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The ethics of stem cells revisited ☆

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ABSTRACT

Stem cells constitute one of the most promising tools for regenerative medicine. Thus, it seems morally compelling to explore all the sources that might provide us with them. However, some of these sources, such as somatic cell nuclear transfer, embryo destruction, or even induced pluripotency obtained by reprogramming have raised deep ethical issues. The aim of this paper is to reflect on the stem cell ethical debate at the current moment through an analysis of the academic literature. It will also provide an analysis of the ethical implications of the most relevant scientific advances that have happened in recent months or those which seem about to merge.

Contents

1. Introduction

Regenerative medicine has experienced an impressive growth in recent years, but it seems that its application in urology is not following the same path. At the present moment, there are more than 700 companies worldwide working in some way on regenerative medicine, that have produced a significant number of therapeutical products, benefitting thousands of patients. In the USA alone, there are at least 12 regenerative medicine products on the market. In the whole world, in March 2014, 17 primary cell-based therapeutic products and 9 stem cell and progenitor cell-based ones have been marketed. Cell-based immunotherapy and gene therapy results remain somewhat behind, with only one product marketed and approved, respectively [1]. However, none of these products are directly related to urology, even if some changes may be already foreseen. In urology, there are currently five products in the clinical phase in regenerative medicine. Three are related to primary cell-based therapies, two of which, AMDC and ICES13, address stress urinary incontinence (which still remain in Phase III of clinical trials) and one – AC607 – linked to acute kidney failure (still in phase II). Regarding cell transplantation therapy, it must be remarked that in 2013 human ES cell-based clinical trials for retina regeneration had already begun, and the world's first iPS cell-based pilot clinical study was approved at that time by the Japanese government [2]. However, it might be worth remembering that some of the most promising experiments related to induced pluripotent stem (iPS) cells finally had to stop [3].

The same thing could be said in terms of academic research. The number of publications referring to stem cells has increased "from 4402 publications in 1996, which represented 0.4% of global publication output, to 21,193 publications in 2012, or 1% of global output. Between 2008 and 2012, they showed a compound annual growth rate of 7.0% compared to the world average growth rate of 2.9% across all disciplines. The field of ES cell research has grown more slowly than the stem cell field as a whole, with a growth rate of 4.9% from 2008 to 2012. This

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trend was also reflected in the subset of embryonic stem (ES) cell research focused on human embryonic stem (hES) cells, which showed a growth rate of 5.1%. In contrast, the emerging field of iPS cell research has grown rapidly, from 108 papers in 2008 to 1061 in 2012, representing a compound annual growth rate of 77%" [4]. However, in the case of urology, it must be stated that iPS cell-related publications do not seem to have produced impressive results. One of the most promising milestones was reached by Moad and colleagues, who obtained the successful reprogramming of fibroblasts derived from the prostate and urinary tract into iPS cells [5]. At the same time, they "nicely demonstrated the ability of their generated iPS cells to form teratocarcinomas in vivo and ideally should have applied a similar gold standard to the lineage-committed cells by demonstrating their ability to form prostatic acini or a stratified urothelium in vivo" [6]. Indeed, they claimed to have demonstrated 'generation of both the urinary tract-derived induced pluripotent stem cells (UT-iPSCs) and prostate stroma-derived iPSCs (pro-iPSCs)' [7]. Another interesting development might be the publication, by a team from the University of California, of 'an efficient in vitro protocol for the induction of hESCs into urothelium through an intermediary definitive endoderm step and free of matrices and cell contact' [8]. In theory, this should lead to a future derivation and propagation of urothelium from hESCs and h human IPCs (hIPCs).

Anyway, it is necessary to point out that stem cells still show relevant problems in terms of promoting tumour growth. This is especially remarkable in the case of iPSCs, because for a time they seemed to be a perfect solution both for scientific and ethical issues related to stem cells. However, the results obtained until now show that they involve some serious medical issues that could impede their routine clinical application, at least in the short term [9]. For instance, questions remain on whether the epigenetic reprogramming is complete or if there are some recurring iPSC-specific aberrations that impede their full pluripotency potential [10]. Their low efficiency of derivation and the heterogeneity of the obtained colonies are also main issues that need to be definitively solved. Furthermore, the possibility that they might become tumour-friendly is also always present. For instance, we know from a time that gene c-Myc promotes tumour growth in some cases [10,11]. More recently, it has been stated that stem cells incomplete reprogramming entails epigenetic changes (failed repression of Polycomb targets and altered DNA methylation) in cells that drive cancer development [12]. On the other hand, it seems relevant to note that IPS cells can also be used as a novel source of haematopoietic cell types for cancer immunotherapy [13].

2. Exploring the ethical challenges

Regenerative medicine and, in particular, stem cells also involve enormous challenges on both ethical and political fronts. In fact, we have been discussing these issues since at least the end of the 1990s, but it does not seem that we are about to arrive at a final general agreement. Nevertheless, it would be unfair to consider that the pieces of the puzzle have not moved at all during this time. The main intention of this paper consists of reflecting on the current state of the art of the ethical side of the discussion, taking into consideration the most relevant scientific developments produced in recent years, which are many. As not all stem cell sources involve ethical problems specifically linked to the way they are obtained (adult stem or cord blood stem cells are good examples, as far as they involve ethical problems), I will focus particularly on those that do include major ethical issues related to their origin: embryonic stem cells, somatic cell nuclear transfer (SCNT) cells and iPS cells. However, prior to that, a debate should be introduced: that of the challenges that the new scientific developments introduced to the configuration of the concept of the embryo. This is extremely important, as far as the election of a concrete concept of embryo entails deep consequences in the ethics arena.

3. What is an embryo?

Twenty years ago, the question that entitles this paragraph would have been addressed by a biologist, and easily answered: an embryo was the structure that resulted from fecundation. This was not well conceived, as it enclosed, in a single concept, entities such as different as groups of cells able to produce an adult being and moles, for example. Nevertheless, almost nobody really wondered about that until the moment when the birth of Dolly dramatically changed the scientific facts. From then on, it was clear that restricting the definition of 'embryo' to the previously mentioned was a "misleading anachronism" [14] that could no longer be held. At the present time, it seems perfectly possible to produce a human being through SCNT, as we will reflect later on. Thus, if it is not intended to hold the ancient definition for tricky purposes [15,16], the necessity of a new one based on factors such as potentiality, for instance, has become undeniable.

Moreover, the current scientific knowledge complicates even more the terms of the discussion, as it makes it possible to split embryos into parts, to alter a nuclear transfer prior to the fusion so as to try to avoid the creation of an embryo, to fuse human/animal genetic material to create a hybrid, etc. In these cases, it is hard to arrive at an ethical agreement if we do not even share a common definition of what is and what is not a human embryo, something that has been debated in recent years.

This debate is indeed especially important as it overwhelms the ethical arena, invading the political and legal frameworks. For instance, some of these criteria have even been included in extremely important legal tools, such as the Oliver Brüstle vs. Greenpeace ruling, which is essential in terms of patentability in Europe [17]. The main results of that discussion are the proposal of several different criteria that aim to distinguish between embryos and non-embryos or embryo-like bodies, such as the DIANA criteria, for instance [18,19], or the general reference to potentiality included in the Brüstle vs. Greenpeace ruling [15].

DIANA criteria are based on the idea that the proper biological potential for developing neural activity specific to a human body's spontaneous movements provides the observable basis for ascertaining the presence of a spiritual soul. Thus, only the presence of DIANA insufficiencies in a cellular entity's genomic information (insufficiencies that Directly Inhibit the Appearance of Neural Activity) ought to be considered a sure sign that such a cellular entity is not spiritually ensouled and, therefore, is not a human being [16]. In any other case, we should consider that a group of cells originated by any of the ways that might create a human embryo is, in fact, a human embryo.

Brüstle vs. Greenpeace ruling criterion, instead, considers that "any human ovum after fertilisation, any non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted and any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis constitute a human embryo" [17, point 38]. The rationale of this statement relies on the belief that "Although those organisms have not, strictly speaking, been the object of fertilisation, due to the effect of the technique used to obtain them they are, as is apparent from the written observations presented to the Court, capable of commencing the process of development of a human being just as an embryo created by fertilisation of an ovum can do so" [17, point 36]. Unfortunately, none of these proposals seem to have acquired a definitive acceptance at the present moment. Moreover, the polemic nature of some of their assertions does not allow us to feel optimistic about their future acceptance. Thus, it must be stated that defining the embryo remains an unsolved issue, causing important troubles in the current ethical, political and legal discussions.

4. Human embryonic stem cells

One of the most clinically promising sources of stem cells is embryonic stem cells. However, in the case of human beings, this process includes a major ethical issue: at the current moment, they cannot be

obtained without causing the destruction of a human embryo. This fact makes their use extremely problematic for those who consider a human embryo morally equivalent to an adult human being. Moreover, even some of those who do not strictly share that evaluation, but yet confer human embryos some kind of intrinsic moral value, firmly oppose their creation for therapeutic or research purposes. These moral objections are usually based on the defence of human life or human dignity, which obliges us to treat all human beings as ends-in-themselves, and not as mere means. In contrast, those who consider that human embryos are not morally relevant state that there is nothing wrong in using them for the purposes indicated above. Moreover, authors such as Savulescu and Devolver [20] have strongly supported the position that obtaining human ES cells is not only morally acceptable but a moral obligation, on the basis of the beneficence principle (even if they do not mention it explicitly): as far as research with ES could lead us to significant benefits in terms of diagnosis and therapy, banning their use contradicts the moral imperatives coming from that principle. Of course, these two extreme positions are hard to reconcile, as they are based on completely different moral bases and traditions, a fact that also explains the huge differences in the legal framework related to human ES cell research permission and funding between different countries.

Apparently, one could think about an intermediate moral position, the so-called "discarded-created distinction", which has acquired special relevance since the Obama's Administration based its stem cell policy on it. According to it, it is immoral to create human embryos for the sole purpose of serving as a source of stem cell lines, but not to use the lines obtained from surplus embryos for this purpose, as they were created for laudable reasons and it was misfortune that altered their destiny. Therefore, the researchers using these cell lines could not in any way be accused of complicity in the destruction of the embryos that originated them, as they did not create them for research purposes, nor sustained their creation or provoked it in any way [21]. Instead, it would make no ethical sense to let these embryos die without obtaining stem cell lines from them. Thus, all those holding this argument state that even if we consider human embryos as alive in the sense of constituting a living human being (and thus capable of dying, something which is not at all accepted by everyone), it would be morally acceptable to make use of them.

This position relies on several different arguments, such as the beneficence/non maleficence argument [22,23], the proportionality principle [24], the least controversial approach [25], etc. Nevertheless, the most famous and probably solid of all of them is the "nothing is lost principle" [26], whose origins can be traced to Ramsey's [27] and Williams' [28] works and may be described according to this formula: since discarded in vitro fecundation (IVF) embryos are to die soon in any case, and patients suffering from terrible diseases and disabilities health could be improved, if we destroy those embryos to create stem cell lines, there would be no moral harm if we proceed to do so [29–32].

This argument has been barely refuted from either conservative or liberal moral trends for several different reasons. Firstly, some authors have argued that, even if we share the moral roots of this reasoning, it could never be applicable to the case of spare embryos, as they are not about to die: they will die if somebody takes the decision to destroy them. Otherwise, they could remain frozen forever [33]. However, this refutation could be responded to by stating that there is no great difference between dying and remaining frozen forever [29]. The second refutation is based on an analogy that tries to highlight the evilness of the moral reasoning implicit in the nothing is lost principle: if we accept it, then we would be justifying that children refused by their parents and will be adopted by no-one else could also be used for research and therapy [33]. Nevertheless, authors such as Outka have tried to show that both cases are not comparable: 1) we can do something for those children, and 2) even if we could not save their lives, we could treat them in an appropriate manner. However, in the case of frozen embryos, we can neither save them nor treat them in a more appropriate manner, as we cannot show them positive kindness or otherwise affect their prospects [29]. A third refutation relies on the fact that once we decide to use embryos for research purposes, they become mere means, no matter why they were originally created. Therefore, these intermediate positions are incoherent: one could sustain that creation and use of embryos is morally acceptable or not, but should not provide different answers in both cases [34]. Nevertheless, some other scholars have replied that it is not the same to use an embryo that will die due to a circumstance the researcher did not contribute to in any way to create than to create an embryo just in order to destroy it so as to obtain stem cell lines [29]. From their point of view, only the second behaviour harms the embryo's dignity.

As a conclusion, it must be remarked that the ethical discussion about the use of human embryos as a source of stem cell lines remains extremely intense, no matter whether we talk about embryos created for research purposes or spare embryos. The most promising hope to finish this debate may be to develop a scientific technique capable of producing stem cell lines (which nowadays almost nobody considers to be embryos themselves) that are suitable to be used for research and therapeutic purposes without destroying human embryos [35,36], a result which might be about to be reached [37].

5. Somatic cell nuclear transfer

The capability of SCNT to provide us with stem cell lines has only recently (2013) been demonstrated by Shaktar Mitalipov's team [38], after multiple attempts and even an extremely famous scientific fraud, the Hwang Woo-suk affair [39–41]. This circumstance involves that the utility of these cells in regenerative medicine remains still unclear, as experiments using this technique have merely started, but they appear extremely promising [42,43]. Therefore, it is important to stress that the utility of stem cell lines obtained from cloned embryos should not be dismissed. Indeed, they could be not only an excellent therapeutic tool, but also a useful vehicle for drug discovery, toxicity testing and, moreover, as valuable in vitro models to study rare genetic diseases or to test gene therapies [44]. Thus, it makes perfect sense to keep the ethical debate on SCNT open, especially as far as it involves several extremely important issues.

The first and principal ethical objection against SCNT as a stem cell source is based on the idea that cloned embryos and natural embryos share a common moral status, a statement that is usually shared by both those who consider that embryos are not relevant at all and those who think they are. There are only some isolated exceptions to this general thought. Hansen, for instance, stated that SCNT produces mere artefacts with no natural purpose or potential to evolve into a human being and thus we do not have a moral obligation to treat them in the same way as natural embryos [45]. In a similar sense, Kiessling [46] and McHugh [47] considered cloned embryos different to IVF embryos due to the fact the latter are created with a main purpose, i.e. reproduction, but this is not so in the case of the clones. Nevertheless, these trends do not seem to have a great weight in the debate. The equal value of both types of cells derives from the fact that both of them share the same totipotency, as finally demonstrated by Mitalipov. Thus, it can be concluded that both embryos produced by IVF and SCNT share a similar moral statute (at least if we accept that totipotency is the key factor to consider an entity an embryo) and, thus, the ethical issues concerning the use of human embryos for therapeutic and research purposes above exposed are also applicable to them. The only difference in this respect is that the use of embryos produced by SCNT cannot be justified on the basis of the nothing is lost principle, as these are not cloned spare embryos.

A completely different objection to the use of somatic cell nuclear transfer to create stem cell lines comes from all those that, even if supporting the destruction of cloned embryos for research and therapeutic purposes, severely criticise the moral implications for the need of ova, which a general use of this technique would necessarily imply. In that sense, some scholars have stated that the necessary amount of

ova needed could only be obtained through payment. However, paying for ova involves a number of huge ethical problems related both to the exploitation [48] or the commodification [49] of the woman who sells them and to the commodification of a part of the human body, the ova [50]. Several alternatives, such as the use of animal oocytes, foetal oocytes, oocytes from adult ovaries obtained post mortem or during operations, stem-cell-derived oocytes or 'egg-sharing' have been proposed [51]. However, none of these seem to be promising in the short term. Nevertheless, this main issue may have been recently resolved through a new method developed by Shoukhrat Mitalipov and his team [52]. Basically, the novelty of their method consists of transferring the nucleus of the adult cell into a 2-cell embryo, instead of an ovum. For some reason, this seems to increase the chance of the new cell's successful development [53] without using female ova. If these results are confirmed in humans, then the problem of the shortage of ova will be negated. Of course, the ethical cost of that will not be zero, as it will always imply the destruction of human embryos. However, this will only be an issue for all those who oppose cloning due to their opposition to the creation of human embryos for research purposes, and not for those who were against cloning only due to this second factor.

6. Induced pluripotent stem cells — An ethical panacea?

In the ethical debate arena, many authors have stated that iPS cells could be a perfect solution for the ethical dilemma that we had been involved in for so long, as they would provide for the same advantages of human ES cells without presenting any of their ethical issues [54]. Leaving apart the scientific misunderstandings that this belief might involve, it currently seems quite clear that the idea that iPS cells would not be ethically suspicious was far too optimistic. In fact, in recent years, several ethical objections to iPSC have been raised. The first one refers to the possibility that the reprogramming process creates a totipotent stem cell, maybe accidentally or maybe on purpose. In that sense, several authors have wondered how to ensure that de-differentiation goes only so far and no further [55–60], a concern which is extremely relevant for all those who oppose the use of human ES cells for research and therapeutic purposes. Indeed, if we cannot ensure whether or not reprogramming will produce a totipotent cell, then we should consider reprogramming technology as ethically unacceptable as SCNT. These concerns have been contradicted by other authors, such as Condic, Lee or George [61]. Condic is especially vehement when writing that "it is not possible for reprogramming to accidentally produce a totipotent cell" [62]. However, the discussion still remains.

The second major issue related to iPS cells is directly connected to the former one, but may be distinguished, as long as it does not stand that some reprogrammed cells might be human embryos, but that all iPS cells are embryos in the same way that cloned embryos are. In order to understand this affirmation, it is necessary to bear in mind a fundamental scientific event. In July 2009, two research groups [63,64] independently reported the first successful generation of an adult mouse from induced pluripotent stem cells thanks to a technique called tetraploid complementation. This announcement provoked a huge discussion about the real potentiality of iPS cells and therefore, their real ethical statute. Authors such as Singer [65], Devolver [66], Watt or Kobayashi [67], have claimed that, as far as it was perfectly possible to create an adult mammal using iPS cells, it should be concluded that iPS cells are as totipotent as embryos resulting from a gamete fusion or a SCNT. Thus, they should share a common moral status. However, these arguments are based on a scientific assumption that is not shared by everybody: that tetraploid embryos cannot develop normally and do not result in an adult animal, as they have twice the normal number of chromosomes. Condic recently reminded us that, in fact, "the capacity to generate a full developmental programme (i.e. to progress through the complete sequence of developmental events, despite abnormalities) persists in tetraploid embryos" [62]. Thus, it is mistaken to conclude from the results of the experiments quoted that iPS cells may be considered totipotent cells, as they do not undergo a process of complete development on their own, but only respond to developmental signals still remaining in the tetraploid embryos. In her opinion, we could only state that iPS cells share the same totipotency that natural or cloned embryos hold if they were able to generate a complete developmental sequence independently, i.e. without any help from an embryonic structure. Other authors, such as Lee have also adhered to this opinion [68].

The debate on the ethical statute of iPS cells has become even more complex since a recent paper by a Spanish research group [69] demonstrated that reprogramming in vivo is feasible and leads to the produced cells having totipotency features that are absent in standard iPS or ES cells. In that sense, the researchers highlighted that the mice iPS cells obtained presented the capacity to undergo a trophectoderm lineage differentiation. Meskus and De Miguel Beriain [70] suggested that this finding has implications for the demarcation of totipotency from pluripotency in stem cells. In fact, they stated that it is reasonable to wonder whether it makes sense to talk about pluripotent stem cells if we are dealing with cell lines with totipotency features. Moreover, they suggest that this dilemma goes much further than a nominalist one, as it includes important ethical and legal consequences. Condic tried to override this objection stating that the kind of totipotency demonstrated by these in vivo iPS cells corresponds to the weak sense of totipotency, – the capability of differentiating into any cell or tissue – but not the strong one, i.e. the capability of developing into a complete organism. However, it seems difficult to sustain such a strong statement, keeping in mind the amazing results obtained in biological experiments in the last twenty years (e.g. Dolly). Therefore, it could be argued that further knowledge is needed to determine the real potentiality of these cells. In the event that future research demonstrates that these cells are totipotent in the strongest sense of the term, we would have to face a new situation: a type of cell that is pluripotent if cultivated in vitro and totipotent if cultivated in vivo. Of course, this would lead us into a disturbing ethical scenario: we would have to consider that the same kind of cell is ontologically different and, thus, holds a different moral status depending on where it is placed.

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