Oncolytic Virotherapy: Potential of Viruses for Cancer Treatment

Anna Yagüe Sanz
Bachelor of Biotechnology. Universitat Autònoma de Barcelona (June 2014)

INTRODUCTION

Oncolytic virotherapy is an emerging technology that uses oncolytic viruses (OVs) to treat malignancies specifically. OVs are non-pathogenic viruses that have been selected or engineered to selectively replicate in cancer and associated endothelial cells to finally kill them via several mechanisms, without causing harm to normal tissues[1,2].
The world's first OV for cancer treatment (H101) was approved in 2005 in China and at present there are numerous studies underway to evaluate safety and efficacy of OVs. Most are phase I/II clinical trials, with the exception of OncoVex$^{GM\text{-}CSF}$, a genetically engineered herpes simplex virus that will be approved soon by the American FDA[3].
However, oncolytic virotherapy is still considered an experimental procedure because despite its great potential it also presents unique scientific, regulatory and biosafety issues.

Objectives: to provide an overview of the current state of the field and to discuss the strategies to overcome the potential hurdles

DESIRABLE FEATURES

A prospective oncolytic agent should comply with some characteristics regarding efficacy, safety and manufacturing[4] *(fig1)*.

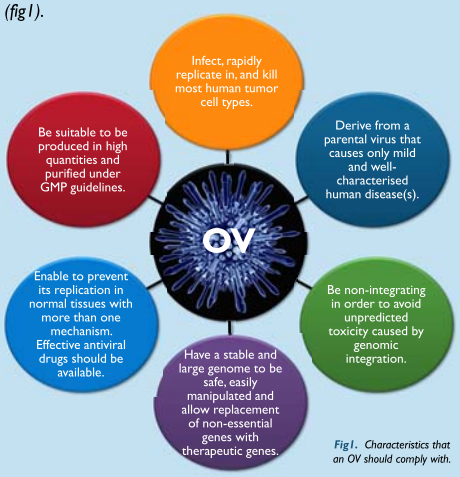


Fig1. Characteristics that an OV should comply with.

MECHANISMS OF ACTION

The antineoplastic activity of OVs is derived from different killing mechanisms[1,5] *(fig2)*.

- **Expression of viral or exogenous cytotoxic products and direct oncolysis** kill infected cancer cells. New virions are able to infect other neighbouring cells.
- **Elicitation of a potent antitumor immunity**, causing indirect cytotoxicity for cancer/stromal cells. It is stimulated due to the release of tumor-associated antigens (TAAs) and danger signals after cell lysis, which activate naive T cells. Pro-inflammatory cytokines are produced.
- **Other indirect mechanisms**, such as the bystander effect or angiogenesis inhibition, kill uninfected cancer cells.

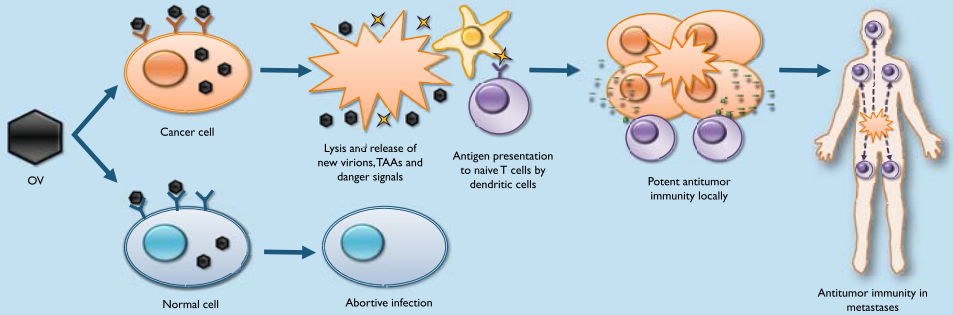


Fig2. Mechanisms of action of OVs. The activity of the immune system against cancer is what determines the long-term success of anticancer therapies.

STRATEGIES TO IMPROVE EFFICACY

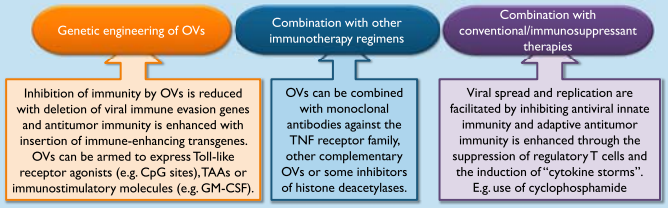
IMPROVING TUMOR TARGETING

Tumor targeting is possible because many of the cellular mechanisms suppressed during cancer are quite similar to the response mechanisms used by normal cells against viral infections, promoting favourable environments for attenuated OVs to replicate[5].
There are different types of targeting to improve tumor selectivity (and reduce toxicity)[3]:

Transductional	Genetic manipulation of the envelope/capsid to make it specific for cells with a tumor-associated surface marker.
Transcriptional	Incorporation of tumor/tissue-specific promoters into the viral genome to limit expression of some genes necessary for replication in tumor cells.
Translational	Insertion of essential viral genes downstream of internal ribosome entry sites (IRESs) that cannot be used as translational origins in specific tissues.
Post-transcripcional	Fusion of a "destabilizing domain" to a gene, giving essential chimeric proteins inherently unstable unless a chemical able to reverse this instability is administered in a tissue-restricted way.
Oncogenetic	Deletion of one/a few virulence factors, resulting in an attenuated strain able to replicate only in cells with cancer-associated alterations in some signal transduction pathways.
MicroRNA	Insertion of tissue-specific microRNA target sequences in the 3'-UTR of essential viral genes.

ENHANCING ANTINEOPLASTIC ACTIVITY

Apart from exploiting the natural infectious capabilities and immunogenicity of viruses, strategies to increase their toxicity to cancer cells have been undertaken[2,3]:



LIMITATIONS AND BIOSAFETY ISSUES

The two main limitations to efficient oncolytic virotherapy are efficient systemic delivery of OVs to the tumor *(fig3)* and adequate viral spread through the tumor *(fig4)*. Others are the need for better preclinical models, better methods to monitor spread and biosafety issues[1,3].

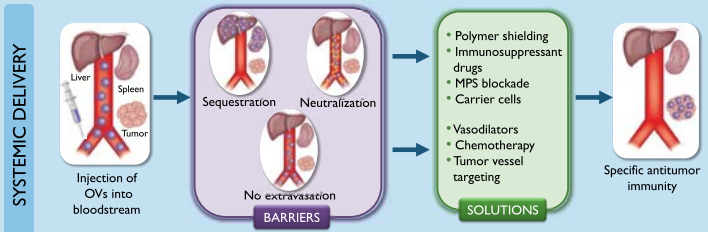


Fig3. Barriers to efficient systemic delivery of OVs to tumor and solutions to circumvent them.

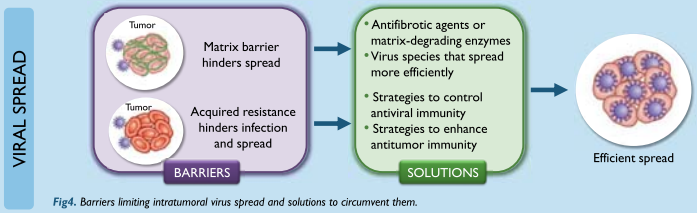


Fig4. Barriers limiting intratumoral virus spread and solutions to circumvent them.

SAFETY

The main concern is the risk of virulent strains arising during replication. Before testing safety with late-stage patients, some parameters must be determined in animal models[1,5]:

Characteristics of the disease caused by the parental strain → Level of pre-existing immunity in the population → Ability of the virus to escape the immune system → Ability of recombination → Toxicity in normal tissues → Transmissibility

There are many strategies designed to increase safety and strict governmental regulation.

CONCLUSIONS AND FUTURE DIRECTIONS

Oncolytic virotherapy is a new cancer treatment under research that uses OVs to destroy cancer cells by different mechanisms of action from those of conventional therapies, so it can be successful in cases of tumor resistance and avoiding side effects of current treatments.. The basis for its success is that it triggers a potent antitumor response, which can eventually reach metastases.
However, important hurdles still need to be overcome. OVs as single agents are often insufficient, so different combination strategies are being designed to increase therapeutic efficacy, which is mainly limited by the difficulty in spreading of OVs to distant metastases. Therefore, the preferred route of administration in the future will be intravenous delivery.
The most promising approach is to use OVs expressing immunostimulatory molecules in combination with immunosuppressant drugs.
OVs will soon move from the bench to the bedside, so more efforts should be invested in both preclinical and clinical studies.

RELEVANT REFERENCES

[1] Russel, S; Peng, K.; Bell, J. (2012) Oncolytic virotherapy. *Nature Biotechnology* 30, pp. 658-670.
[2] Bartlett, D.; Liu, Z.; Sathaiah, M.; Ravindranathan, R.; Guo, Z.; He, H.; Sheng Guo, Z. (2013) Oncolytic viruses as therapeutic cancer vaccines. *Molecular Cancer*, 12:103
[3] Vacchelli, E.; Eggermont, A.; Sautès-Fridman, C.; Galon, J.; Zitvogel, L.; Kroemer, G.; Galluzzi, L. (2013) Trial watch: oncolytic viruses for cancer therapy. *Oncolmmunology* 2:6, e24612.
[4] Liu, S.; Dai, M.; You, L.; Zhao, Y. (2013) Advance in herpes simplex viruses for cancer therapy. *Science China Life Sciences* 56, pp. 298-305.
[5] Sze, D.; Reid, T.; Rose, S. (2013) Oncolytic virotherapy. *Journal of Vascular and Interventional Radiology* 24:8, pp. 1115-1122.