

New strategies for gene therapy

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Gene therapy is aimed for treating diseases with the help of nucleic acids. Thus, by overexpressing the therapeutic gene or directly inhibiting the expression of deregulated gene this strategy targets the mechanisms, not symptoms of diseases. Therefore, this method can be potentially applied to every disease, both inherited and acquired, as all pathologies, even those caused by external stimuli, have a genetic background.

The first gene therapy has been applied for treatment of inherited diseases, however, at present the main targets are acquired disorders, mostly tumors. The first controlled clinical trial of gene therapy has been performed in 1990 in children with severe combined immunodeficiency syndrome (SCID), caused by the mutation in adenosine deaminase gene. To date more than 900 clinical trials have been initiated, but the real success, exhibited by permanent cure has been achieved only in about 20 patients with X-SCID, another form of combined immunodeficiency. Nevertheless, the effectiveness of gene therapy in this fatal disease is very high, and offers a real therapy for a number of X-SCID patients which are not amenable for bone marrow transplantation. In those gene therapy-cured X-SCID patients the transfer of retroviral vector, harbouring the correct gene of α c chain cytokine receptor restored the proper function of immune system. Unfortunately, in two children undergoing this therapy the insertion of vector into the LMO2 oncogene resulted in the development of leukemia. This serious side-effect hindered the progression of clinical trials, which were, however, re-initiated this year and the two patients exhibited side-effects have been successfully cured from leukaemia during the last two years.

The lack of real therapeutic effectiveness in the majority of clinical trials and the side effects necessitate the investigations into the new therapeutic genes and new delivery strategies. Recently the main area of research concerns the construction of efficient and safer viral vectors. Two groups of vectors are promising, and these are adeno-associated vectors (AAV) and helper-dependent adenoviral vectors (HdAd). Modification of the capsid of the viral vectors allows the specific targeting of a vector and hence a therapeutic gene to a given tissue. Additionally, regulation of the expression of therapeutic genes creates possibilities of limiting side-effects caused by the unregulated, high expression of introduced gene. Such strategies are tested mostly in cancer and cardiovascular diseases.

Besides proper overexpression of therapeutic gene the treatment can be also achieved by non-coding nucleic acids. Short sequences of DNA or RNA are used for inhibition of the expression of deregulated genes. Recently the main pathway of investigations concerns short interfering RNA sequences and DNA oligonucleotide decoys. The first represent the very promising, although still experimental tool which can specifically inhibit gene expression. The second are double strand DNA molecules containing sequences binding specific transcription factor. The EF2 decoys have been already tested in clinical trials for prevention of vessels narrowing after arterial bypass, and those experiments provided convincing hints of their effectiveness.

It can be hypothesized that efficient usage of the vast data available thanks to human genome sequencing will allow finding the new targets of gene therapy of inherited and acquired diseases. Improvement in gene transfer technology and directed regulation of the expression of therapeutic genes is believed to increase the effectiveness of clinical trials. This road is necessary to follow with the aim to transform gene therapy from experimental to really therapeutic approach.