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Human embryonic stem cell lines: socio-legal concerns and therapeutic promise

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Abstract – Stem cell lines would be very valuable for the repair of diseased or damaged organs. Stem cells derived from adult tissues raise few ethical problems, and would not be rejected if derived from the patient. They show considerable plasticity and might be appropriate for some clinical conditions, but they tend not to grow well in culture. Stem cells derived from the early human embryo proliferate indefinitely in culture and can give rise to many different tissues, but their derivation requires destruction of the embryo, which is not ethically acceptable in some countries. Other countries allow strictly regulated destructive research on human embryos, usually those that have been produced for infertile couples in infertility clinics. Embryos that are no longer required for the couple's own reproductive project could be donated for research rather than just discarded. Different approaches are being developed to avoid immunological rejection of embryonic stem cells used for therapy. Derivation of embryonic stem cell lines by somatic cell nuclear transfer ('cloning') from the patients themselves might be one possible approach, but is unlikely to be used in routine clinical practice if more cost-effective methods are available. ***To cite this article: A. McLaren, C. R. Biologies 325 (2002) 1009–1012.*** © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

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Résumé – Les lignées de cellules souches embryonnaires : problèmes légaux et de société, espoirs thérapeutiques. Les cellules souches pourraient être très efficaces pour la réparation de tissus malades ou lésés. Les cellules souches d'origine adulte ne soulèvent que peu de problèmes d'ordre éthique et n'entraîneraient pas de rejet si elles étaient issues des patients à traiter eux-mêmes. Elles présentent un degré très élevé de plasticité et pourraient être utiles dans certaines situations cliniques. L'inconvénient est qu'elles poussent très mal en culture. Les cellules souches provenant d'embryons aux premières étapes de leur développement prolifèrent indéfiniment en culture et donnent naissance à de nombreux types cellulaires. Le problème est que leur isolement implique la destruction de l'embryon, ce qui est éthiquement inacceptable pour certains pays. D'autres pays permettent cette destruction à des fins de recherche, à condition qu'elle soit strictement encadrée et que les embryons soient produits dans le cadre d'opérations de procréation médicalement assistée pour des couples stériles. Il s'agit d'embryons qui ne sont plus nécessaires pour le projet parental et qui, à défaut d'être utilisés en recherche, seraient détruits. Différentes recherches sont en cours pour éviter le rejet immunologique de cellules souches greffées à des fins thérapeutiques. La production de lignées embryonnaires dérivées à partir de cellules somatiques du patient à greffer, cellules énuclées et « renoyautées » par transfert nucléaire, pourrait être une solution aux rejets. Cette approche, extrêmement laborieuse et coûteuse, ne sera probablement pas utilisée si des méthodes moins onéreuses deviennent réalisables. ***Pour citer cet article : A. McLaren, C. R. Biologies 325 (2002) 1009–1012.*** © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

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Reports of pluripotent human stem cell lines derived either from early embryos [1] or from primordial germ cells [2] were first published in 1998. These reports focussed attention on the great promise of cell and tissue therapy for damaged or diseased organs resulting from, for example, spinal cord injury or degenerative diseases such as Parkinson's, Alzheimer's, stroke, multiple sclerosis, hepatitis, ischaemic heart disease, diabetes and rheumatoid arthritis. For such therapy, transplant surgeons would require readily available supplies of cells of the appropriate type - neural, hepatic, muscle including cardiac, pancreatic islet cells, blood and cartilage.

Stem cells of many types can be derived from these pluripotent stem cell lines, but stem cells also exist in the body from birth onwards, as well as in blood from the umbilical cord. These so-called 'adult' stem cells tend to be few in number: for example, bone marrow, which has been widely used for therapy, contains only one stem cell in ten thousand total cells. Haematopoietic stem cells from bone marrow proliferate indefinitely in vivo, but other types of adult stem cell show only limited powers of self-renewal, and most are hard to maintain or multiply outside the body.

On the other hand adult stem cells appear to show much greater plasticity than was originally believed. For example, purified haematopoietic stem cells from mouse bone marrow injected into lethally irradiated host mice that had a metabolic liver defect were able not only to rescue the immune system, but also colonised the liver, generating normal functional hepatocytes that compensated for the liver defect. Use of a genetic marker established beyond doubt that the normal hepatocytes were indeed derived from the donor cells [3]. Even more remarkable is the finding that neural stem cells derived from adult mice appear to possess the potential to differentiate into various types of tissue, representing all germ layers [4].

The use of adult stem cells raises few ethical problems and may well be of value for treating certain clinical conditions, especially if they could be derived directly from the patient and thus avoid immunological rejection. However, even those who work on adult stem cells mostly take the view that research on embryonic stem (ES) cells should also be actively pursued, since their potential value for clinical treatment is very great. ES cells are derived from blastocyst-stage embryos (in the human, these contain 100–150 cells, and develop 5–7 days after fertilisation), they have been shown in the mouse to be capable of forming every tissue in the body though they cannot on their own make an embryo, and they will proliferate indefinitely in culture, remaining chromosomally stable. Human ES cells have been induced to differentiate in vitro into a variety of different cell types, including neural [5, 6]. In mice, various models of human clinical conditions have been used to demonstrate the potential therapeutic value of ES cells. For example, mouse ES cells can generate cell lines that self-assemble into pancreatic islet-like structures that release insulin in response to glucose, not only in vitro but also in vivo after grafting subcutaneously into streptozotocin-diabetic mice [7].

Many problems remain before clinical trials of differentiated ES cells could be contemplated. The derivation and maintenance of the cells would need to adhere both to ethical guidelines and to GMP (Good Medical Practice) guidelines. Purification of the cells would be important: tumours might develop if undifferentiated stem cells were transplanted, while cells differentiated in an inappropriate direction might also prove a hazard.

As with organ transplants, there is a potential problem of immunological rejection when donor and host are different, non-identical individuals. Immunosuppressive drugs are used routinely in organ transplantation, and side-effects are a concern, though less so than in the past. Because of the blood-brain barrier, transplants to the brain are less susceptible to rejection than are those to other sites: in a series of grafts of fetal tissue to the brains of Parkinson patients, some of the grafts were still intact after 10 years, even though immunosuppressive drugs were only used for the first 12 months [8].

For future cell and tissue therapy, various alternatives to immunosuppression are being actively considered. A large enough bank of stem cell lines would allow cells to be selected that were maximally compatible with the patient. Alternatively, a stem cell line could be modified genetically so that it would no longer elicit an immune response – in effect, a 'universal donor'. Thirdly, specific tolerance to the stem cell line could be induced in the patient: in mice, purified haematopoietic stem cells derived from an ES cell line and injected into irradiated hosts do not provoke a graft-versus host reaction, but do produce a state of partial chimerism that renders the host tolerant to any cells or tissues subsequently transplanted from the same stem cell line [9]. Fourthly, somatic cell nuclear transfer, the same technology used for animal cloning, could be used to make embryos from which stem cell lines could be derived. If the nucleus were taken from the patient, stem cell transplants would not evoke an immune rejection. This strategy has been shown to work in mice [10], but may not be possible or realistic in humans. It will be discussed in detail elsewhere in this volume.

Use of adult stem cells for therapy raises no greater ethical issues than any other experimental clinical

treatment. The derivation of embryonic stem cells, however, involves the destruction of a blastocyst-stage embryo. Embryos that are produced by IVF for an infertile couple but are no longer required for their own or any other couple's reproductive purposes may be donated by them for research. With no possibility of transfer to a uterus, such "spare" embryos would in any case die within a few days. Human embryo research, including derivation of embryonic stem cells, is prohibited in some European countries (Germany, Austria, Norway, Ireland, Switzerland), since the blastocyst-stage embryo is considered already a person. France had a 5-year moratorium on human embryo research, but is now bringing in new legislation that would allow strictly regulated research. The Netherlands and Portugal are also considering new legislation, while in Spain the situation remains unclear. Human embryo research is permitted by legislation in the UK, Denmark, Sweden, Finland and Hungary.

The UK was the first country to introduce legislation regulating human embryo research. Louise Brown, the world's first baby conceived by in vitro fertilisation (IVF) was born in 1978, and 12 years later the British Parliament passed (by a large majority in both Houses) the Human Fertilisation and Embryology Act (1990). This Act established a statutory authority, the Human Fertilisation and Embryology Authority (HFEA), to license and monitor not only clinics carrying out IVF and donor insemination treatments, but also centres carrying out human embryo research. Research projects on embryos, whether donated by couples in IVF clinics or, produced for research for example, by inseminating donated eggs, could be licensed if they were considered necessary and desirable for any of 5 specified purposes: improving the treatment of infertility, investigating the causes of either miscarriage or diseases arising at fertilisation, developing more effective contraceptive techniques, or developing methods of early diagnosis of gene or chromosome abnormalities.

None of these 5 purposes could be construed as including the development of new methods of treating diseases, such as cell and tissue therapy. However, the 1990 Act provided for the possibility of adding "other purposes as may be specified in regulations". Once the promise of human embryonic stem cell lines became apparent, after 1998, the UK government drafted regulations specifying further purposes, namely increasing knowledge about the creation and development of embryos and about disease, and using such knowledge to develop treatments for disease. These new purposes were approved by both Houses of Parliament in 2001, again by large majorities.

A research project aiming to derive embryonic stem cells from a human embryo could be licensed by the HFEA if it was thought necessary and desirable, irrespective of whether the embryo was produced by fertilisation or by somatic cell nuclear transfer. However, a further Act of Parliament has made it a criminal offence to transfer to the uterus any embryo other than one produced by fertilisation. Thus in the UK cloning for stem cells could be permitted, but cloning for babies ('reproductive cloning') is prohibited.

In view of the wide divergence among European countries in respect of the legal and ethical position concerning human embryo research and derivation of embryonic stem cell lines, it seems unlikely that any attempt at harmonisation of legislation would be successful. Article 18b of the Council of Europe's Convention on Human Rights and Biomedicine states that the creation of human embryos for research purposes is prohibited; however, any Member State can ratify the Convention while making a reservation in respect of Article 18b, if it has a law in force that "is not in conformity with the provision". The UK would be able to make such a reservation, and other countries are also considering legislation that would not be in conformity with Article 18b. An Additional Protocol to the Convention prohibits "any intervention seeking to create a human being genetically identical to another human being". The Explanatory Memorandum explains that the scope of the expression 'human being' is to be left to domestic law to define, thus allowing the prohibition to pertain to cloning for both babies and stem cells in some countries (e.g., Germany), but only to babies in others (e.g., UK).

The European Group on Ethics was asked by the European Commission to give an Opinion on human stem cell research and use. On embryonic stem cell derivation from 'spare' embryos donated for research, the Group concluded that for those Member States where human embryo research regulated by public authority is allowed, there was no reason not to extend its scope to develop treatments for serious diseases, and no reason to deny EU funding to research projects in this area. Fertilisation of donated eggs specifically for stem cell research was not considered ethically acceptable while 'spare' embryos donated by IVF patients were available, and derivation of embryos by somatic cell nuclear transfer was regarded as premature at the present time.

Conclusion

There is little doubt that stem cell research shows great promise for regenerative medicine. Research

should be pursued on human embryonic as well as adult stem cells, since it is not yet clear which will be the more appropriate for clinical use. Both may be required, according to the condition to be treated. Much animal stem cell research is also needed, both in vitro, and in vivo before any clinical trials could be contemplated. It is therefore important not to raise patients' hopes unduly or prematurely.

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