French Republic

NATIONAL ASSEMBLY SENATE

PARLIAMENTARY OFFICE FOR SCIENCE AND TECHNOLOGY ASSESSMENT

Research on the operation of human cells

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Report no. 3498 National Assembly – no. 101 Senate – consultable on the NA and Senate sites

Cell biology is a central news topic as it embodies the hope of new treatments but also the threats of eugenics. The new attention paid to human cells has focused over the past decade on stem cells.

Summary

The 'genomic revolution' has not lived up to its promises

The 'genomic revolution' of the 1990s has not led to the elucidation of the functions of the gene nor to the development of gene therapies. These still remain today very largely at the experimental stage, despite a few successes, in particular that of Mr Alain Fischer and Mrs Marina Cavazzana-Calvo in the treatment of the 'bubble babies' syndrome. By taking account of the environment of genes, the epigenetics concept has been developed. Studying genetic modifications non coded by DNA sequences, epigenetics has led to a revival of cell biology.

Cells then appeared as the central units of the living world, some being capable of dividing to keep their number constant and forming stem cells.

These are distinguished by their capacity to transform into specialised cells (differentiation): totipotent, pluripotent, multipotent or unipotent stem cells. They also differentiate depending on their origin, into adult or embryonic stem cells.

cellule animale = animal cell; ribosome = ribosome; lysosome = lysosome; appareil de Golgi = Golgi apparatus; réticulum endoplasmique = endoplasmic reticulum; membrane nucléaire = nuclear mebrane; noyau = nucleus; nucléole = nucleolus; microtubule = microtubule; mitochondrie = mitochondrion; peroxysome = peroxisome; chromatine = chromatin; centriole = centriole; microfilament = microfilament; cytoplasme = cytoplasm; vacuole = vacuole; membrane cytoplasmique = cytoplasmic membrane; cil = cilium.
Source: Le grand dictionnaire terminologique. Office québécois de la langue française

Adult stem cells

Adult stem cells, like those of the epidermis, bone marrow and blood, have been known for long. Some are quite easy to obtain, like hematopoietic stem cells, from bone marrow or from peripheral blood. Others remain difficult to identify and characterise. Their possible plasticity, in other words their capacity to differentiate is the focus of scientific controversy.

Embryonic stem cells

These are cells arising from the first divisions of the zygote. They are totipotent as they can recreate an entire organism if they are isolated. Their discovery is recent (1981). They were isolated for the first time in 1998 by Mr James Thomson and his team at the University of Wisconsin.

Embryonic stem cells can be obtained: from spare embryos left over from in vitro fertilisation (IVF); after preimplantation genetic diagnosis (PGD); from frozen embryos no longer

required for fertility treatment; or by nuclear transposition.

The growth of this type of cells still raises many problems: culture media must not contain animal products; their differentiation may tend to escape control; and genomic instability may occur.

Potential applications of stem cells

In the long run, there will probably be many potential stem cell applications. But, for the moment, a few false ideas must be discarded.

In effect, unlike what is sometimes announced, it will not be possible, at least in the short term, to cure, using stem cells, disorders that are today incurable. However, a few cell therapy applications already exist regarding the regeneration of blood cells and of skin cells, and in the treatment of some heart disorders. Umbilical cord blood stem cells already allow the treatment of serious diseases like acute leukemias, but cord blood grafts are too little to treat adults.

Nuclear transposition consists in fusing an enucleated ovocyte with a somatic cell. Cells must then be extracted from the internal mass of the blastocyst thus created in order to try and derive embryonic stem cell lines from it. Their genome will then be identical to that of the somatic cell. Only one team worldwide has today managed to create in this manner a blastocyst, without however having managed to derive embryonic stem cell lines from it.

A certain number of applications are theoretically envisageable: possibility of having better knowledge of human diseases by creating stem cell lines characterising various pathological states; better understanding of the mechanisms of embryogenesis allowing spontaneous abortions or miscarriages to be better foreseen; and the elaboration of new research instruments to find new drugs by the systematic screening of molecules.

An important application will be cell therapy by allogeneic or autologous transplantation of stem cells, which could be used in all degenerative diseases like diabetes, Parkinson's disease or myocardial infarction.

Nuclear transposition is fundamentally different from reproductive cloning because, even if it begins by nuclear transfer, its aim is to create embryonic stem cell lines and not a human being.

Bearing in mind the uncertainties and gaps in knowledge that still dominate this field, ten years after the birth of Dolly, the first mammal created by reproductive cloning, and eight years after the first derivation of human embryonic stem cell lines, research must be pursued.

Need to pursue research

To come into its own, this research must be protected from pressure from the media as the length of the research process is not at all in keeping with time viewed by the media.

France must invest heavily in these two fields (adults stem cells and embryonic stem cells), on pain of being outdistanced by its international competitors which are making major efforts.

France suffers from a weakness of the financial and human means devoted to this research which is now governed by the provisions of Article 25 of Act no. 2004-800 of 6 August 2004 on bioethics. These provisions are ambiguous as they ban research on the embryo while providing for possibilities of derogation during a five year period. Derogations are subject to the condition that research is likely to *'allow major therapeutic progress and provided it cannot be pursued by an alternative method of comparable efficacy.'* Clearer and less complex provisions are needed. The provisions adopted in 2002 at first reading, providing for the authorisation of research on the embryo resulting from in vitro fertilisation under certain conditions (abandonment of fertility treatment, non-reimplantation), were better. On the other hand, the creation of the Biomedicine Agency to monitor this sector is a very positive contribution of the 2004 Act.

France must invest heavily in this field, and nuclear transplantation must be authorised with a strict control regime.

At European level, the situation is highly varied. Indeed, while three countries (United

Kingdom, Sweden, and Belgium) authorise nuclear transplantation, others ban any research on the subject (Austria, Poland, Ireland) or have not adopted any legislation on this point (Malta, Cyprus, Estonia).

The United Kingdom is one of the most active countries in this field thanks to its flexible legislation, the efficacy of its regulatory authority as regards research protocols, and the scale of the funds invested. A public consultation on ovoycte donation has just been launched there.

The differing situations in European countries has been the source of difficulties in elaborating the 7th Framework Programme for Research and Development (FPRD), insofar as several countries that have just joined the European Union are hostile to embryonic stem cells.

The United States bans neither reproductive cloning nor nuclear transposition. Federal funds cannot be used to fund research involving the creation or destruction of embryos, but only for stem cell lines existing on 9 August 2001. Private funds can support all types of research. The states are also beginning to fund this research, like California which is going to devote 3 billion dollars to it over ten years, following the vote in 2004 of Proposal 71.

Asian countries could enjoy major success in research on stem cells in the years ahead. They have scientists of an excellent level and living organisms are the focus of the development strategy of many of them. This is the case in particular in Singapore and Japan, whereas South Korea does not appear to have yet overcome the consequences of Mr Hwang Woo-suk's scientific fraud in 2004 and 2005.

Ethical challenges

Apart from combating scientific fraud, the pursuit of research on human embryonic stem cells requires rising to two ethical challenges: that of ovocyte donation and that of the merchandising of living organisms.

Ovocyte donation

Nuclear transposition requires the availability of very many ovocytes. If it develops, there is a serious danger that women, especially the most vulnerable among them, may thus be transformed into sellers of ovocytes, which is unacceptable. The very real physical risks of ovocyte donation must also be very seriously taken into consideration.

The marketing of ovocytes must therefore be completely ruled out. This donation must be very strictly regulated according to the following principles: ban on minors making such a donation; prior and enlightened consent; donation free of charge (ban on remuneration); reimbursement of costs incurred; compensation for wages not received; post donation medical follow-up reimbursed 100%; collection of ovocytes only in public centres; total separation between collection centres and research laboratories; and complete anonymity for donors to research laboratories.

Merchandising of living organisms

Patents facilitate innovation and the dissemination of knowledge. The same difficulties already encountered regarding genes are found again with stem cells and particularly with embryonic stem cells for which the patents of the University of Wisconsin are dominant. These patents are not valid in Europe: the European Patent Office (EPO) currently does not issue patents for embryonic stem cell lines for ethical reasons.

As with genes, only application patents are to be authorised. Product patents are to be ruled out as they would lead to patenting knowledge. The patentability of stem cells must therefore be refused.

Social and economic challenges

Social challenges

Before being forced to do so by advances in science, it is essential to begin to study the possible repercussions of the introduction of cell therapies on social protection systems and on their

funding modes: who will be the possible beneficiaries of this type of medicine? What will the funding procedures be for cell therapy treatment? As strictly individualised treatments, won't the possible future cell therapies be likely to lead to an individual insurance logic?

Economic challenges

The absence of private capital investment in this sector makes public funding necessary. Public funding must be considerable and perennial to allow this field to develop.

Three principles should be reconciled:

- Freedom of the researcher who must know what limits society intends to set for his activity;
- The rights of the sick and of the handicapped to have their sufferances lessened and their hopes for a cure raised;
- Respect for the human person and body.

December 2006

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