Antitumor-specific T-cell responses induced by oncolytic adenovirus ONCOS-102 in peritoneal mesothelioma mouse model

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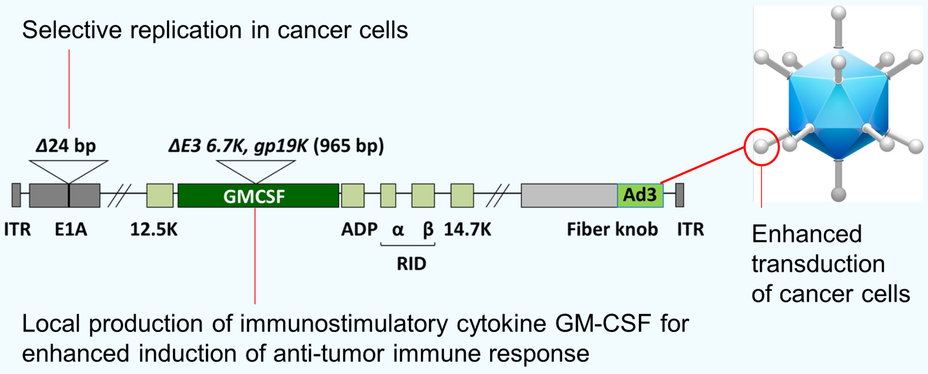
INTRODUCTION

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 adaptive tumor-specific CD8+ T cell response (Fi.g 2). Its immunological activity has already been demonstrated in Phase I clinical study. In this phase 1 study, local treatment of pleural mesothelioma with ONCOS-102 induced a systemic antitumor CD8+ T-cell response, prominent infiltration of CD8+ lymphocytes and Th1 type polarization.

Fig. 1. ONCOS-102

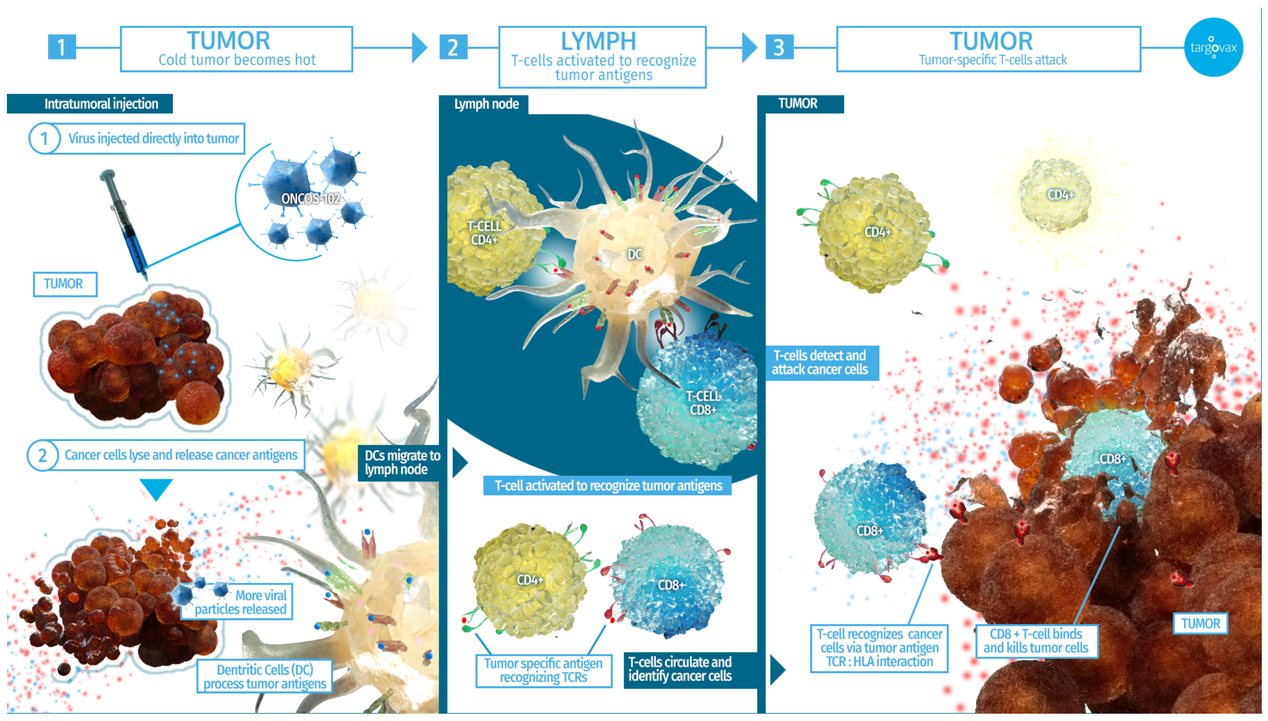


PURPOSE OF THE STUDY

The aim of this study was to evaluate anti-tumor immune properties of ONCOS-102 in peritoneal mesothelioma mouse bearing the mesothelin tumor cells.

ONCOS-102 MoA

Fig 2. Mechanism of Action of ONCOS-102.



METHODS

Mesothelioma xenograft mouse model

Mesothelioma murine cell line AB12 (positive for mesothelin antigen) was implanted intraperitoneally (5×10^5 cells/200 µL) in BALB/c mice (2 groups: 1 treated with ONCOS-102 and the other with PBS; n = 6 mice). Repeated intraperitoneal injections of 1×10^{11} oncolytic adenoviral particles/200 µL were given on days 0, 3, and 6 after tumor formation. Tumor size was measured with caliper on 2 dimensions on day 20.

IFN-γ ELISPOT

At endpoint (day 20), spleens and isolated to determine counts of T-cells responding to mesothelin, human adenovirus 5 E1A, and hexon peptides by secretion of IFN-γ. Harvested splenocytes were stimulated with peptide pools of the complete murine mesothelin protein sequence, human adenovirus 5 E1A, and hexon proteins. IFN-γ production by T-cells was evaluated by using IFN-γ ELISPOT.

RESULTS

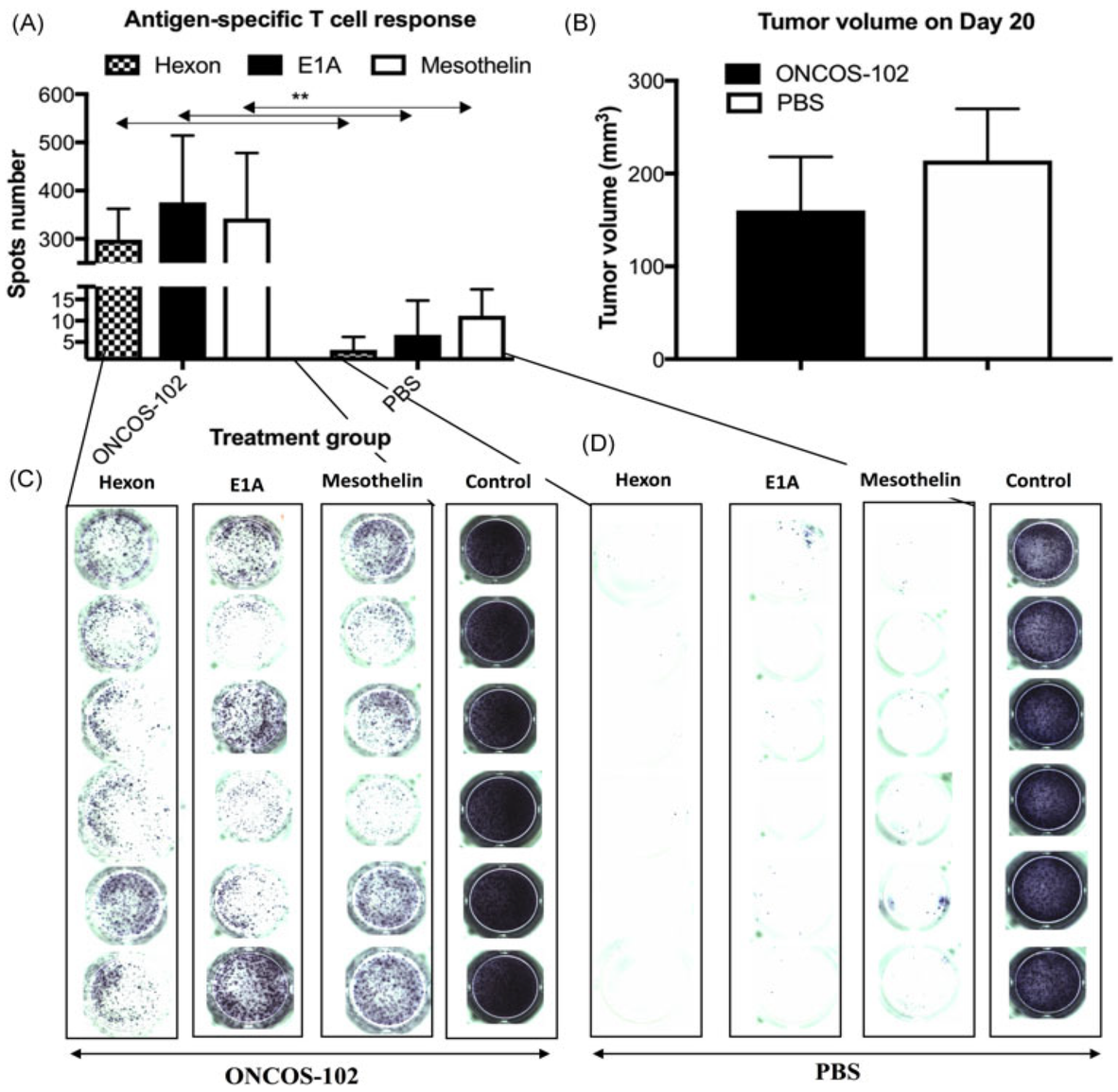


Fig. 3 IFN-γ ELISPOT. (A) Antigen-specific T-cell response. IFN-γ ELISPOT was performed with splenocytes from untreated and ONCOS-102-treated mice to determine the specificity of tumor-related T-cells for the antigen mesothelin tumor treated with ONCOS-102. **(B)** Mesothelioma murine cell line AB12 was implanted intraperitoneally ($5x10^5$ cells/200 µL) in BALB/c mice (2 groups: 1 treated with ONCOS-102 and the other with PBS; n = 6 mice). **(C)** Left panels for the tumor treated with ONCOS-102 and **(D)** PBS, respectively, stimulated with hexon pool, E1A pool (haplotype b), mesothelin pool, PMA, and Ionomycin, respectively (positive control). Error bars, mean ± SD: *p < .05, **p < .01, ***p < .001.

CONCLUSIONS

- We have reported anti-tumor immune activation properties of ONCOS-102 through its ability induce tumour specific T cells (mesothelin T cells) (Fig. 3).
- We also demonstrate the effectiveness of the ELISPOT assay to detect the induction of T-cells recognizing mesothelin, hexon, and E1A antigens in ONCOS-102-treated mesothelioma-bearing BALB/c mice.
- The ELISPOT assay could be useful to monitor the progress of therapy with ONCOS-102.

Adenoviruses as novel clinical treatments (ADVance)
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