Gene Therapy in Haemophilia B: Efficacy and Optimization

Sara Sánchez-Úbeda

1Grau en Genètica, Universitat Autònoma de Barcelona

Introduction

Haemophilia B is a monogenic hereditary X-linked bleeding disorder that results from a defect in the gene encoding coagulation factor IX which frequency in males of 1/25,000. People with severe haemophilia have <1% of the normal clotting factor in their blood and levels considered therapeutic are slightly above the 1% threshold and can convert severe haemophilia into a moderate form.

Current treatment involves frequent intravenous injection of clotting factor concentrates two or three times a week. This treatment is prophylactic rather than curative, moreover, in some cases there is a complication with the formation of antibodies 'inhibitors' which block the recombinant protein.

Gene therapy would be a very attractive treatment to cure the disease allowing endogenous production of FIX. For these reasons, researchers are developing new and improved cassettes and vectors designs, doses optimization and they are finding new alternatives with non-viral vectors.

The objective of this study is to investigate the approaches which allow more efficient vector design and cassettes to optimize haemophilia gene therapy.

Approaches

Transposon-transposase System: it allows the transgene FIX insertion in the murine genome with a liver-specific promoter and results in a stable and long-term expression

Zinc Finger Nucleases: it induces double-strand breaks to insert the cassette in the murine genome and results in a long-term expression

The aim to improve the cassette design is to achieve a long-term expression and decrease the immune response. It could be achieved by specific-promoter, hyperfunctional mutation, codon usage optimization, silent sequences among others

Alternative Serotypes

The safest and most efficient serotypes are AAV2/7, AAV2/8 and AAV2/9 because they do not develop inhibitors and it maintain transgene expression

Alternative Strategies

Liver
Muscle

Non-invasive administration
Non-invasive administration

Normally produces and secretes FIX into the blood system
Capacity of produce FIX and secretes it into the bloodstream

Long-term and therapeutic level expression of the transgene
Alternative target in cases of liver disease

T-cell cytotoxic response
Inhibitor antibodies

Liver diseases
Long-term expression but in sub-therapeutic levels

Target tissues

Future Directions

A clinical trial has been reported which achieves the cure of haemophilia B, but in some restricted patients.

Problems

Solutions

Gene therapy will become the definitive treatment to cure haemophilia B

References


