

Keeping undifferentiated hES cells fresh

Source: <http://sci.tech-archive.net/Archive/sci.bio.evolution/2006-02/msg00409.html>

- *From:* "whitesickle@xxxxxxx" <whitesickle@xxxxxxx>
 - *Date:* Fri, 17 Feb 2006 13:52:34 -0500 (EST)
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UCI researchers discover key factor for survival of human embryonic stem cells

Using neural growth factor could allow researchers to mass produce stem cells for treatment of disease

Irvine, Calif., February 16, 2006

Human embryonic stem cells (hES) offer great hope for the treatment of some devastating diseases, but finding a way to keep enough of these cells usable and healthy for transplantation in patients has been an ongoing problem. Now, scientists at UC Irvine have discovered a way to keep large quantities of these cells alive, a finding that could potentially lead to mass production of hES cells for therapeutic use at lower cost.

These findings appear in a paper in the early online version of the journal *Nature Biotechnology*.

UCI stem cell researchers Peter Donovan and Leslie Lock, along with April Pyle of Johns Hopkins University, found that molecules known as neurotrophins have a significant effect on whether hES cells survive in the laboratory. Although stem cells have the ability to self-renew and to differentiate into any cell in the body, it has been a challenge to keep them alive as single cells in an undifferentiated state.

In their studies, Donovan and Lock added neurotrophins to hES cells in the laboratory to see the effect they would have on cell survival. Neurotrophins normally encourage the survival of tissue in the nervous system. When three members of the family of neurotrophin growth factors – brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4) – were added to hES cells in culture, the cells' survival increased 36-fold.

"Keeping hES cells alive as single cells has been extremely difficult," Donovan said. "This fact has kept us from producing enough cells to be useful for therapy, and has limited our ability to genetically manipulate the cells, which we must do before they can be transplanted into patients. It appears that if we treat hES cells with

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neurotrophins, we can produce more of them faster and, hopefully, at much lower cost."

Understanding the role that neurotrophins play in stem cell survival could also help researchers with another major problem they face in using hES cells for therapy. Rather than treating disease, undifferentiated stem cells that are transplanted into the body often form tumors instead, causing harm to the patient. A significant challenge has been to prevent the formation of tumors by ensuring that all cells are differentiated before they are transplanted. The studies by Donovan and Lock show that this is even more crucial when that transplantation is made into areas of the body rich in neurotrophins.

"Much of the research regarding stem cell therapy today focuses on areas involving the nervous system, such as the spinal cord," Donovan said. "Neurotrophins help the growth of tissues in those areas and are commonly found in the nervous system. Therefore, when we use stem cells for therapy in those areas, we must be especially careful that no undifferentiated cells are transplanted where they could respond to neurotrophins and form tumors." The work by Donovan and Lock provides a potential solution to the problem. By treating stem cells in culture with chemicals that block the action of neurotrophins on hES cells, Donovan said, scientists can kill the undifferentiated stem cells before they are implanted into the body.

According to Donovan, the studies also offer further proof that new stem cell lines need to develop beyond those already in existence. Federally approved hES lines currently used for research were not created in the presence of growth factors such as neurotrophins. The work undertaken by Donovan and Lock indicates that cell lines not created in these optimal conditions may eventually mutate and lose their usefulness for therapeutic purposes.

This study was funded through grants from the National Institutes of Health and Johns Hopkins University.

Donovan and Lock recently joined UCI's Stem Cell Research Center, which provides campus and visiting scientists an infrastructure to capitalize on recent stem cell breakthroughs, particularly in the areas of nerve repair and regeneration. In addition to holding a joint appointment in the School of Biological Sciences and the School of Medicine as a professor of developmental and cell biology and biological chemistry, Donovan is interim co-director of the Stem Cell Research Center. Lock holds appointments as assistant adjunct professor in developmental and cell biology and in biological chemistry. The university also is seeking support to construct a \$60 million Stem Cell Research Institute facility aimed at propelling stem cell technology from the research lab to the clinic.

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