

IV. Stem cells

ESHRE Taskforce on Ethics and Law*

These pages contain guidelines and other articles compiled by ESHRE Special Interest Groups and others, and agreed by the ESHRE Executive Committee. They are not submitted to journal peer review.

In this fourth statement of the ESHRE Taskforce on Ethics and Law, the focus is on ethical issues raised by the possible therapeutic use of stem cells, and in particular from embryo stem cells. General ethical principles are discussed, including autonomy, beneficence, maleficence and freedom of research. Specific points are raised concerning the source of embryos for stem cells and of oocytes for somatic cell nuclear transfer.

Key words: ESHRE/ethics/research/stem cells/therapeutic use

Introduction

In view of the possible therapeutic benefits expected from the use of stem cells, and of international activities on all fronts, scientific, ethical and legal, the taskforce considered the issues related to the research and use of these cells.

Scientific background

Definition of stem cells

A stem cell is a cell which retains the ability to self-renew and to differentiate into one or several cell types. Stem cells may be derived from the embryo, fetus or adult; however, a particular mention should be made of embryonic stem (ES) cells (derived from the blastocyst) and embryonic germ cells (derived from the young fetus), which have the unique ability to differentiate into all the tissues of the adult, including the germ line. All adult tissues are derived from stem cells, and most of them contain the corresponding stem cells. For instance, all gut brush border cells are renewed every 5 days in the human (every 3 days in the mouse) and all our red blood cells are renewed continuously.

Since the early 1980s, two directions were followed: fundamental research on cell differentiation, and therapeutic use of ES cells. Three main results recently emerged from these studies: (i) stem cells were found in unexpected sites (e.g. haematopoietic stem cells were isolated from skeletal muscle); (ii) it was demonstrated that various stem cells may elicit a

remarkable plasticity (e.g. neural stem cells transdifferentiated into blood cells; and (iii) few, but very promising, studies indicate that stem cells and/or their differentiated derivatives may be used for clinical purposes.

The goals of research

Research on stem cells may serve different purposes according to the cell type used. In the case of ES cells, it may increase the knowledge of the development of the human embryo whilst studying different systems of differentiation. In the case of both adult and embryo stem cells, research may be conducted with the hope of achieving not only fundamental knowledge, but also of performing cellular therapy—for instance, it may help to replace damaged cells such as in Parkinson's disease.

Because of the practical differences between the two types of stem cells (embryonic and adult), there are subsequent differences in the ethical questions raised. Furthermore, it is also essential to distinguish the research on, and possible use of, several types of ES cells: those issued from blastocysts either supernumerary or created *de novo*, and those created by nuclear transfer from somatic cells. The latter method is usually referred to as cloning, and in this paper 'cloning' refers to the method described and resulting in the birth of the sheep Dolly, where only the nucleus of the daughter cell is identical to that of the original somatic cell and the cytoplasm is that of the recipient inoculated oocyte. This is different from the definition of cloning which implies regeneration of totally identical cells starting from one cell only.

Current technical problems

In the animal, ES cells able to colonize germ cells can only be obtained in mice and even then only in specific strains of mice. In addition, further knowledge of the factors which control the specific differentiation of these cells is needed.

For human ES cells, the problems are even more complex.

*The members of the taskforce are: F.Shenfield¹, G.Pennings, C.Sureau, J.Cohen, P.Devroey and B.Tarlatzis

¹To whom correspondence should be addressed at: Reproductive Medicine Unit, Obstetric Hospital, 2nd Floor, University College Hospital, Huntley Street, London WC1 6AU, UK.
E-mail: mfi@easy.net.co.uk

In humans, studies are scarce (and the cells originate from three laboratories only to this day). The main concerns are: (i) the difficulty of maintaining the cells in an undifferentiated state. Indeed, the culture conditions actually in use do not prevent a more or less important rate of spontaneous differentiation; and (ii) the absence of data on the factors controlling differentiation.

In the case of somatic cell nuclear transfer, further problems arise: (i) the normality of the ES cells from cloned blastocysts; (ii) the lack of data on factors controlling specific differentiation; and (iii) the theoretical danger of neoplasia or tumour formation.

In the case of somatic cell nuclear transfer, an important problem may arise pertaining to the normality of the ES cells derived from blastocysts obtained by this route

Finally, both supernumerary blastocysts from assisted reproduction technology or blastocysts created for this purpose represent an heterologous source of stem cells necessitating associated immunosuppressive treatment if/when used for therapy.

Fundamental ethical principles

General ethics principles

The following fundamental ethical principles should govern both the research and the eventual therapeutic use of stem cells: (i) the principle of autonomy as expressed in the informed consent of cells donor(s). In view of the special nature of stem cells and their longevity, it should be specifically mentioned that the embryos will be used for research into the establishment of cell lines which can be kept indefinitely, may eventually be used for therapeutic purposes, and will never be replaced into a uterus. It should also be made clear whether the cells may be used for commercial and/or clinical purposes; (ii) the principle of beneficence and non-maleficence. This includes safety and the usual standards which apply to the introduction of new therapies; and (iii) the principle of freedom of research

There are differences in the application of these principles depending on the source of the stem cells (embryonic, fetal, cord blood or adult). Taking into account the enormous benefits which might follow from the therapeutic use of stem cells, we think that all possibilities should be explored simultaneously. Furthermore, the comparison of the efficiency of stem cells from different sources demands far more research before indications may arise as to which source is the most promising.

Specific ethical considerations according to source of cells

Adult stem cells

The donors of the material should authorize the use of their material for research. It should be emphasized that the research undertaken may not be of direct benefit to the donor.

ES cells

There are a number of ethical concerns expressed regarding the creation of embryos specifically for research, i.e. embryos which are not destined for procreation. We do not object to embryo research on supernumerary embryos, nor do we find any major ethical differences with embryos created for research within the constraints expressed in a previous Task Force

publication (ESHRE Task Force on Ethics and Law, 2001): 'the creation and the possibility of research on pre-implantation embryos specifically created for the purpose is appropriate only if the information cannot be obtained by research on supernumerary zygotes.'

Fetal stem cells

The separation principle regarding the abortion should be respected. This means that the decision concerning the abortion should be independent from and precede the decision to donate any ensuing material. The most effective way of enforcing this rule is to forbid both direct donation and commercialization of the fetal tissues. The mother should authorize the use of the fetal material for stem cell research given the possibility of prolonged survival of the material.

Umbilical cord blood

The storage of this material should be performed only in centres which conform to a code of practice and apply standards which are normally imposed on tissue banks. Furthermore, it is advisable that regular monitoring should be applied. A possible conflict between private interest and solidarity is a specific concern.

Other issues

Patenting cell lines and technology

The question of patenting evokes a number of ethical and legal questions. This declaration of the taskforce does not enter explicitly into this topic but wishes to emphasize that the patenting policy should not hamper the development of new technologies or slow down the acquisition of knowledge. Given the huge potential benefits for a considerable number of patients suffering from various diseases, the health of the population in general should take priority over commercial goals. Moreover, patenting should not unduly restrict the fundamental principle of freedom of research.

The source of oocytes in somatic cell nuclear transfer techniques for ES cells

If nuclear transfer techniques may be useful, there is no alternative but to create embryos first for research and eventually for therapy. Furthermore, the major problem of the source of oocytes for the purpose of enucleation and somatic cell nuclear transfer then arises. In view of the already well documented imbalance between need and supply in the case of oocyte donation, the limited number of oocytes which become available should preferentially be allocated to reproduction. Potential abuse of vulnerable women who might be enticed to sell their oocytes for research is of specific concern. Direct donation of oocytes for somatic cell nuclear transfer for a family member could be acceptable if all steps have been taken to ensure that the woman has consented freely and voluntarily.

Acknowledgements

Charles Babinet (Pasteur Institute, Paris, France) and Jacqueline Mandelbaum (Hopital Tenon, Paris, France) were consulted as external experts.

Reference

ESHRE Task Force on Ethics and Law (2001) I. The moral status of the pre-implantation embryo. *Hum. Reprod.*, **16**, 1046–1048.