Gene therapies targeting the liver

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Liver-directed gene therapy

Monogenic disorders due to defect in gene expressed in liver cells

Liver viral infections

Multifactorial disorder treated by targeting a single gene

Gene therapy strategies

Gene addition:
- Introduction of a wild type form of a mutated gene into an affected tissue using viral vectors
- Can offer a permanent cure (depending on disease and vector type)
- Efficient expression of transgene driven from engineered promoters (thyroxine binding globulin and hepatic control region-human α-1 antitrypsin promoters)

Adenovirus
- Non-enveloped, dsDNA vector
- Can package up to 37 kb transgene
- Generally used in oncology
- Efficient liver transduction
- Elicits strong immune responses

Lentivirus
- Enveloped, ssRNA vector
- Can package up to 10 kb of transgene
- Allows long term gene expression (transgene integration into host genome)
- Low pre-existent immunity in humans
- Possible genotoxicity limited by good vector design

Adeno-associated virus (AAV)
- Non-enveloped, ssDNA vector
- Can package up to 4.7 kb of transgene
- Generally delivered by non-viral vectors
- Requires repeated administration

Gene editing
- Targeted DNA cutting and editing using nucleases (ZNFs, TALENs, Cas9)
- Editing tools can be delivered using viral (AAVs, integration deficient lentiviruses) or non-viral vectors
- Requires in situ correction of mutations
- Can produce gene knockouts
- Possible off-target effects

mRNA therapy
- Regulation of protein stability and translation using chemically modified RNAs
- Generally delivered by non-viral vectors
- Allows dose control and transient expression of proteins
- Requires repeated administration

Examples of current treatments, strategies and stage of development. Selected therapies target hepatocytes in vivo to produce cytosolic or secreted proteins or to knockdown specific genes.

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Hepatology Snapshot

The liver is a key organ in the human body involved in a variety of functions that influence other organs. Among other roles, it is essential for digestion, metabolism, detoxification, immunity and blood clotting. Hepatocytes constitute the bulk of cells in the liver parenchyma and are affected by the majority of monogenic liver inherited disorders, viral infections and malignancies.

Whilst conventional therapies can alleviate symptoms of some liver disorders, very few curative treatments currently exist. Recently, several gene therapy strategies have arisen as attractive treatment options for monogenic disorders or multifactorial disorders with specific gene targets.1

This snapshot illustrates the delivery methods, as well as the advantages and disadvantages of some of these technologies. It also offers examples of the development stage of gene therapy products for selected disorders.

The best-known gene therapy strategy is gene addition which allows the phenotypic correction of a disorder by providing a wild-type form of a mutated gene to affected tissues. Viral vectors such as aden-associated viruses (AAVs), adeno-viruses and lentivirus have been used as carriers for these genes. Depending on the disease and vector type, gene addition can achieve life-long benefits. AAV-derived vectors are non-enveloped, single-stranded DNA viruses that can package up to 4.7 kb of a transgene.2 AAVs efficiently transduce hepatocytes, have low immunogenicity and are mostly preserved as episomes inside cells, which might limit their efficacy in dividing cell systems, such as the growing liver.2

Adenoviruses are non-enveloped, double-stranded DNA viruses capable of carrying around 37 kb of a transgene and transducing liver cells with high efficiency. They can elicit strong immune effects and are generally used in oncolytic therapy.3

Lentiviral vectors are single-stranded RNA viruses that can efficiently accommodate 10 kb of a transgene.4 They integrate their genetic material into the host genome, allowing long-term expression of the therapeutic gene. Depending on design, they present a low risk of genotoxicity, as they integrate into intronic regions of actively transcribed genes.5 To date, lentiviral vectors have been approved for ex vivo gene therapy,6 but there is interest in using lentiviral vectors for in vivo liver-directed treatments.

Non-viral delivery is an alternative to the viral vector transport systems. For this, engineered particles such as lipid nanoparticles, exosomes or polyethyleneimine -coated particles can be produced to encapsulate several therapeutic compounds including mRNAs for mRNA therapy, or small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs) for gene-silencing therapies.7,8 The cellular uptake of nanoparticles is reduced by this method and the treatment effect is short-lasting, requiring frequent re-administration. Alternatively, siRNAs and ASOs can be delivered directly into the circulation, with certain chemical modifications enabling efficient hepatocyte transfection.8

Another gene therapy strategy is genetic correction using platforms such as Zinc-Finger Nucleases or CRISPR/Cas9 complexes. These systems can be delivered using both viral and non-viral strategies and allow in situ correction of mutations. However, their in vivo use is limited by possible off-target effects, which can lead to carcinogenesis.9

The table included in the snapshot was up to date on 01.04.2020 and contains examples of treatments employing some of the aforementioned technologies.10 The genetic treatments included in the table are delivered in vivo.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors’ contributions

PG conceived the idea and contributed to writing and editing, ACC wrote manuscript and designed the figure, JC contributed to writing and editing.

Supplementary data

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