Principles of therapy of hereditary diseases

Gene therapy options for a number of diseases are currently being explored.

Germ gene therapy

- intervention in the **gamete**, zygote or embryonic cells at a very early stage of development
- genetic change is found in all **cells** of the newly formed organism
- The influence of bb, from which **gametes are formed** , is therefore transmissible to offspring
- we cannot estimate **the results in future generations of**, ethical barriers before performing germline gene therapy

Somatic gene therapy

- performing a genetic change in **somatic calls**, or tissues
- tissues are selected according to the **type of disease**
- **manipulation in cells** can be performed ex vivo, in vivo
- **Ex vivo** = cells are harvested into a suitable environment and returned after therapy
- **In vivo** = suitable for bb, which is impossible to cultivate or return to the body

- **the vector carrying the gene** could be inserted directly into the tissue
- the success of these experiments is **very low**
- most suitable bb for gene therapy -**long life**, proliferate, can be easily obtained
- **Bone marrow stem cells**are an example - but they are poorly insulated

Somatic cell modification

Several approaches:

- **introducing a functional copy** of the gene into bb, the mutant gene remains unchanged
- **repairing** the mutant gene or placing a working copy of the gene in place of the mutant gene
- **targeted inhibition** of gene expression
- **targeted destruction of specific cells** (significant in tumors)
- destruction of specific cells of **the immune system**

The goal is **long-term expression of the introduced gene.**

Thus, the foreign gene must **integrate into the chromosome of the** host cell, and bb must have the ability to further divide. The foreign gene is then transferred to the **daughter cells -** the **gene integrates differently**, o it is located in other places in subsequent cycles.

Viral vectors

- viruses have developed efficient systems for inserting their **genomes into human bb**
- the virus must be **modified** so that its genome does not harm the human cell
- most of the **viral genome** is deleted, replaced with human promoter and **regulatory regions**
- **high efficiency**

Retroviral vectors

- **the genome of retroviruses** jonsists of RNA, contains 3 genes (gag, pol, env) and the sequence phi, which is recognized by **viral proteins** - assembly of the viral particle
- they have their own **reverse transcriptase**
- upon entry into the **host cell** during division (membranes are disrupted)
- cDNA attaches to **host information** při dělení (jsou porušené membrány)
- **the cloning capacity** is 8 kb
- **The human gene** vector is introduced into special cells that make many copies of **human sequence retroviruses**
- **modified retroviruses** are then incubated with the patient's somatic cells (lymphocytes)
- the **human gene is** inserted into the DNA of the host cells with high efficiency
- **disease** : severe combined immunodeficiency (SCID)

Adenoviral vectors

- dsDNA remains in the nucleus of a **human cell**, but does not integrate into its genome
- the vector must be **modified as well as the retrovirus**
- **infect** bb that do not divide (respiratory system)
- **cystic fibrosis** – therapy - human CFTR gene in adenovirus - modified virus was applied to the epithelial airway in the form of an **aerosol**

- low potency, only transient **gene expression**

Adeno-associated viral vectors

- ssDNA, the replication of which depends on the **presence of the virus**
- do not elicit any **immune response**
- as adenoviruses can **infect undivided** se bb
- hold **a small insert** – 5kb
- factor IX vector for people with hemophilia B

Lentiviral vectors

- **complex retroviruses** , can also infect non-dividing bb
- holes in the **nuclear envelope enter the nucleus**
- **cloning sequence** approx. 8 kb
- **antivirus** = e.g. HIV

Problems associated with viral gene therapy

- **transient expression**, low gene expression
- **difficult to** obtain specific bb, tissues (neurons)
- the need for **precise regulation** of gene activity
- **potential danger** of tumor transformation of the cell (accidental insertion of the virus into the cell may affect the expression of **a minor gene**, which may be a proto-oncogene)
- **immune response of the** organism against the viral vector

Non-viral vectors

- **direct injection** of DNA into tissue
- **firing of metal particles** , that contain DNA
- **the association of DNA** with a molecule that is bound by receptors to the cell surface is followed by **endocytosis**
- very **low efficiency** in these methods

Liposomes

- artificially formed **phospholipid bilayer** , particles that can hold a relatively **large DNA insert**
- they can **fuse with the cell**, transferring the DNA insert into the cytoplasm
- they do not contain peptides = they do not elicit an **immune response**

Blockade of gene expression

- gene products function in **complexes of molecules** (dimers)
- **the mutated protein** in the complex may affect their function
- inhibition of transcription does not result in **gene expression**
- replacement of gene damage by **homologous recombination**

disease	target cells	product advertisement
SCID	lymfocytes, bone marrow stem cells	adenosin deaminase
hemophilie B	hepatocytes	factor IX
cystic fibrosis	epithelium. Bb airways	CFTR
familial hypercholesterolemia	hepatocytes	LDL receptor
Duchenne muskular dystrophy	myoblasts	dystrophin
AIDS	TH lymfocytes	retroviral mutation

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1. **Gene therapy**
   - eg. transformation by cloned genes
     - disease: adenosine deaminase deficiency (severe combined immunodeficiency)[1]
2. **Enzyme induction**
   - eg barbiturates
     - disease: congenital non-hemolytic jaundice (see differential diagnosis of jaundice)
3. **Enzyme replacement**
   - eg tissue transplantation
     - disease: mucopolysaccharidosis
   - eg enzyme substitution
     - disease: trypsin deficiency

4. **Protein substitution**
   - eg antihemophilic globulin
     - disease: hemophilia
5. **Vitamin substitution**
   - eg. vitamin D
     - disease: vitamin D resistant rickets
6. **Product substitution**
   - ex cortisone
     - disease: adrenogenital syndrome
   - eg thyroxine
     - disease: congenital hypothyroidism
7. **Substrate restriction in the diet**
   - eg. AMK – Phenylalanin
     - disease: phenylketonuria (see Poruchy metabolismu aromatických a větvených aminokyselin)
   - eg sugars - galactose
     - disease: galactosemia
   - eg fats - cholesterol
     - disease: hypercholesterolemia (see Disorders of aromatic and branched chain amino acid metabolism))
8. **Drugs that reduce the excess product of defective metabolism**
   - eg. cholestyramin (https://en.wikipedia.org/wiki/Colestyramine)
     - disease: hypercholesterolemia (obsolete in the era of statins)
   - eg. penicilamin (https://en.wikipedia.org/wiki/Penicillamine)
     - disease: M.Wilson
9. **Replacement of the institution**
   - eg kidney transplantation
     - DISEASE: polycystic kidney disease
10. **Removal of organ**
    - eg colectomy
      - disease: familial colon polyposis

Links

related articles

- Genetic manipulation and genetic engineering
- Treatment of diseases caused by disorders of amino acid and carbohydrate metabolism
- Treatment of metabolic diseases from fatty acid beta-oxidation disorders and peroxisomal diseases

Sources

- ŠTEFÁNEK, Jiří. Medicine, diseases, study at the 1st Faculty of Medicine, Charles University [online]. [feeling. 2009]. < http://www.stefajir.cz >.

1. Primary immunodeficiency