BIOETHICAL ASPECTS AND THERAPEUTIC POTENTIAL OF HUMAN EMBRYONIC STEM CELLS

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Human embryonic stem (ES) cells are pluripotent cells, which are derived from the inner cell mass of early preimplantation embryos at the blastocyst stage (about 5 days after fertilization). ES cell lines can be propagated indefinitely in the laboratory and eventually prompted to differentiate into many of the cell types forming the human body, thereby yielding tissues that through transplantation could repair or replace damaged organ tissues. Such Regenerative medicine could provide new treatments, for example for diabetes by transplanting insulin producing pancreatic islet cells or for heart infarctions by transplanting cardiac muscle cells. For neurological diseases, recent studies show the prospect of using human ES cells for producing dopaminergic neurons that could be transplanted for the treatment of Parkinson disease, and possibly different neuronal types for other neuro-degenerative diseases. Another effort, to which our laboratory participates, is the production of oligodendrocyte precursors (OP) capable of migrating, maturating and reforming myelin sheaths after transplantation. Human ES cell derived OP have been shown to remyelinate in shiverer mouse brain (a model for inborn deficiency in myelin), and may have potential for spinal cord traumas. Through anti-inflammatory effects combined with remyelination, human ES cell-derived OPs may be hoped to have some use in autoimmune diseases such as multiple sclerosis. Likewise, many studies aimed at developing regenerative medicine focus on adult stem cells present in fetal tissues and subsisting in the adult. Adult stem cells have usually a specialized range of differentiation, depending on their tissue origin. Certain zones in the brain and spinal cord, contain neural stem cells forming neurons and glia; cord blood and bone marrow contain hematopoietic stem cells as well as mesenchymal stem cells, the latter giving cartilage and bone, and being available also from adipose tissue. Nevertheless, the blastocyst-derived ES cell lines appear to have the highest potential for expansion in large quantities and for development into the broadest variety of cells and tissues.

While adult stem cells can raise ethical issues (in particular if extracted from aborted fetuses or from cadavers), the extraction of stem cells from human preimplantation embryos has raised the more fundamental ethical questions. The International Bioethics Committee of UNESCO addressed these questions in a pluralistic way and published in 2001 a report on "The Use of Human Embryonic Stem Cells in Therapeutic Research" (see www.unesco.org/ibc), which proposes international guidelines. In the medical process of in vitro fertilization (IVF), widely practiced for the treatment of infertility, a number of the human embryos produced in vitro remain in excess after the completion of the IVF treatment, and the parents no longer destine them for their reproduction purposes. These supernumerary IVF embryos are kept in frozen state for indefinite periods of time; there are over 400,000 excess embryos kept in this way today in the USA, there are 30,000 in Israel, and the same situation exists in many countries. In the absence of any plan to use them for reproductive purposes (i.e. to implant them in utero), these frozen embryos have no potential for development into human beings. Based on these considerations, many countries decided to authorize the donation of such supernumerary embryos for the preparation of human ES cell lines to be used for research aimed at medical applications. Other countries do not permit extraction of ES cells, reflecting diverging views on the status of the early embryo and on whether blastocysts have already human status. The Catholic Church prohibits in vitro fertilization for reproductive purposes altogether, and opposes storage or uses of blastocysts even for therapeutic aims. These diverging views, based on philosophical, political and religious grounds, are still fueling a worldwide debate. However, considering the medical importance of ES cell research, an International Stem Cell Forum was recently established to foster scientific collaborations and harmonize ethical regulations on parental consent for supernumerary IVF embryo donation and on ES cell derivation between those countries that allow ES cell research.

Efforts are being made to obtain ES cells that would be devoid of the danger of immune rejection following transplantation. Among several techniques that may possibly achieve this goal, production of blastocysts by nuclear transfer (so-called therapeutic cloning) would entail the important advantage that the ES cells obtained would have the same genetic makeup as the donor of the nucleus, i.e. the patient in need of a transplant. Blastocysts from nuclear transfer would never be implanted and since the way they are produced is quite distinct from fertilization of an ovum by sperm, it should not be viewed as creating a human embryo for research. Human reproductive cloning is presently universally rejected, but an increasing number of countries, which prohibit reproductive cloning by Law, do not prohibit research on cloning for ES cells, specifically barring implantation of cloned blastocysts in utero. However, it has become clear in recent years that there are enormous difficulties in establishing whether the nuclear transfer technology for the production of human ES cell lines could at all be sufficiently efficient to permit its application for producing patient-specific ES cells. Due to the large number of oocytes that would be needed for making it successful, it is realized that much more research is needed. Autologous transplantation is in principle possible with stem cells derived from the patient's own bone marrow cells or adipose cells, but these sources have limitations in quantity and plasticity. Several new techniques are evolving for obtaining patient-adapted ES cells such as cloning using already existing embryos (zygotes), manipulating the antigenicity of ES cells or using a 4-gene transformation of cells to induce pluripotency. Success in deriving patient-adapted pluripotent ES cells would have a major impact on making regenerative medicine a reality and a cure for many chronic degenerative diseases.