Prevention and molecular treatment of AIDS with lentivirus: A historical perspective

Núria Pedreño López

“Thirty years after the first described AIDS case, fifteen years after the advent of Highly Active Antiretroviral Therapy, miracles continue.”

Introduction

Currently, viral vectors are the most efficient vehicle on the transfer of genes to their infectivity in a high proportion of cells and with a very good capability of carrying transgenes in its modified genetic machinery. In addition, note the potential to produce adverse effects in the application to humans, their immunogenicity and the risk to produce homologous recombination or toxicity.

The most widely used viral vectors are developed from adenovirus, retrovirus, vaccinia virus, AAV, poxviruses and lentivirus among others. Because of the long history of the characterization of viral particles and its genome, infectivity to the target cell, transgenic capacity and accessibility to establish cellular lines helps for the production of recombinant stocks to infect target cells [1]. Lentivirus is the type of retrovirus responsible for the acquired immunodeficiency syndrome (AIDS) and has been seen it has very interesting properties for the establishment of these vector systems.

In recent years, these HIV-based vectors have been studied and tested for the efficacy of gene transfer, furthermore to its biological safety to exclude the possible reconstitution of a competent pathogenic replication in infected patients.

The 90’s

**ATTENUATED LENTVIRUS IN GENE NEF WITH A COMPETENT REPLICATION**

*Experimental*: 1-SIV nef (vaccine) 2-SIV wild-type

*Control*: 1-SIV wild-type

*Results*: Extremely low viral load

*Conclusion*: The researchers believed that the nef gene was responsible for pathogenicity:

- SIV in rhesus monkeys affects similar to HIV in humans [2]
- If there was no nef at the beginning of the infection, it was believed that the antiretroviral immune response could be efficiently set up [3]

**Problems**:

- Cell-to-cell pathway to transmission
- Nef wasn’t the responsible for pathogenicity
- There weren’t other factors
- Nef regulated the degree of replication

**NON-VIABLE = TOO MUCH RISK [2]**

First years of XXI century

**GENE THERAPY BASED IN RNA INTERFERENCE**

*Strategy didn’t get a total blockade:*
- RNAs didn’t mutated completely the expressions of genes in a natural way
- The genetic barrier imposed was too high for the virus to overcome the inhibition of the four expressed shRNA

*Handicap: the specificity of the shRNA for the HIV-1 didn’t cover the other multiples genetics-subtypes of HIV [4,5]*

*Prevention of escape with four short hairpin RNAs (Extracted from [5]):*

- a and e as a positive control: in c, a initial virus replication was totally abolished. After 41 days, new virus spread was seen in b as a culture from empty experiment but, in d, the viruses were completely in the control of line, indicating that these viruses emerging is a worm not resistant.

Conclusions and future prospects

- It is important to emphasize that, in order to fight the infection caused by HIV, it is necessary to combine different therapeutic strategies.
- The HIV is which has taught more to the scientific community about the abilities and weaknesses of our own immune system in comparison to any other pathogen discovered.
- According to the WHO, there are approximately 34 million infected people in the world, but the high cost of antiretroviral drugs makes impossible the distribution to these developing countries. For that reason, the best option would be the development of replication competent and secure viral vector that allows in vivo the release of anti-HIV genes that confer resistance or selective death to the infected cells [12,13,14].
- The best alternative in order to cure the infection is through interference RNA and, specifically, through short-hairpin RNA but, before its use, appropriate vectors that are stable and will allow a lasting expression of these RNA will be needed. Because of this, lentivirus has been chosen for its effectiveness and biological safety in gene transfection, but still need to improve different aspects before it becomes clinically viable shRNA-based therapy [15].
- The HIV-1 uses a error-prone replication machinery that allows a quick adaptation to new conditions, being the cause of making drug-based therapies fail because they allowed the emergence of resistant viral mutants [15].
- The possibility to have an additive effect with drugs evaluated through drug-dose response curves in cellular lines expressing different shRNA
- No cellular free; HIV-1 wild-type; single anti-HIV shRNA, BEO
- Lentivirus, ADN (compliments RNA-Bacitracin)

**SYNERGY EFFECTS**

- Prevent possible break of the virus with targets develop with lack of redundancy [5-9]
- Strategy to block the appearance of mutants and improve the antiretroviral activity
- Improves the deletion if it acts at different levels of virus replication
- Inhibitory effect: Anti-HIV > anti-host
- shRNAs + Drugs > Increases susceptibility from drugs [10,11]

Additives antiviral activity of shRNAs and antiretroviral drugs (Extracted from [9])

The possibility to have an additive effect with drugs evaluated through drug-dose response curves in cellular lines expressing different shRNA:

- No cellular free; HIV-1 wild-type; single anti-HIV shRNA, BEO
- Lentivirus, ADN (compliments RNA-Bacitracin)

**CONCLUSION**

- The future prospects that are expected from these strategies are very wide and if clinical phases are passed successfully, use RNAi to treat other worldwide diseases such as tuberculosis or malaria will be imminent.

---