Journal of
Stem Cell Research & Therapy

Editorials

Embryonic stem cell: Editorial

Results:

PEmbryonic stem cells (ES cells or ESCs) are pluripotent stem cells derived from the inner cell mass of a blastocyst, an early-stage pre-implantation embryo. Human embryos reach the blastocyst stage 4–5 days post fertilization, at which time they consist of 50–150 cells. Isolating the embryoblast, or inner cell mass (ICM) results in destruction of the blastocyst, a process which raises ethical issues, including whether or not embryos at the pre-implantation stage should have the same moral considerations as embryos in the post-implantation stage of development.

Researchers are currently focusing heavily on the therapeutic potential of embryonic stem cells, with clinical use being the goal for many laboratories.Potential uses include the treatment of diabetes and heart disease. The cells are being studied to be used as clinical therapies, models of genetic disorders, and cellular/DNA repair. However, adverse effects in the research and clinical processes such as tumours and unwanted immune responses have also been reported.

Growth

ESCs divide very frequently due to a shortened G1 phase in their cell cycle. Rapid cell division allows the cells to quickly grow in number, but not size, which is important for early embryo development. In ESCs, cyclin A and cyclin E proteins involved in the G1/S transition are always expressed at high levels.[10] Cyclin-dependent kinases such as CDK2 that promote cell cycle progression are overactive, in part due to downregulation of their inhibitors. Retinoblastoma proteins that inhibit the transcription factor E2F until the cell is ready to enter S phase are hyperphosphorylated and inactivated in ESCs, leading to continual expression of proliferation genes. These changes result in accelerated cycles of cell division. Although the shortened G1 phase has been linked to maintenance of pluripotency, ESCs grown in serum-free 2i conditions do express hypo-phosphorylated active Retinoblastoma proteins and have an elongated G1 phase. Despite this difference in the cell cycle when compared to ESCs grown in media containing serum these cells have similar pluripotent characteristics.Pluripotency factors Oct4 and Nanog play a role in transcriptionally regulating the ESC cell cycle.

Cell replacement therapies

Current research focuses on differentiating ESCs into a variety of cell types for eventual use as cell replacement therapies (CRTs). Some of the cell types that have or are currently being developed include cardiomyocytes (CM), neurons, hepatocytes, bone marrow cells, islet cells and endothelial cells.However, the derivation of such cell types from ESCs is not without obstacles, therefore current research is focused on overcoming these barriers. For example, studies are underway to differentiate ESCs into tissue specific CMs and to eradicate their immature properties that distinguish them from adult CMs.

Clinical potential

Researchers have differentiated ESCs into dopamine-producing cells with the hope that these neurons could be used in the treatment of Parkinson's disease.

ESCs have been differentiated to natural killer (NK) cells and bone tissue.

Studies involving ESCs are underway to provide an alternative treatment for diabetes. For example, D'Amour et al. were able to differentiate ESCs into insulin producing cells and researchers at Harvard University were able to produce large quantities of pancreatic beta cells from ES.

An article published in the European Heart Journal describes a translational process of generating human embryonic stem cell-derived cardiac progenitor cells to be used in clinical trials of patients with severe heart failure.

Adverse effects

The major concern with the possible transplantation of ESC into patients as therapies is their ability to form tumors including teratoma.Safety issues prompted the FDA to place a hold on the first ESC clinical trial, however no tumors were observed.

The main strategy to enhance the safety of ESC for potential clinical use is to differentiate the ESC into specific cell types (e.g. neurons, muscle, liver cells) that have reduced or eliminated ability to cause tumors. Following differentiation, the cells are subjected to sorting by flow cytometry for further purification. ESC are predicted to be inherently safer than IPS cells created with genetically-integrating viral vectors because they are not genetically modified with genes such as c-Myc that are linked to cancer. Nonetheless, ESC express very high levels of the iPS inducing genes and these genes including Myc are essential for ESC self-renewal and pluripotency, and potential strategies to improve safety by eliminating c-Myc expression are unlikely to preserve the cells' "stemness". However, N-myc and L-myc have been identified to induce iPS cells instead of c-myc with similar efficiency. More recent protocols to induce pluripotency bypass these problems completely by using non-integrating RNA viral vectors such as sendai virus or mRNA transfection.

Potential method for new cell line derivation

On August 23, 2006, the online edition of Nature scientific journal published a letter by Dr. Robert Lanza (medical director of

Advanced Cell Technology in Worcester, MA) stating that his team had found a way to extract embryonic stem cells without destroying the actual embryo.[64] This technical achievement would potentially enable scientists to work with new lines of embryonic stem cells derived using public funding in the USA, where federal funding was at the time limited to research using embryonic stem cell lines derived prior to August 2001. In March, 2009, the limitation was lifted.

Induced pluripotent stem cells

Main article: Induced pluripotent stem cell

The iPSC technology was pioneered by Shinya Yamanaka's lab in Kyoto, Japan, who showed in 2006 that the introduction of four specific genes encoding transcription factors could convert adult cells into pluripotent stem cells.[66] He was awarded the 2012 Nobel Prize along with Sir John Gurdon "for the discovery that mature cells can be reprogrammed to become pluripotent."

In 2007 it was shown that pluripotent stem cells highly similar to embryonic stem cells can be generated by the delivery of three genes (Oct4, Sox2, and Klf4) to differentiated cells.The delivery of these genes "reprograms" differentiated cells into pluripotent stem cells, allowing for the generation of pluripotent stem cells without the embryo. Because ethical concerns regarding embryonic stem cells typically are about their derivation from terminated embryos, it is believed that reprogramming to these "induced pluripotent stem cells" (iPS cells) may be less controversial. Both human and mouse cells can be reprogrammed by this methodology, generating both human pluripotent stem cells and mouse pluripotent stem cells without an embryo.

Contamination by reagents used in cell culture

The online edition of Nature Medicine published a study on January 24, 2005, which stated that the human embryonic stem cells available for federally funded research are contaminated with non-human molecules from the culture medium used to grow the cells. It is a common technique to use mouse cells and other animal cells to maintain the pluripotency of actively dividing stem cells. The problem was discovered when non-human sialic acid in the growth medium was found to compromise the potential uses of the embryonic stem cells in humans, according to scientists at the University of California, San Diego.

However, a study published in the online edition of Lancet Medical Journal on March 8, 2005 detailed information about a new stem cell line that was derived from human embryos under completely cell- and serum-free conditions. After more than 6 months of undifferentiated proliferation, these cells demonstrated the potential to form derivatives of all three embryonic germ layers both in vitro and in teratomas. These properties were also successfully maintained (for more than 30 passages) with the established stem cell lines.