

Gene therapy of the Wiskott-Aldrich Syndrome

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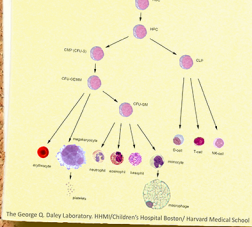
The Wiskott-Aldrich Syndrome (WAS) is a rare X-linked disease that affects hematopoietic cells due to a mutation in the WAS protein, an enabler of the polymerization of actin. This syndrome affects the development of the immune system and platelets among others causing eczema, autoimmunity and thrombocytopenia. This divulgative poster intends to explain the fundamentals of WAS as well as the development of new treatments to cure the disease by Gene Therapy, focused primarily on the use of retroviral and lentiviral vectors. Finally, it will also remark the project of "Wiskott-Aldrich. A Rare Disease", a children's book which objective is to help understand patients of WAS about the disease as well as the advances in Gene Therapy.

The Syndrome

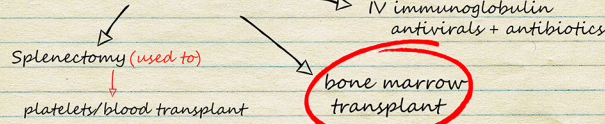
The Wiskott-Aldrich Syndrome (WAS) is a rare X-linked recessive disease characterized by eczema, thrombocytopenia, immune deficiency and in some cases autoimmune diseases.

The responsible gene for the syndrome was discovered in 1994 and called WASp gene, it is expressed only in hematopoietic cells and contains several unique domains involved in actin polymerization and signal transduction, being its mutations the cause of not only WAS but other blood related diseases. The inability of actin to achieve the correct polymerization without the regulation given by the WAS protein results in failures at the structure of blood cells and immune cells, as well as problems with the development of signaling structures such as immune receptors or MHC.

hematopoietic cells

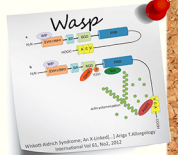


Actual Treatment



Symptoms

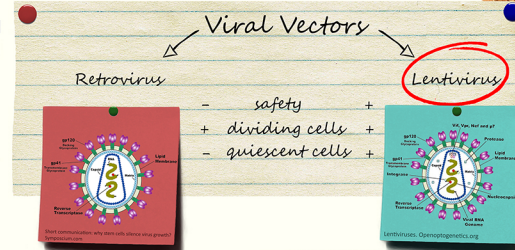
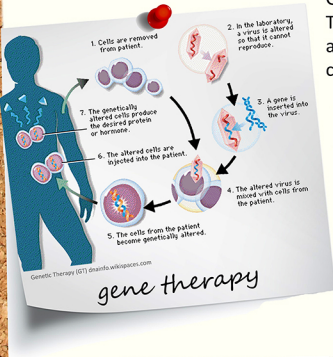
eczema
thrombocytopenia
immune deficiency
autoimmunity



Gene Therapy

Gene Therapy in Wiskott-Aldrich Syndrome is focused on the use of viral vectors. The first approach was through retroviral vectors, but later on due to safety issues and the inability of lentiviral vectors of infecting non-dividing cells lentivirus were chosen as the optimal vectors for gene therapy.

Transplantation of autologous hematopoietic stem cells (HSC) genetically modified ex vivo using viral vectors represents a potentially curative treatment for inherited disorders of the hematopoietic system such as WAS, and the development of safe lentiviral vectors have made this possible.



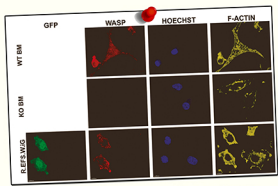
lentivirus (HIV-1) (self inactivating)

XVPU X400pb LTR
XVPR
XNEF ✓hWASP
XVIF
XTAT

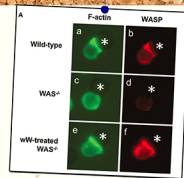
endogenous promoter



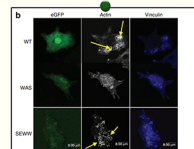
Results



Analysis of Wasp expression and actin polymerization in BM cells after gene therapy with retroviral vectors¹

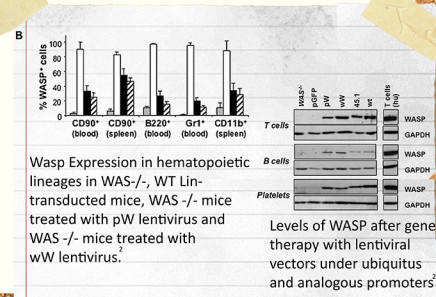


Expression of WASp and actin in BM cells after gene therapy with lentiviral vectors²



Expression of actin and podosomes in BMDC after gene therapy with a lentiviral vector. Podosomes are remarked with yellow arrows³

Experiments show promising results in the fields of restoration of WASP expression and actin polymerization



Wasp Expression in hematopoietic lineages in WAS^{-/-}, WT Lin-transduced mice, WAS^{-/-} mice treated with pW lentivirus and WAS^{-/-} mice treated with wW lentivirus.²

The Book

