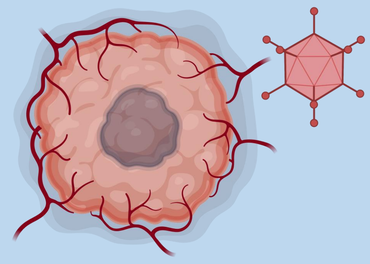
Oncolytic virotherapies against glioblastoma multiforme

Montané Gil, P. Bachelor's degree in Biotechnology, 2018-2022.

Universitat Autònoma de Barcelona



INTRODUCTION

Glioblastoma multiforme is the **most common cause of death** due to brain tumours in humans. It carries a grim prognosis with a **median survival of around 14 months** when treated with current standard of care. It remains one of the most difficult tumours to treat with conventional therapies due to several hurdles like the **blood brain barrier**, the **immunosuppressive tumour environment**, and the **tumour heterogeneity** [1].

Currently, standard therapy for GBM consists of **tumour resection** followed by **radiotherapy** and **concomitant TMZ** which remains insufficient to mitigate the disease's deadly effects [2]. Therefore, it has been promoted the development of alternate immunotherapies, such as **oncolytic virotherapies**, that are emerging as a safe and feasible treatments for a variety of malignancies.

OBJECTIVES

- To study and acknowledge the characteristics of glioma tumours: its microenvironment and genetic traits.
- To describe and compare two different viruses used in oncolytic therapies.
- To know which challenges the oncolytic virotherapies face and how the viruses overcome them.

METHODOLOGY

In order to fulfil the proposed objectives, a **bibliographic research** has been carried out. The published articles in important scientific databases, such as **NCBI** have been the main source of information, which has been **cross-checked** with different sources.

GLIOBLASTOMA

GBM has genetic and epigenetic mutations, causing atypical cells, nuclear hyperchromasia, abnormal proliferation and growth, and angiogenesis.

IMMUNOSUPPRESSIVE MICROENVIRONMENT

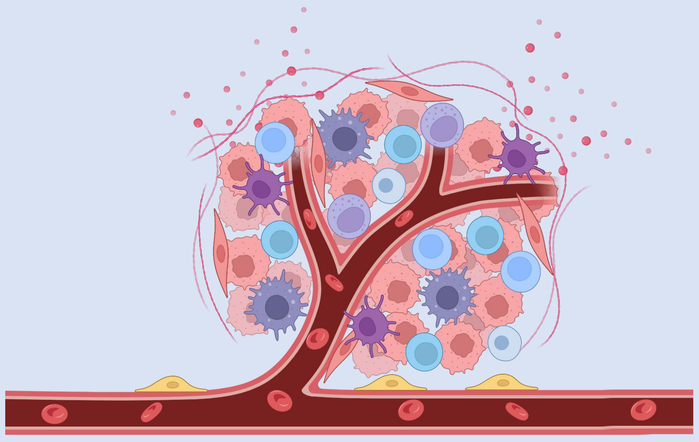


Figure 1 [3]***.*** *Glial cells, glioma stem cells (GSCs), monocytes, macrophages and lymphocytes infiltrate the GBM microenvironment and promote an immunosuppressive environment.*

↓	↑	Loss of
T cells	Treg	CDKN2A
NK cells	M2	Rb
M1	MDSCs	p53

Defective IFN pathway → Low antiviral response

ONCOLYTIC VIRUSES

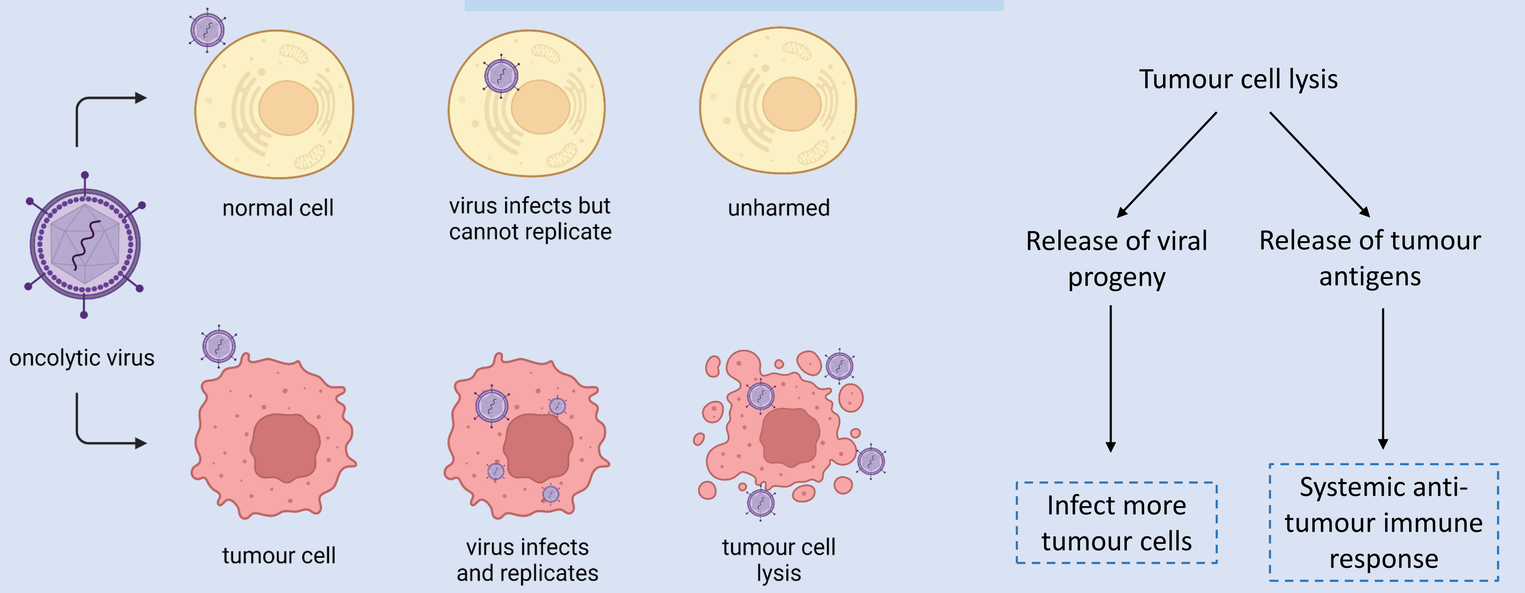


Figure 2 [3]***.*** *Schematic representation of OV's infection of tumour cells.*

LIMITATIONS

BLOOD BRAIN BARRIER	Physical barrier	Non-fenestrated blood channels	Carriers to go through
ANTIVIRAL RESPONSE	Trigger of immune response	Activation of antiviral response	Balance between two responses
TUMOUR HETEROGENEITY	Inter and intratumour heterogeneity	Entrance receptors	Molecular differences

ADENOVIRUS

Unspecific **tropism**:

- CAR
- HSPG
- MHC-I
- VCAM-I
- Integrins

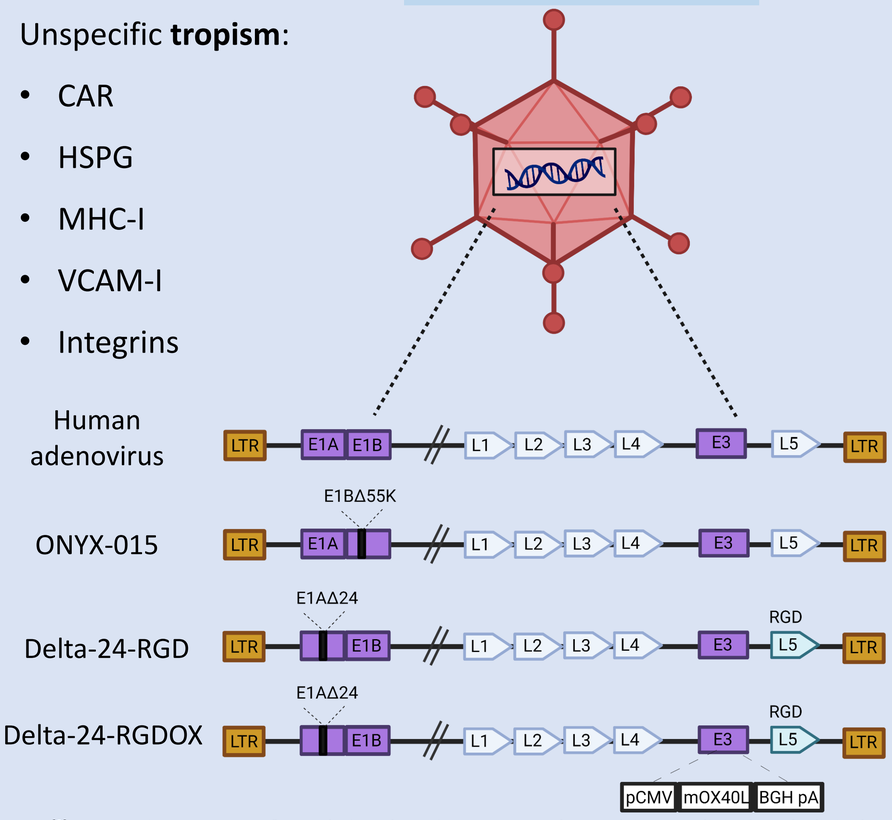


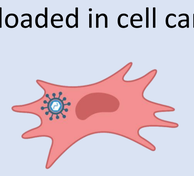
Figure 3 [3]***.*** *Genomic structure of oncolytic adenoviruses currently used in pre-clinical and clinical studies on glioblastoma. ITR, inverted terminal repeat. E1AΔ24: a deletion of 24 base pairs within the E1A region. RGD: an RGD integrin-binding motif in the HI loop of the fiber. pCMV: the cytomegalovirus promoter. mOX40L: mouse OX40L cDNA. BGH pA: bovine growth hormone poly-adenylation signal. The mOX40L expression cassette replaces the E3 region in Delta-24-RGDOX* [4]*.*

COMMON TRAITS

Multimodal combined therapy

Synergistic effects in GBM treatment

Ovs loaded in cell carriers



NDV

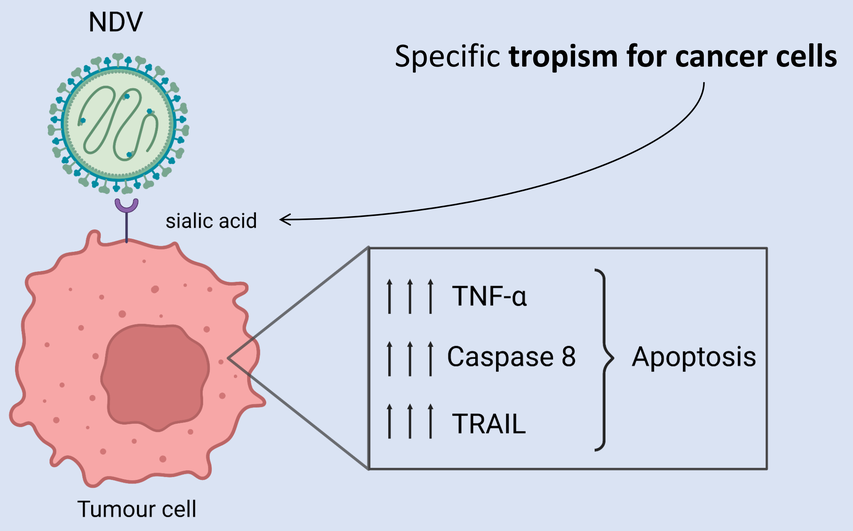


Figure 4 [3]***.*** *Infection of NDV via sialic acid receptors, overexpressed in cancer cells. Once NDV infects, it induces apoptosis independent of p53 by increasing the production of TNF-α, TRAIL and caspase-8.*

MTH-68/H
NDV-HUJ
Live strains

rNDV-p53

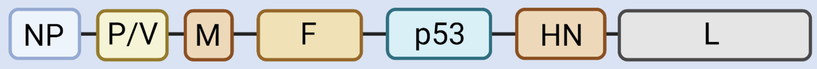


Figure 5 [3]***.*** *Schematic representation of rNDV-p53 genome. NP: nucleocapsid, P: phosphoprotein, V: nonstructural protein, M: envelope matrix protein, F: fusion, p53: human wild type p53, HN: hemagglutinating surface glycoprotein, (L): large protein*

CONCLUSIONS

- OVs are a **promising alternative** to current glioblastoma treatments, not only because of its **tumour cell lysis** ability but also because of its **synergic effect** activating the **antitumour immune response**.
- Both CRAd and NDV possess different traits and abilities that enable them to **surpass the intrinsic barriers** of oncolytic virotherapies without jeopardizing the patient's safety.
- Loading the OV in a **specific carrier** becomes a feasible approach to increase the effectivity of the **OV's delivery** beyond the BBB, it avoids **triggering the immune response** and enhances the infection of **heterogenous tumours**.
- The use of OVs in **synergistic combination therapies** to maximize therapeutic outcome is a promising approach that requires further development to become a solid glioma treatment.

REFERENCES

[1] Suryawanshi, Y.R.; Schulze, A.J. Oncolytic Viruses for Malignant Glioma: On the Verge of Success? *Viruses* 2021, *13*, 1294. https://doi.org/10.3390/v13071294

[2] Rong, L., Li, N. & Zhang, Z. Emerging therapies for glioblastoma: current state and future directions. J Exp Clin Cancer Res 41, 142 (2022). https://doi.org/10.1186/s13046-022-02349-7

[3] Created with biorender.com

[4] Kiyokawa, J., & Wakimoto, H. (2019). Preclinical And Clinical Development Of Oncolytic Adenovirus For The Treatment Of Malignant Glioma. Oncolytic virotherapy, 8, 27–37. https://doi.org/10.2147/OV.S196403