ADENOVIRUS IN THE FIGHT AGAINST CANCER

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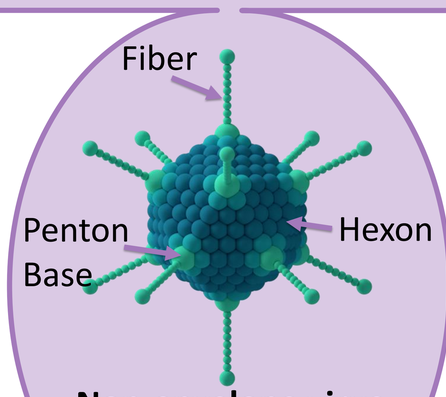
ONCOLYTIC VIROTHERAPY

Cancer is a group of diseases caused by an abnormal cell growth with the potential to invade and spread into other parts of the body. Since is one of the leading causes of death nowadays, many strategies are being developed to fight it. The therapeutic use of oncolytic viruses modified by genetic engineering is one of the newest and more promising therapies to treat cancer. It is called **Oncolytic Virotherapy.**

ONCOLYTIC ADENOVIRUS FEATURES

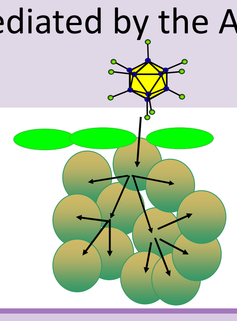
1. Selective replication in tumorous cells
2. Should derive from viruses that causes mild and well-characterised illness in humans
3. Should be non-integrative to avoid genomic alterations
4. Genetically stable and easily manipulated
5. They should contain a off-switch mechanism
6. Great production and purification rates under GMP
7. Should cause lysis on the infected cells



Non-envelope virus
Icosahedral capsid
dsDNA linear

MECHANISMS OF ACTION

VIROCENTRIC	IMMUNOCENTRIC
Lysis and cytotoxicity of tumorous cells directly mediated by the Ad virus	Lysis and cytotoxicity of tumorous cells by an antitumoral immune response, induced by the virus



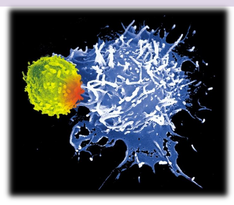


Figure 1. Alemany R., 2014

DESIGN OF TUMOR SELECTIVE ONCOLYTIC ADENOVIRUS

The knowledge of the biology and viral life cycle of Adenovirus has allowed the modification of these agents to achieve specific replication into tumorous cells:

1. Deletions in essential genes for viral replication in normal cells which are compensated by the phenotypic alterations present in tumorous cells. Example: ΔE1B.

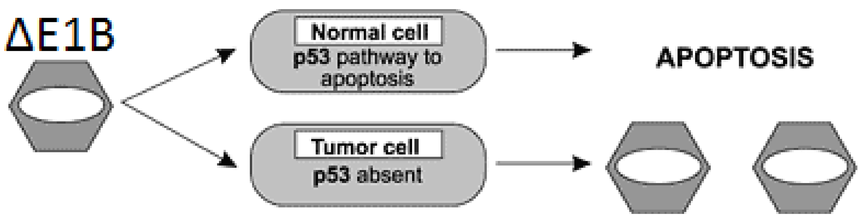


Figure 2. Modified from Kasuya H. et al, 2002

2. Transcriptional and translational targeting: insertion of tissue or tumor-specific promoters in their genome to regulate viral replication. Examples: promoter of telomerase reverse transcriptase (TERT) or α-fetoproteïna for hepatic carcinoma.
3. Transductional targeting: modification of capsid proteins (fiber, hexon and pentose base) with tumor-specific ligands to achieve preferential infection of tumorous cells. Example: RGD motif.
4. Insertion of tissue-specific miRNA in the 3'UTR of viral genes
5. Translation regulation of viral proteins to control its replication. Example: addition of a 5'UTR sequence allows the translation only in cells with high concentration levels of eIF4E such as tumorous cells.

ADENOVIRUS CLINICAL OVERVIEW

PRECLINICAL STUDIES ⇨ Remarkably safe, with high efficiency inhibiting the tumor growth and even elimination of some treated tumors in animal models

CLINICAL STUDIES ⇨ Most clinical trials with oncolytic Ad are at Phase I, but some of them have reached Phase II and Phase III trials or even have been commercialized. In combination with traditional cancer therapies there is an improvement of results. Some examples are:

Oncorine Adenovirus (commercial, solid tumors)

Telomesyn (Phase I/II, hepatocellular carcinoma)

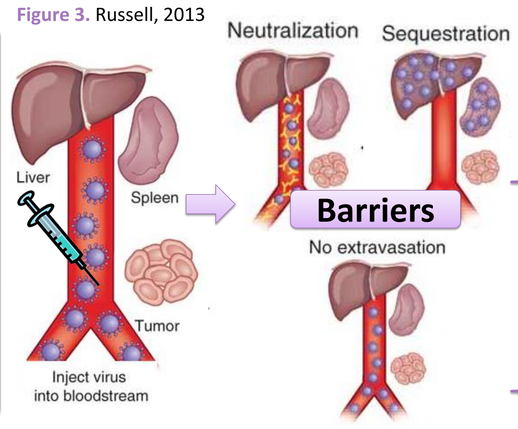
ICOVIR-5 (Phase I, melanoma)

VCN-01 (Phase I, Pancreas)

ADENOVIRUS LIMITATIONS

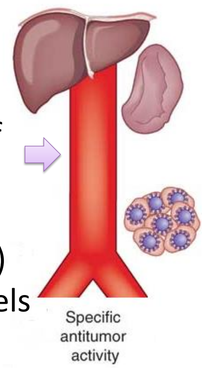
Systemic tumor targeting

Figure 3. Russell, 2013



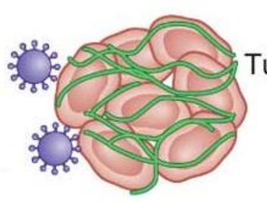
Solutions

- Carriers cell
- Synthetic vectors or nanoparticles
- Genetic modification of the capsid
- MPS blockade
- Polymer shielding (PEG)
- ↑ Permeability of vessels
- Target endothelium
- ↓interstitial fluid pressure

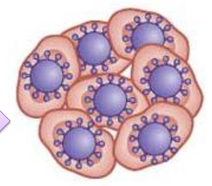


Intratumoral spread

Barrier



- Screening and selection of Ad with high diffusion rate
- Using stroma degradation (metalloprotease, hyaluronidase) enzymes expressed by Ad or by Ad vectors applied with the Ad
- Targeting fibroblasts residents in the tumor stroma by SPARC promoter



Efficient spread

Immune response

Points of view

Virocentric ⇨ Immune system as an enemy
- Immunosuppression
- Genetic modification of the capsid
- Using less frequent serotypes
- Polymer shielding
- Carrier cells

Immunocentric ⇨ Immune system as an ally
- Immunostimulation
- Remove immune evasion genes
- Tumor antigen expose in fiber or hexon

CONCLUSIONS

Virotherapy with oncolytic Ad is a viable option to add to the current cancer treatments.

It does not create resistance or ubiquous adverse reactions like many other treatments.

The progression of oncolytic Ads through the steps of clinical testing is slow, and more representative animal models would be necessary.

The main problem that virotherapy faces is the amount of economic resources and workload needed to take new viruses at least to the first clinical phase.

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