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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.

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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