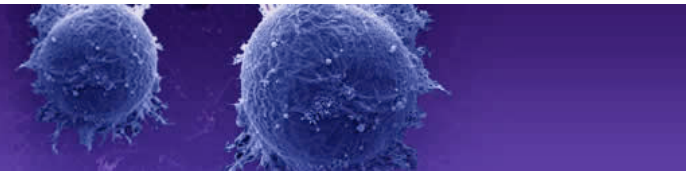

Research Highlights

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Human embryonic stem cells hit a nerve

Monya Baker[1]

A new technique can differentiate more neurons from hES cells in less time

Embryonic stem cells differentiate readily toward neural cells in culture, but most techniques to push them down this path still rely on undefined or random factors. Either human embryonic stem cells are exposed to the hotchpotch of secretions from neural-inducing cell cultures or they are allowed to differentiate into embryoid bodies, from which the desired cells must be extracted over multiple steps. Now, research led by **Lorenz Studer** and **Stuart Chambers** of the Memorial Sloan-Kettering Cancer Center in New York has shown that neural lineages can be induced from human embryonic stem cells with over 80% efficiency using fully defined conditions and without relying on inducing cells or embryoid bodies[1]. Not only are there fewer variables involved in making the cells, but also neurons can be made much more quickly — in about 9 days as opposed to 25–35 days. The process worked equally as well with human induced pluripotent stem cell lines.

Studer himself says the team was surprised by the results. "In the past, neural induction has been somewhat of a black box," he says. "It is remarkable that such a simple manipulation is sufficient." **Sally Temple**, a neuroscientist and stem cell expert at Albany Medical College in New York, says she's certain the technique will be widely adopted. "It takes weeks to direct differentiation towards neural progeny and uses vast quantities of expensive growth factors," she says. "The Chambers protocol cuts the time in half, markedly reduces growth factor use and avoids the complexity of feeder cells or embryoid body formation."

The researchers had a hunch that blocking an important signaling pathway might allow better neural induction. Previous work had identified both the polypeptide Noggin and the small molecule SB431542 as elements that boost levels of neural induction in protocols that require either coculture or work with embryoid bodies. (Both Noggin and SB431542 affect the SMAD signaling pathway, which is linked to bone morphogenic protein (BMP) and transforming growth factor-beta (TGF-beta). Noggin inhibits BMP and SB431542 prevents phosphorylation of receptors involved in signalling by TGF-beta and related factors).

When used alone, neither Noggin nor SB431542 had much effect — fewer than 10% of cells expressed the PAX6, a marker showing early neuroectodermal differentiation. Together, however, the effect was impressive: more than 80% of cells expressed PAX6. The researchers believe this is because the components both destabilize pluripotency and prevent cells from differentiating into the broad cell classes of trophectoderm, mesoderm and endoderm. That leaves the route open for cells to differentiate into ectoderm, which includes skin and neurons. From here, established techniques could take cells reliably to dopaminergic neurons and motor neurons. Studer says he was particularly surprised that the timing of differentiation was so much faster compared with that seen in normal development. "This suggests that at least part of the timing is controlled by endogenous signaling pathways that can be overridden using such inhibitor approaches presented here."

Studer cautions that these cells still need to be assessed *in vivo*. In particular, he wants to see whether there are differences between induced pluripotent stem cells and embryonic stem cells once their derivatives are functioning within intact neural tissue. He hopes the increased speed and purity of this protocol in creating these cells in culture translate into benefits *in vivo*, such as lowering the risk of tumour formation or the generation of inappropriate cell types.

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Reference

1. Chambers, S.M. *et al.* Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling. *Nature Biotechnol.* advance online publication, doi:10.1038/nbt.1529 (1 March 2009). | **Article** |

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1. Monya Baker is editor of *Nature Reports Stem Cells*.

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