Ethical issues in the induced pluripotent stem cell era

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Many new ethical issues have been raised in the hiPS era. One of the most heated debates questions the necessity of further research on human embryonic stem (hES) cells. While scientific community disagrees about similarities and differences between these cells and human induced pluripotent stem (hiPS) cells, some politicians embrace translational hiPS cell research as a replacement for translational hES cell research. In this context, "translational" means research that is aimed at taking stem cell-based therapeutic applications from the laboratory to the clinic, or, as it is often said, "from bench to bedside".

Can we already today say that we no longer need such research? Any position on this issue will have to be backed up by both scientific and normative reasons. From an ethical perspective, we can only treat hES cell-based therapies and hiPS cells-based therapies differently if there is a *morally relevant* difference between them. Given the current state of knowledge, what are the essential differences between these types of therapies? Can well-founded preferences be made in hypothetical scenarios with varying levels of patient safety, treatment efficacy, treatment accessibility and ethical controversy?

There are still many disagreements, uncertainties and knowledge gaps concerning questions such as patient safety, treatment efficacy, suitability of these cells for drug testing and disease studies or their theoretical ability to contribute to a human embryo under suitable conditions. Disagreements and knowledge gaps also concern more social questions, like the accessibility to treatment or the impact of stem cell research on women. In order to answer the question whether we still need hES cells for research and for stem cell-based therapies we need to, among other things, indicate current state of knowledge and knowledge gaps.

Most scientists note that it is important to examine the levels of similarity between the applications of hES cell- and hiPS cell-based therapies in regenerative medicine (1). Therapies based on each type of cells have their advantages and limitations (2). However, there are some who argue that hiPS cell-based therapies are identical to hES cell-based ones concerning certain aspects, such as patient safety, treatment efficacy and the theoretical ability of hiPS cells and hES cells to contribute to a human embryo in the right circumstances.

What are the differences between hES cell- and hiPS cell-based therapies concerning patient safety?

There is considerable disagreement among the scientists concerning safety of hES cell- and hiPS cell-based therapies and that there are essential knowledge gaps which need to be filled by more research. It is still an open question to what extent hiPS cells can replace hES cells in stem cell-based therapies – and with what success. We should consider the issue of safety from different aspects, such as the risk of tumorigenicity, the risk of immune reaction, or the risk of encountering unpredictable adverse effects after receiving either the hES cell- or hiPS cell-based therapy. The safety of hES cell- or hiPS cell-based therapy is a complex issue, and if we consider all the aspects of safety, it is hardly possible to determine which therapy based on which type of cells would be safer according to the present state of knowledge.

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Did you know that:

- Both hES cells and hiPS cells have the potential to form teratomas (tumours characterized by the presence of cells corresponding to all three embryonic germ layers) if transplanted into patients (3, 4) and the risk of tumorigenesis (3, 5-7).
- hiPS cells, generated from somatic cells that might have been altered by aging or toxins contrary to a pure unaffected hES cell line, may add unpredictable risks if used for therapies (8). However, some solutions have been proposed for solving this problem.
- Immune rejection hinders the use of non-autologous hES cell lines for therapeutic purposes (9). Contrary to hES cells, hiPS cells can be patient-specific and hence would not be rejected by the patient's immune defense system[1] (3, 5, 6, 10, 8, 11, 12).

What are the differences between hES cell- and hiPS cell-based therapies concerning treatment efficacy?

There is considerable disagreement among the scientists concerning efficacy of hES cell- and hiPS cell-based therapies and there are essential knowledge gaps which need to be filled by more research. Provided that these knowledge gaps are filled, the safety of hiPS cells-based therapy is proven and provided that a reproducible, inexpensive and rapid method to determine the quality of newly established iPS cell lines is found (3), direct reprogramming seems to provide a possible way of generating sufficient numbers of patient-specific pluripotent stem cells, at least for the treatment of some diseases. However, hiPS cell-based therapies may have to face regulatory hurdles by FDA standardization requirements (14) which would make hiPS cell-based therapies more cumbersome and problematic to carry out.

Did you know that:

- Even with hiPS cells patient-specific therapy can be impractical and costly (7, 8).
- The most likely approach for stem cell-based therapy will be to create banks of cell lines, generated from donated embryos or iPS cells with different immune properties that would provide acceptable matches with most of the population (8, 11).
- To date it is unclear how transplanted hES or iPS cells might achieve lasting organ regeneration and repair (15).
- Direct reprogramming provides a realistic way of generating sufficient numbers of patient-specific pluripotent stem cells for regenerative medicine, in contrast to SCNT (1). SCNT procedure is technically challenging, inefficient and dependent on voluntary donation of a large number of unfertilized oocytes (1), whereas hiPS cell research would not face at least some of these problems.
- hES cells can only be derived from early-stage embryos thus precluding the establishment of autologous cell lines for patients (9), whereas this would not be the case with hiPS cells (3, 5, 6, 8, 10, 11, 12, 16).
- In cases where sporadic form of a disease is solely due to epigenetic alterations, hiPS cell-derived somatic cells could be therapeutic, as the reprogramming process should reverse the disease-causing epigenetic modifications (3).

[1] This statement has been contested by Dressel et al. who have argued that the adaptive immune system has in principle the capacity to kill pluripotent and teratoma-forming stem cells (13). If that is the case, this would mean that the difference between hiPS cells and hES cells regarding their possibility to be rejected by the patient's immune defense system would at least become less significant.

What are the differences between hES cell- and hiPS cell-based therapies concerning the accessibility of stem cell-based therapies to large numbers of patients?

hiPS cell-based therapies are likely to be more advantageous than hES cell-based ones concerning their accessibility to large numbers of patients, provided that:

- both therapies are proven to be safe and efficacious, and
- therapeutically efficacious hiPS cells can be obtained from cord blood banks and similar easily accessible sources of cells.

As long as this knowledge gaps exist, it is not yet clear whether hiPS cell-based therapies have advantages over hES cell-based ones.

When considering the choice of a stem cell-based therapy, it is important to consider when and to whom these therapies should be available. Will they be available to the rich in the already rich countries, or will they be accessible also to those who need them in the developing countries? At the present time it seems difficult to identify any clear differences between hES or hiPS cell-based therapies in this respect. In addition, the fact that hES cell- and SCNT-based therapies involve the ethical dilemma raised by blastocyst destruction and oocyte donation (9, 11, 17) is likely to make such therapies non-accessible in the countries where hES cell research is viewed as morally unacceptable.

Did you know that:

- Administration of either hES- or hiPS-based therapies would require a functioning infrastructure, highly educated physicians, advanced healthcare, etc.
- Neither hES- nor hiPS-based therapies are likely to be accessible to all those who need them for a long period of time.
- The discovery that iPS cells can be derived from cord blood may lead to enhanced therapeutic applicability of this cell source (18, 19).

In which ways are the ethical controversies raised by hES cell- and hiPS cell-based therapies different?

This is one of the most controversial issues raised by hES cell- and hiPS cell-based therapies. There are essential knowledge gaps concerning the following questions:

a) Whether the fact that only some somatic cells can be reprogrammed into iPS cells affect the "natural potentiality" of iPS cells to contribute to an embryo, and thus the moral value attached to these cells;
b) Whether the structure of the oocyte cytoplasm and further organization of a zygote is an indispensable component for the existence of "natural potentiality" to contribute to an embryo;
c) Whether hiPS cells can contribute to a human embryo – so far the ability to contribute to embryos and live animals has been proven only in mice.

It is still an open question whether hiPS cells really have the so-called "natural potentiality" to contribute to a human embryo and subsequently a human being, and whether there are any morally significant differences between hiPS and hES cells. Some argue that the possibility to convert one cell type into another by human technological intervention does not prove that there are no meaningful differences between different cell types and that "passive potency" of the cell (i.e. what it can be converted into by technological intervention) should not be confused with its active potency for self-development (20). It is the cell's active potency for self-development that determines what the cell actually is (20). For example, simply because a house can be converted into a pile of rubbish by the action of a tornado does not eliminate the important differences between a house and a pile of rubbish (20).

It can also be argued that, if hES cells have a special moral status because they can contribute to a human embryo under appropriate conditions, and if also hiPS cells can contribute to a human embryo, at least theoretically, then consistency would require that they should have the same special moral status. But if we provide hiPS cells with a special moral status, consistency would require that the special moral status should be attributed also to the skin cells from which they were derived.

The ethical controversies raised by hES cell-based therapies according to some may extend to hiPS cell-based ones even in case hiPS cells are proven not to have the "natural potentiality" to contribute to a human embryo. For example, Demetrio Neri has argued that directing the attention to the sources of the cells – hiPS or hES cells – fails to identify the meaning and scope of the moral requirements involved in the demand of some opponents to hES cell research not to exploit human life (21). What exactly does the term "exploit" mean in this context? There can be a number of scenarios involving the exploitation of a human embryo without directly destroying it, e.g. using the cell lines already derived by or differentiated cell lines obtained from other scientists (21). It can be mentioned that some opponents to hES cell research consider that "using cells already derived by others always implies complicity, which exists independently of whether the last user approves or disapproves of the first agent's act", as Neri points out (21). Even if research on iPS cells would not require the use of hES cells derived by others, it is based on knowledge obtained by hES cell research conducted earlier. Neri has argued that the fact that one exploits human embryos by using derived materials or derived knowledge should be deemed as morally irrelevant (21).

Did you know that:

- Direct reprogramming of iPS cells initiates a cellular process that, given appropriate supportive interventions and the right circumstances, has the biological capacity to generate an organism intrinsically capable of developing into a fetus (22).
- With additional DNA reprogramming, scientists can move the cells from pluripotent status to totipotency and turn the iPS cell into an embryo, which, once implanted, can lead to pregnancy and birth (23).
- Some iPS cells can pass the most stringent test of pluripotency – the ability to build a healthy and fertile animal with no contribution from cells other than the iPS cells themselves (17, 19, 24, 25-27).
- At least some but not all iPS cells are pluripotent (28), which, if true, would make them different from ES cells, which all are pluripotent.

What are the less debated differences between hES cells and hiPS cells?

There are also other, less debated differences between hES cells and hiPS cells, concerning their use as tools for drug testing and disease modeling, their possible application in reproductive medicine as well as the impact of hES cell and hiPS cell research on women. They do not constitute ethical dilemmas at the same extent as the earlier reviewed differences do. Some scientists also disagree whether hES or hiPS cells are more suitable as tools for drug testing and disease modeling.

Did you know that:

- At least for studying some diseases, such as psychiatric diseases, neurological and genetic disorders or unexplained infertility, patient-specific hiPS cell lines are invaluable tools (17, 19, 29, 30).
- Although for most diseases hiPS cells are good models, in some disorders, especially where the phenotype is epigenetically regulated, the model in hiPS cells may differ from that in hES cells (31). For modeling phenotypes iPS cell-based model is a good one, but for modeling genotypes hES cell-based model is a more suitable one (31).
- iPS cell technology offers the unique opportunity to assess the quality of disease-relevant cell types by directly comparing cells derived *in vitro* with their genetically identical *in vivo*

counterparts (3). Although it takes many years for the pathological features of some diseases (e.g. amyotrophic lateral sclerosis (ALS) or Parkinson's disease) to become evident, the disease process might be initiated much earlier, and the analysis of iPS cell-derived neurons might identify more subtle early phenotypic changes in these diseases (3).

- The phenotype difference observed in the patient-specific hiPS cells may be caused by the genetic background of patients as well as the artificial genetic and epigenetic aberration introduced in the process of iPS cell methods (7).

The need for cautiousness

One should be careful when comparing and contrasting the work of different scientists on a particular subject, especially in cases where they arrive at different conclusions. Why have the authors arrived at different conclusions? Are their papers designed in such a way that they are comparable? This can reflect not only different ways of phrasing the problems but also different conceptions of what constitutes evidence and/or different ways of constructing certainty. In other words, it need not be related to different ethical views on some of the underlying controversial issues. It could have to do with the way the studies are designed. This strengthens the point that at present it would be premature to answer the question whether we still need hES cell research with "no" – in view of the many still existing uncertainties and knowledge gaps.

Can we answer already today whether we still need translational hES cell research?

There are at least three possible answers to the question whether we still need human embryonic stem cells for stem cell research and stem cell-based therapies: "yes", "no", and "too early to tell". If the problem is interpreted as referring to the present situation, the answer seems to be "yes". But if the problem is understood as referring to the future, the answer will be the third one. In view of the infancy of the fields, the existing uncertainties and knowledge gaps, it is premature to take a dogmatic position at the present. Research in the area of both hES cells and hiPS cells is in rapid development, and if the scientific picture changes, the moral relevance of scientific and other differences must be re-assessed.

In view of considerable disagreements among scientists and many uncertainties, black and white thinking and dogmatic conclusions seem premature at the present time. The knowledge gaps and uncertainties should be openly acknowledged, since they influence the risk assessment and risk management. Research efforts should be directed at filling the knowledge gaps. Thus, it is premature to say that we do not need translational hES cell research aiming at finding stem cell-based therapies or that we need such research only for comparative purposes.

The most contested differences between hES cell- and hiPS cell-based therapies, namely, concerning patient safety, treatment efficacy, accessibility to large numbers of patients and ethical controversy, are ethically relevant in the light of different value premises, endorsed by different types of ethical theories. Such ethical relevance of the above-mentioned differences also has to be examined in order to answer the question of whether we still need hES cell research aimed at taking stem cell-based therapeutic application from the laboratory to the clinic.

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