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Non-Viral Mediated Physical Approach for Gene Delivery

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Abstract

Non-viral mediated physical approach for gene delivery is becoming popular for the therapeutic treatment of genetic diseases. Non-viral physical methods of gene therapy such as microinjection, hydrodynamics, biolistic, electroporation, sonoporation etc are more preferred than viral vectors because of its simplicity and rapid gene transfer rate.

Keywords: Microinjection; Sonoporation; Biolistic; Electroporation

Introduction

Physical non-viral methods for delivering genes use different physical forces to transfer DNA fragments precisely into the host cell. Such methods are simpler and easy to perform. However offers low gene transfer efficiency and short-lived gene expression but are widely used for gene modification [1].

Physical non-viral methods jet injectors

Physical methods of gene transfer enables the transfer of DNA to the nucleus of the host cell by producing transitory defects in its outer membrane using physical forces such as laser beam, electric pulse, ultrasound, particle impact, local or rapid systemic injection, etc. [2]. The following physical techniques are used for genetic modification of target cells.

Microinjection: Localized microinjection of naked DNA was first introduced in 1990 and then later was used to modify hepatic, dermal and neural tissues.

Principle: Insertion of needle into the host cell produces physical damage enabling the localized DNA uptake [3].

Mechanism: In 1947 a needle free jet injection method was used to introduce DNA into the target cell at a faster rate by means of compression generated by pressurized carbon dioxide gas which produces pores in the membrane of the target cell to allow intracellular DNA uptake. Gas pressure controls the penetration power depending on the pressure tolerance of the target tissue.

Jet injection involves the following steps:

Step 1: loading of usually 3-5 µl DNA solution.

Step 2: Adjusting the strength of the pressure between 1-3 bars.

Step 3: Pointing the injector to the target tissue.

Step 4: Pulling the trigger [4,5].

High levels of gene expression, i.e., 50-folds has been accomplished with jet injector with effective gene transfer without damaging side effects. Because of its simplicity and high safety it is the most preferred DNA transfer metho.However, sometimes when old models of injectors were employed may cause localized pain, edema, and bleeding at the injection site. Table 1 gives a direct comparison between conventional and modern [6] (Table 1).

Features	Conventional jet injector	Microjet injector
Operation mode	Discrete	Continuous
Nozzle diameter	75-200 µm	50-100 µm
Exit velocity	>150 m/s	>100 m/s
Target tissue	Dermis subcutaneous tissues	Epidermis
Dose precision	30-100 µl	2-15 nl
Injection volume	0.1-1 ml	1 µl/min
Penetration depth	2-20 mm	200-400 µm
Active control	No	Yes

Table 1: Comparison between conventional jet and microjet injector.

Applications:

- Plasmid DNAs for carcinoembryonic antigen and interleukin-12 gene was injected in to the muscles to enhance antitumor immunity.
- Suitable method for DNA-based vaccine development, direct transfection of cancerous cells of skin and in contemporary immunization.
- Enables chemotherapeutic treatment of tumours and cancers. For example treatment of breast cancer and malignant tumor.
- Evaluation of DNA-based vaccination by microinjections of therapeutic DNA into muscle or skin [7].

Hydrodynamic Gene Transfer

Transfer of large volumes of DNA for effective transformation of tissues such as cardiac, hepatic, kidney, bronchiole tissues was accomplished using hydrodynamic procedure in 1999 [8].

Principle and mechanism

It uses the elevated compression for injecting large volumes of DNA solution in short time of 3-5 s, producing transient pores in the membrane of the target cell to allow DNA uptake.Tranformation efficiency for this method lies between 30-40% [9].

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Applications

- Efficient gene delivery method in rodents.
- Transgene expression levels achieved using this method was close to regular physiological gene expression levels.
- Ideal method for in *vivo* transfection of kidney liver and muscles to study the function of genes and its regulatory elements, therapeutic effects of tissue specific proteins, etc.
- Suitable for transforming large organisms [10,11].

Gene Gun

DNA-coated particle mediated DNA delivery using a gene gun is also termed as biolistic DNA transfer and was mostly used to transfect plants [12].

Principle and mechanism

This method delivers DNA coated particles (mostly gold, tungsten or silver particles) to target tissues at high velocity driven by pressurized inert helium gas. Factors such as particle size, gas pressure and dose frequency influences penetration efficiency, gene transfer level and degree of tissue injury [13].

Applications

- Genetic immunization for intramuscular, intradermal and intratumor.
- More efficient than microinjection gene delivery procedure [14].

Electroporation

Applying electric current to produce pores by altering cell permeability is known as electroporation, introduced in 1960s [15].

Principle

Intracellular electrophoretic DNA movement was achieved by producing transient pores in the outer by employing electric current [16].

Mechanism

The working mechanism is very simple it involves the application of electric pulse from charged electrodes to inject DNA to the target tissue. Varied voltage, pulse duration, and number of cycles influence DNA transfer. This technique is effective and safer to use. Optimization of its various parameters enhances transfection efficiency of this method [17].

Applications

- Electroporation can be performed in localized manner e.g. in case of hepatic cells transformation.
- Restricted accessibility of electrodes to the internal organs limits its applications to solid tissues [18,19].

Sonoporation

Employing ultrasound to deliver DNA was demonstrated in 1954.

Principle

This technique produces defects in plasma membrane by using ultrasound waves of 1-3 MHz with intensity of 0.5-2.5 W/cm^2 by acoustic cavitation. Propagating ultrasound waves result in energy release which affects the membrane structure. Frequency and intensity of ultrasonic waves and type of target tissue influence its absorption rate [20].

Mechanism

Ultrasound waves aided with contrast agents or air-filled micro bubbles enhanced gene delivery efficiency. Microbubbles cavitate, oscillate, break up upon absorption of ultrasound waves and produce localized shocks in the form of high-velocity microjet that interrupts the nearby membranes resulting in producing defects which subsequently allow DNA transfer [21].

Optison is widely used contrast agent which consists of gas-filled human albumin microspheres of size 1-6 μm. Besides small-sized nanobubbles have also been used but requires higher frequency ultrasound exposure. Lipid or polymer coated micro bubbles enhances transfection efficiency which is also dependant on factors such as frequency and intensity of ultrasound waves, contrast agent, DNA concentration, and duration of exposure. Being safer, noninvasive, and accessibility to internal organs makes it an effective transfection method [22,23].

Applications

- Enhance permeability of blood-brain barrier.
- Precise targeted gene delivery using non targeted micro bubbles or site-specific ligands coated micro bubbles to deliver DNA to specific cells or tissue.
- Enables regeneration of bone tissue and bone formation upon transfer of recombinant human bone morphogenetic protein [24,25].

Conclusion

Such non-viral methods of DNA delivery are cheaper, simpler and safer method to transfect the desired target cell or tissue in comparison to viral DNA delivery approaches. Such physical approaches offer a promising future in genetic engineering and therapy.

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