

Gene therapy for Multiple Sclerosis: Does Interferon Beta regulate MHC class II antigen presenting?

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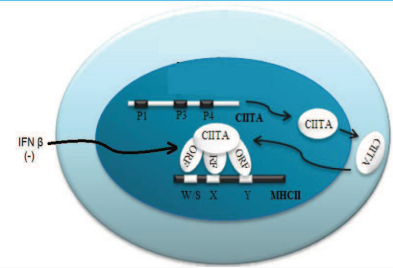


Introduction

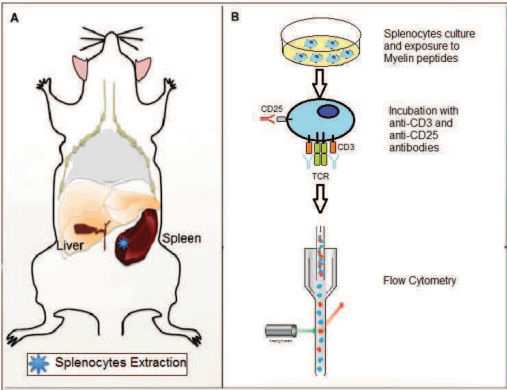
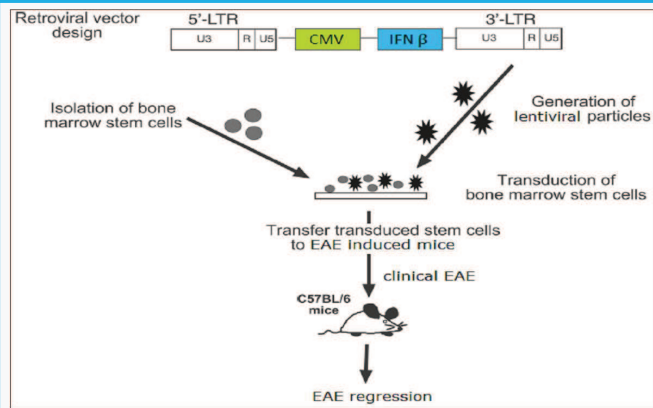
Multiple Sclerosis is a disease affecting 2 million people worldwide. It is caused by a complex immune response against the myelin sheaths around the axons in the Central Nervous System. Antigen presenting cells recognize myelin peptides as exogenous and present them to T cells using MHC class I and II. Those T cells activate the immune response, where antibodies, complement, macrophages recruitment and inflammation cause the destruction of neurons. Typically, Multiple Sclerosis is treated with oral or intravenous Interferon Beta, which has several immunomodulatory properties. Because of the lack of an efficient treatment, an *ex vivo* gene therapy approach with Interferon Beta-producing Mesenchymal Stem Cells has been tested in mice. This treatment has been shown to reduce myelin destruction, inflammation and lymphocytic infiltration. **The aim of this project is to study the effect of this treatment in antigen presenting to further understand the pathways involved in its immunomodulatory effect.**

Hypothesis

In vitro studies have demonstrated that Interferon Beta downregulates class II MHC antigen presenting by blocking the CIITA-driven transcription of class II MHC. Because of this, treatment with Interferon Beta-secreting Mesenchymal Stem Cells should reduce antigen presenting by this same pathway, as one of its many immunomodulatory effects.



Experimental Design



>Splenocytes reactivity to myelin peptides assay: Splenocytes are isolated, cultured in a medium with myelin peptides and their reactivity is studied by antibody staining against T cell marker CD3 and activity marker CD25. Immunomodulatory effect is not expected systemically.

- >Production of a lentiviral vector encoding the gene for Interferon Beta under control of the ubiquitous Cytomegalovirus (CMV) promoter.
- >Human Bone Marrow-derived Mesenchymal Stem Cell culture and transfection with the lentiviral vectors.
- >Treatment of EAE induced mice with the Interferon Beta-secreting Mesenchymal Stem Cells.

- >Survival and Clinical Score study.
- >Class II MHC expression study by Immunohistochemistry: Expected reduction of expression.
- >MHC class II pathway genes activity study by RT-PCR: CIITA mRNA levels are expected to be maintained, and MHC class II mRNA levels reduced.

Materials and Methods

Scientific literature search on PubMed database: Recent papers and reviews were selected according to their quality and data of publication. Two main topics were used for the search:

- >Multiple Sclerosis: its clinics, pathology, actual therapies and new experimental approaches using gene therapy.
- >Interferon Beta: immunomodulatory effects, role in MHC class II antigen presenting, uses in gene therapy.

Interview to a scientist working in the field of gene therapy for the CNS: Miguel Chillón (CBATEG, UAB)

References

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