Oncolytic Adenovirus Ad5/3-D24-GM-CSF Infects, Replicates and Lyses Ovarian Cancer Cells Through Desmoglein-2 Cell Entry Receptor

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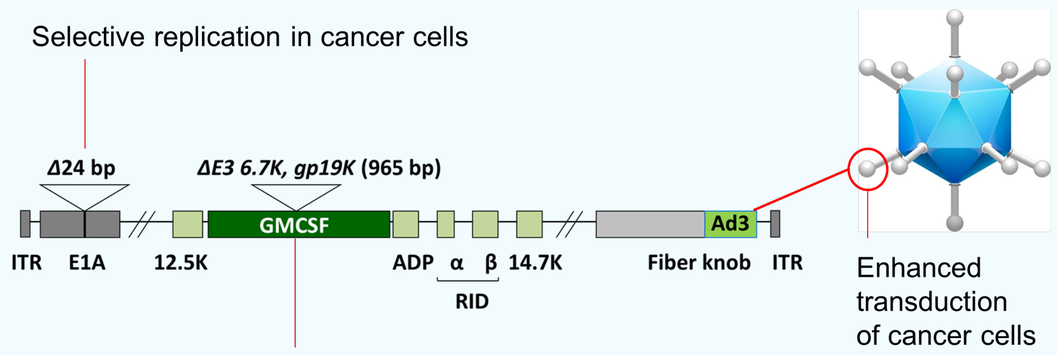
INTRODUCTION

Ovarian cancer is one of the most common cancers in women and ranked as third after cervical and uterine cancer. Importantly ovarian cancer has the worst prognosis and the highest mortality rate. Even though ovarian cancer has a lower prevalence compared to breast cancer, it is three times more deadly, and it is predicted that, by the year 2040, the mortality rate will rise significantly worldwide. The high mortality rate of this cancer is also caused by asymptomatic and secret growth of the tumor, that delays symptoms and consequently diagnosis. Therefore, ovarian cancer has been named as a silent killer.

ONCOS-102 is a serotype 5 adenovirus, comprising a chimeric capsid for enhanced gene delivery to cancer cells and a 24 bp deletion in Rb binding site of E1A region for cancer cell restricted replication. ONCOS-102 is armed with granulocyte-macrophage colony-stimulating factor (GM-CSF) for an enhanced immunostimulatory effect (**Fig. 1**). ONCOS-102 treatment is a promising immunotherapy strategy for advanced cancer as it directly recruits antigen presenting cells (APC) at tumor site leading to an induction of an adaptive tumor-specific CD8+ T cell response (**Fig. 2**). Previously we have shown in the phase I clinical study (NCT01598129) that repeated administration of ONCOS-102 to a patient with chemotherapy refractory ovarian cancer induced CD8+ anti-tumor immune responses with overall survival reaching 40 months.

Fig. 1. Schematic representation of ONCOS-102.

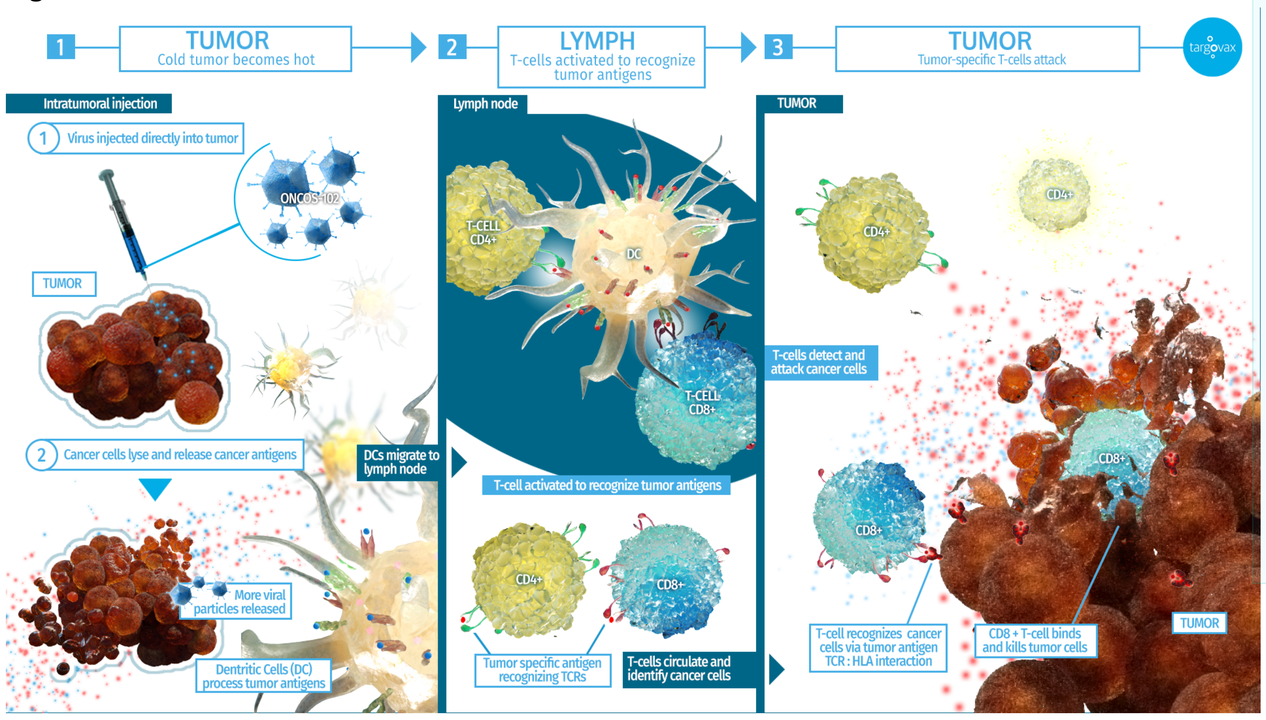


PURPOSE OF THE STUDY

The aim of the study was to assess the role of the dominant receptor desmoglein-2 (DSG2) used by ONCOS-102 in four established epithelial ovarian cancer (EOC) cell lines in order to investigate the cell entry MoA of ONCOS-102.

ONCOS-102 MoA

Fig 2. Mechanism of Action of ONCOS-102.



METHODS

Cytotoxicity *in vitro* – efficacy studies

Oncolytic efficacy was determined with the MTS cell viability assay at 96 hours post-infection. Briefly, the human ovarian cell lines were plated at $2x10^3$ cells/well in 96 flat bottomed tissue culture plates and incubated at 37°C. Cells were either incubated with no viruses (control) or infected with ONCOS-102 at 0.1, 1, 10, 100, or 1000 VP/cell in triplicate.

Receptor expression analyses

Flow cytometry was used to quantify the cell surface expression of the three receptors for adenovirus: CAR, CD46, and DSG2. DSG2 and CD46 cell surface expression were measured on the four human ovarian carcinoma cell lines.

RESULTS

DSG2 was nearly absent in A2780 cells but was expressed in >90% of OAW42, OVCAR3, and OV-90 cells. After 96 hours, ONCOS-102 treatment showed significant oncolytic activity (≧50%) in OAW42, OVCAR3, and OV-90 cells, but minimal activity in A2780 cells, suggesting DSG2 as the dominant receptor for ONCOS-102. Furthermore, retrospective analyses of a phase I clinical trial of ONCOS-102 treatment of 12 patients with varied tumors indicated a correlation between viral genomes in blood and DSG2 RNA expression. These data support the role of DSG2 expression on cancer cells in virus infectivity and the continued development of ONCOS-102 for ovarian cancer treatment (NCT02963831) (**Fig. 3**).

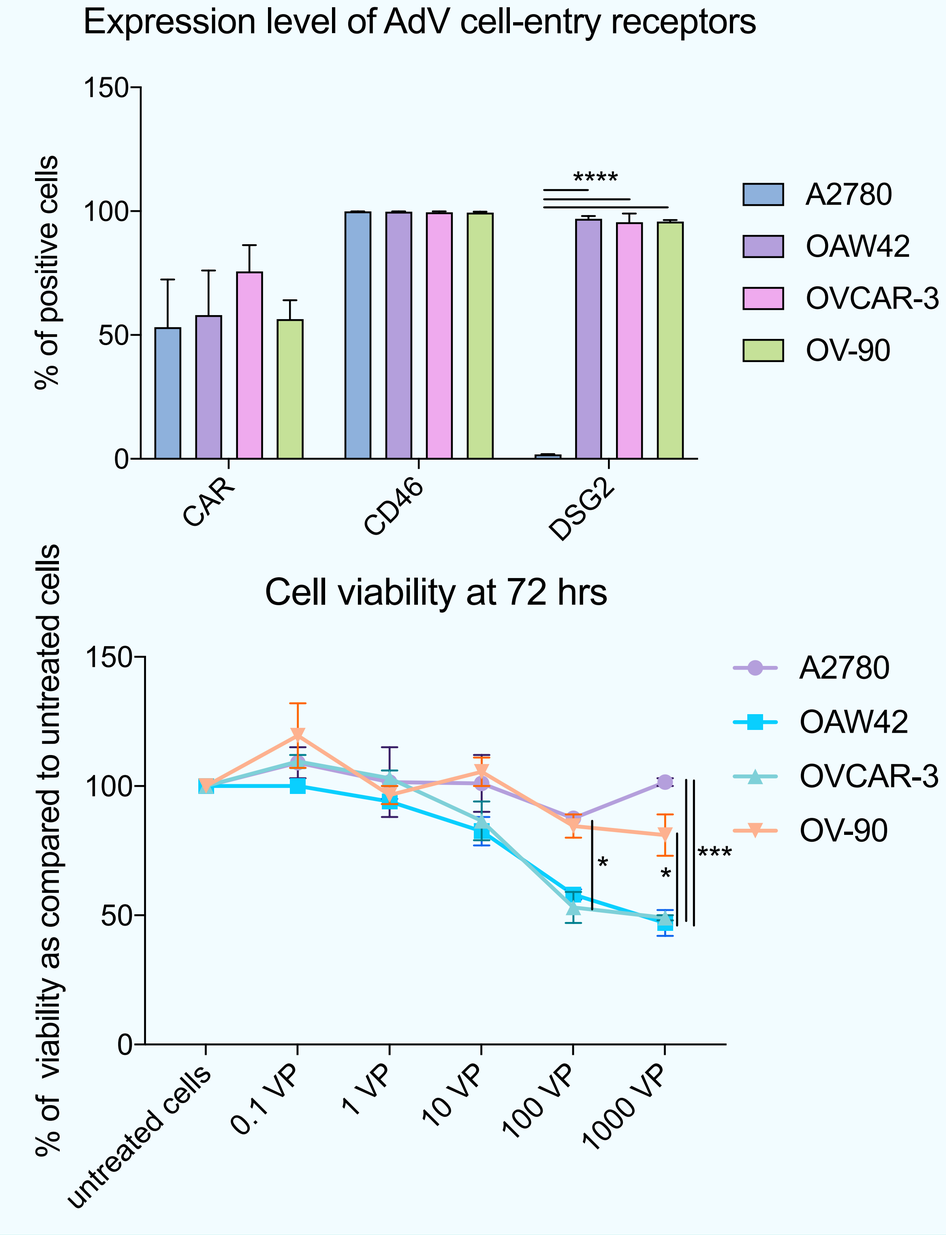


Fig. 3. A: Expression level of AdV cell entry receptors. B: Cell Viability on the four ovarian cells lines. Results are expressed as mean +/- SEM and % of untreated cells. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

CONCLUSIONS

- DSG2 might be the dominant receptor for ONCOS-102.
- These data support the role of DSG2 expression on cancer cells in virus infectivity and further development of ONCOS-102 for ovarian cancer treatment (NCT02963831).

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