GENE THERAPY

INTRO TO BIOLOGY - SCIENTIFIC REPORT

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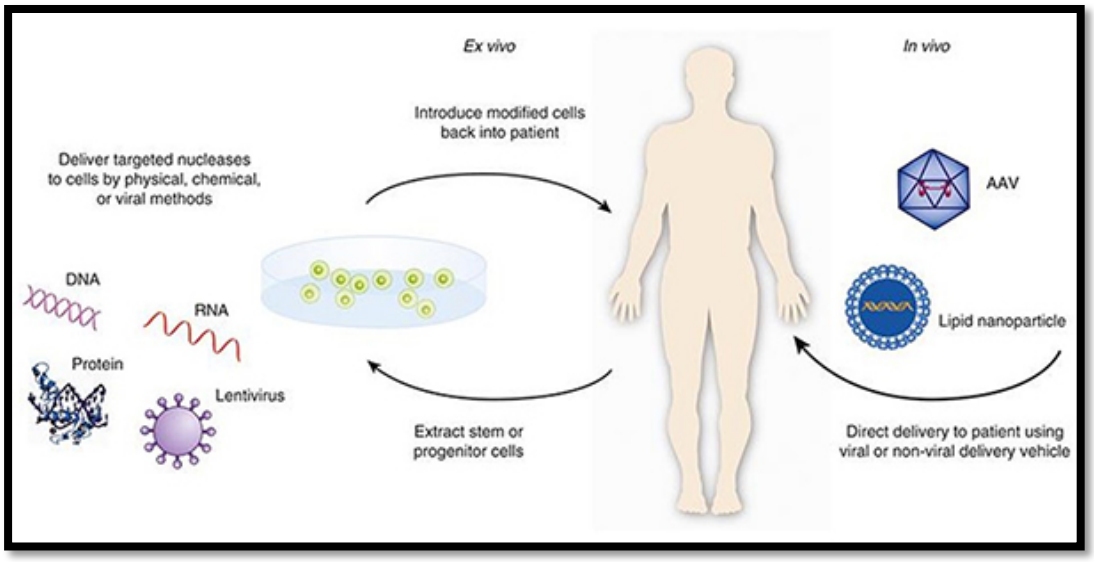
ABSTRACT

All diseases in humans are a product of either environmental or genetic factors. In this report we shall focus on the genetic diseases and how different ways of genetic manipulation can be used as treatment. This manipulation of "problematic" genetic material is called **Gene Therapy [II]**.



(Illustration taken from www.fda.gov)

Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. Gene therapy products are being studied to treat diseases including cancer, genetic diseases, and infectious diseases. The use of viral vectors is most commonly seen in this field **[III]**.

Gene therapy is a technique that modifies a person's genes to treat or cure disease. Gene therapies can work by several mechanisms **[III]:**

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease

In this report we focus on delivering genetic codes via viruses, we focus on one such viral vector AAV which has shown some signs of progress and is mostly deemed to be safe for humans.

1) UNDERSTANDING THE PROBLEM

Genes are sections of DNA that instruct the cell to make proteins that carry out a wide range of bodily tasks. Many diseases are genetically based, which means that altered genes give the cell the wrong instructions, causing the protein to be produced abnormally or to be completely disabled, both of which can result in disease **[I, IV].**

In gene therapy, a patient's own cells are used to deliver a functioning copy of the gene. The normal protein produced by a functional gene has the potential to treat the disease's underlying cause and give restorative benefits. The ultimate goal of gene therapy is to somehow find ways to alter this "faulty" DNA **[I, IV].**

We alter the DNA to either increasing production of disease fighting protein, decrease disease causing protein and/or production of entirely new proteins which are capable to fight the disease.

2) THE DELIVERY MECHANISM

There are multiple ways to alter DNA, the 2 main methods used are **VIVO** and **EX-VIVO,** the difference is that in the former genetic material is modified in the patient's body but in the latter, cells taken from the patient are genetically modified in a lab and then put back in place.

Genetic material can not be directly be put inside a cell, we need a carrier. Typically, viruses are used as the carrier as they are very good in terms of infecting and infiltrating various cells. The infectious part of the virus is removed making it safe for the virus to enter the nucleolus of the cell safely without making the patient sick.

2.1) Why viruses are most commonly used in gene therapy?

Viruses have evolved specialized molecular mechanisms to efficiently transport their genomes inside the cells they infect. Delivery of genes or other genetic material by a vector is termed transduction and the infected cells are described as transduced.

As viruses can be manipulated with relative ease and through evolution have attained the ability to efficiently deliver their genomes to the nucleus of many different cell types and organs, they make good gene transfer vectors. For individual therapies the requirements of a viral vector differ according to the nature of the disease **[V]**.

2.2) Viruses currently being used in clinical trials:

Viral vectors are nature's gene delivery machines that can be optimized to allow for tissue-specific targeting, site-specific chromosomal integration, and efficient long-term infection of dividing and non-dividing cells **[VI]**.

While certain treatments necessitate long-term gene delivery, others call for controlled or even short-term gene delivery. Localized gene transfer is desired in some circumstances, but global gene transfer is necessary in others.

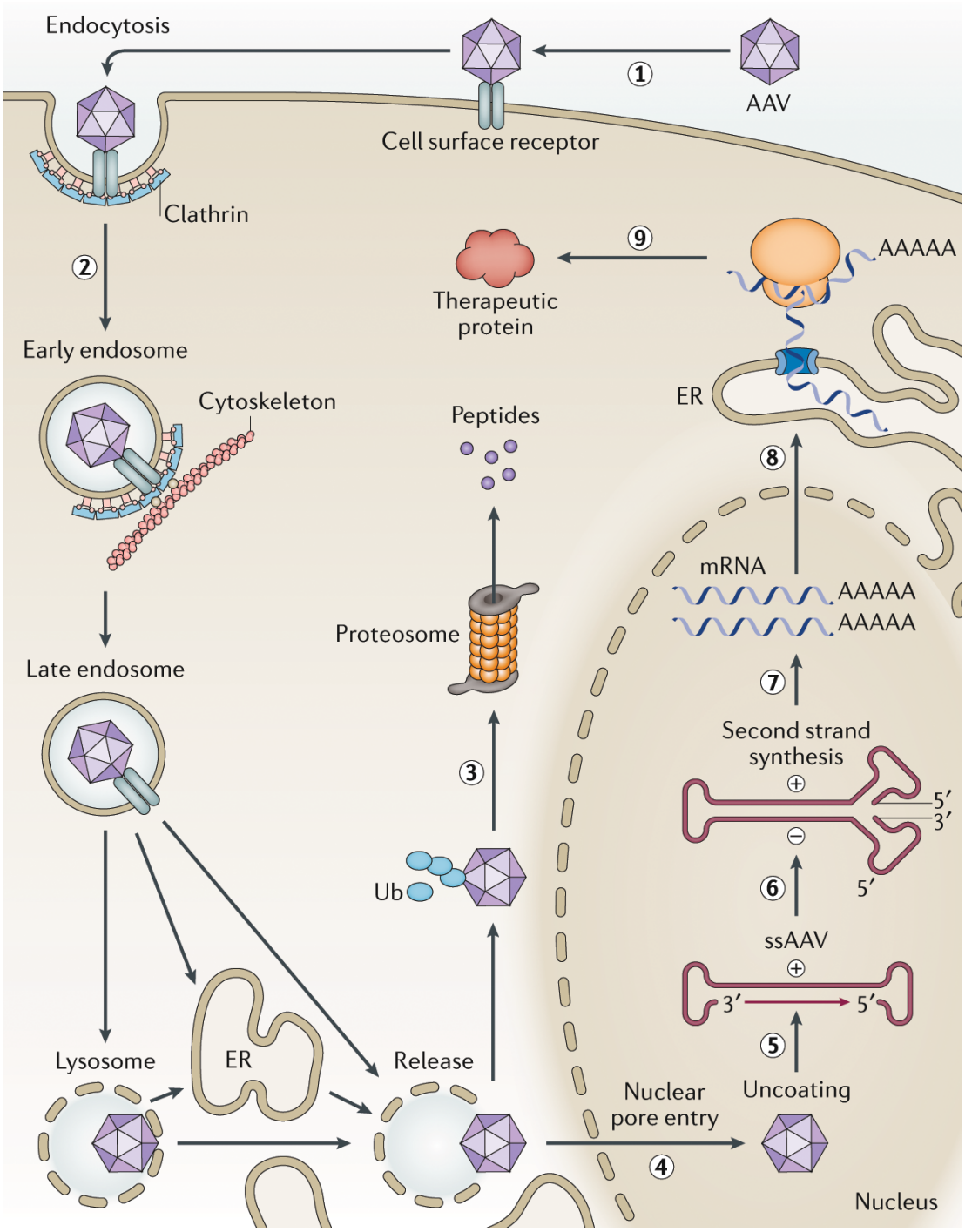
3) THE AAV VIRAL VECTORS

In gene therapy clinical trials the most commonly used gene delivery systems have been based on adenovirus (Ad), retrovirus, poxvirus, adeno-associated virus (**AAV**) and herpes simplex virus (**HSV**), which were cumulatively used in more than 66% of all clinical trials to date. **AAV** is considered to be the safest viral vector system since it is based on a non-pathogenic human virus that can only replicate in the presence of a helper virus co-infection **[VI, V]**.The popularity of **AAV** viral vectors lies in the fact that they are extremely modifiable and don't mutate or undergo any type of reproduction, which means that they can be extremely localized and scientists can safely target only a part of the body without worrying for side effects in other tissues.

Some of the popular delivery strategies of AAV inside the patients body are; Systemic Delivery, Intramuscular Delivery, Central Nervous System Delivery, Cardiac Delivery, Pulmonary Delivery .etc.

The AAV viral vector working mechanism is explained below:

1) (AAV) vector virions bind to receptors and co-receptors on the surface of target cells and are taken into endosomes within these cells through endocytosis.
2) AAV virions are either ubiquitylated and targeted for proteasome-mediated degradation or intracellularly trafficked to the nucleus.
3) Once in the nucleus, AAV virions are uncoated and the AAV genome is released.
4) The AAV single-stranded DNA genome then is converted into double-stranded DNA, followed by **transcription** and the nuclear export of mRNA for **translation** and **expression** of the therapeutic transgene.



https://www.nature.com/articles/s41576-019-0205-4

4) RECENT DEVELOPMENTS

As more and more studies are going to know more about gene editing and modification, due to the advancements in the recent times in sequencing, editing and identification of virus as well as human genetic material, we have come to know more about new treatments and preventional steps for people at a high risk of disease. The possibilities of gene therapy hold much promise. Clinical trials of gene therapy in people have shown some success in treating certain diseases, such as[III]:

- Severe combined immune deficiency
- Hemophilia
- Blindness caused by retinitis pigmentosa
- Leukemia

But several significant barriers stand in the way of gene therapy becoming a reliable form of treatment, including:

- Finding a reliable way to get genetic material into cells
- Targeting the correct cells
- Reducing the risk of side effects

The scientific field for gene therapy products is fast-paced and rapidly evolving – ushering in a new approach to the treatment of vision loss, cancer, and other serious and rare diseases. Of gene therapies up for approval over the next five years, 45 percent are anticipated to focus on cancer treatments and 38 percent are expected to treat rare inherited genetic disorders.

5)CONCLUSION

As of right now, gene therapy is in developing stage, but eventually gene therapy shows capabilities to replace normal medicine. Every single disease related to the human body has some relation with the gene code of the person. Recently research in trying to alter genetic code of the cells present at the scalp of an individual in an effort to remove dandruff causing genes. Such therapies treat diverse clinical indications and tissue targets, including neuromuscular disease, inherited blindness, and cancer. While these approved therapies are life-changing for the affected patients, they offer even broader impact in what they demonstrate more generally for the field and lay a foundation on which treatments for many other conditions can be developed. For example, the success of in vivo AAV gene transfer to the human retina and central nervous system by Luxturna and Zolgensma for Leber's congenital amaurosis and spinal muscular atrophy, respectively, has facilitated the development of AAV-based therapies for gene delivery to the liver and skeletal muscle to treat hemophilia1 and Duchenne muscular dystrophy **[VII].**

Therefore**,** more research must be put into this field and eventually we will reach a stage where most diseases would be treated at the very root of the problem with the help of **Gene Therapy**.

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