Opinion on gene therapy.

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Opinion

Advances in our knowledge of genetics have made it possible to consider acting upon the human cell genome with a view to correcting a genetic anomaly responsible for a hereditary disease or introducing a gene governing the production of a protein that can endow the cell with a therapeutic effect.

CCNE takes a favourable view of human research in this area provided the following conditions are observed:

- gene therapy should be restricted in its scope to somatic cells, and there should be a formal prohibition of all attempts to deliberately modify the genome of germinal cells, and of any gene therapy involving the risk of such a modification. For the same reasons any transfer of genes by viral vectors into the human embryo should be prohibited, because of the risk of damaging germinal cells.

- in the area of hereditary diseases, gene therapy research must only be considered for diseases resulting from an anomaly concerning a single gene (monogenic diseases), and that produce a particularly severe pathology.

If, pursuant to law 88-1138 of December 30th as amended, human genome research protocols were submitted to the Advisory Committees for the Protection of Persons in Biomedical Research, it would be highly desirable that these Committees consult CCNE before returning their opinion.

Scientific report

Advances in our knowledge of molecular structure and gene organisation and regulation now make it possible to consider correction of a genetic anomaly at cell genome level. The purpose of any research must be restricted to somatic gene(1) therapy, and there must be formal prohibition of all types of germinal cell gene therapy that could modify transmissible human genetic capital.

Experimental data pointing to the possibility of gene therapy are based mainly on observations of cell systems and animal models, now that the introduction of genes into a cell in vitro or in vivo has become a routine technique in research.

There remain a number of important questions that have not yet received a satisfactory answer, and in some cases this will only be possible through human trials.

Issues concerning normal gene function

The issues concerning normal gene function are the following :

1 - the introduction of a "new gene" in the cell, and in the genome, either at random, or if possible at a specific site;

2 - the prolificacy of genetically modified cells and the persistence of these traits in the cells generated by the cell first treated;

3 - the activity of this "new gene", the quantitative and qualitative traits of the protein produced, the conservation of the mechanisms that provide for physiological control of this activity, the possibility of compensating for structural cell deficiency.

Issues concerning possible negative side effects

Such negative side effects are due to :

1 - inadequate control of the activity of the gene introduced :

2 - the vector used for introduction of the gene, i.e. in most cases retrovirus "elements" (thus giving rise to problems of oncogenesis);

3 - other unpredictable disruptions to the organisation and function of other parts of the genomes affected by the introduction of the new gene; activation of an oncogen.

General data on gene diseases : in some cases the problem is due to the absence of the protein, a defect that could be corrected by introducing a gene producing the normal protein; in other cases it is caused by the production of an abnormal protein. Should one also consider eliminating cells producing the harmful gene that would be in competition with the normal gene that could once again be produced? In other circumstances, such as haemoglobin diseases, the grafted cells would have to produce a large enough amount of protein to adjust to the natural endogenous production of the chain not affected by the gene defect.

Issues concerning methods of reaching the target cells to be treated

In some diseases , the target cells that are responsible for the pathology can only be reached by a vector introduced via a general pathway (a viral vector in particular). Such therapy cannot be considered in the current state of the art. Moreover it is impossible to exclude the risk of affecting germinal cells, and thus effectively performing germinal gene therapy, when using these viral vectors, particularly in the case of an in utero embryo .

Very recently there has been animal experimentation of techniques involving direct transfer of a gene into in vivo tissue, specifically muscle tissue, which would appear to be a favourable site for micro-injection (muscular dystrophy), and in pulmonary epithelium using a viral vector spray (cystic fibrosis).

With state of the art knowledge, introduction of a gene-carrying "vector" via a general pathway is not being considered; the intention is to only treat target cells outside the body, thus restricting the possible scope for gene therapy to gene defects appearing in circulating cells, in practical terms nucleated cells in the haematopoietic system. This in vitro therapy would be screened before considering reinjecting the treated cells.

It is only a small number of single gene diseases that are possible candidates for this sort of

gene therapy protocol, which is in fact currently only being considered for correction of an adenosine deaminase deficiency (a rare disease) and a purine nucleoside phosphorylase deficiency (an exceptionally rare disease).

The American authorities have just granted approval for a gene therapy protocol concerning adenosine deaminase deficiency(2). The number of children affected par year is in single figures and the protocol restricts indications to those cases where substitute therapies currently available would have been ineffectual. The trial scope is therefore very limited. The question arises whether the cells that have received the treatment and are subsequently reinjected will be able to compete with their non-treated equivalents in the bloodstream.

Experimental work performed in the United States has provided an initial insight into what happens to haematopoietic cells that have received a new gene in vitro and then been reinjected into the body. The work was not performed as part of a "gene therapy" experiment, it was in fact cancer therapy, involving the selection of a certain cell type - TIL: tumour infiltrating lymphocytes - thought to have a specific action upon certain cancerous cells.

In order to assess the in vivo "efficacy" of these cells they are "marked" in vitro with a neomycine resistant gene introduced into their genome, thus making their local antitumour action traceable after reinjection. Initial trials have lead to consideration of a new protocol in which a TNF(tumour necrosis factor)-coding gene would be placed in vitro in TIL lymphocytes which are reinjected to trigger local production (i.e. around the tumour) of TNF, which would endow these cells with a therapeutic effect.

Ethical considerations

Limits must be placed on the objectives assigned to "human gene therapy":

1 - there must be formal prohibition of any attempt to perform germinal gene therapy. Apart from the risk of a modification that could be transmitted to the human genome, there are serious misgivings about the practical implementation of this treatment: firstly, embryos cultivated in vitro would have to be analysed to determine selection of those carrying the deficiency requiring correction, and it would be difficult to imagine reimplantation after gene therapy, since at the same time there would be embryos diagnosed as having no deficiency (such practice being at odds with the opinion given by CCNE on July 18th 1990);

2- only a specific genetic defect with serious pathological consequences for an individual can be considered for correction; any modification of general physical or mental genetic traits, such as height or behaviour, must be prohibited.

Within such restrictions, the possible use of gene therapy involving the somatic cells of a sick patient is not basically different from organ transplants, bone marrow in particular. The success of bone marrow transplants on children with thalassemia shows what can be achieved.

In the absence of any other available treatment, somatic gene therapy will perhaps prove to be the only option possible for some hereditary diseases.

Notes

1. Germinal (germen) gene therapy: a modification of the genetic capital of the reproductive

cells (ovocytes, spermatozoa and their precursors), which would lead to a change of an individual's genome.

Somatic (soma) gene therapy: modification of genetic capital concerning only non-reproductive cells in the body that would only affect an organ or a cell system.

2. Adenosine deaminase (ADA) deficiency produces very serious immunodeficiency. A substitute treatment (PEG-ADA) has been developed, but it requires repeated injections and is extremely expensive. The amount of ADA sufficient to correct the deficiency is variable and with gene therapy the treated ADA-producing cells need no control system, which makes these particularly favourable trial conditions.