Overcoming Triple-Negative Breast Cancer (TNBC) Resistance To Oncolytic Virotherapy By Histone Deacetylase Inhibitor, Trichostatin A

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INTRODUCTION

Triple-negative breast cancer (TNBC) is a tumor classification that lack receptors for the hormones estrogen, progesterone and HER2 protein. These malignancies are characterized to be of poor prognosis, refractoriness to conventional therapy and high rates of recurrence. Virotherapy with oncolytic adenovirus (OAd) consists of cancer selective viruses that replicate, spread, and kill cancer cells by oncolysis, without affecting the normal cells..

OBJECTIVE

To determine if the histone deacetylase inhibitor TSA in combination with oncolytic adenoviruses can potentiate its antitumoral efficacy on TNBC cells.

METHODS

Human TNBC MDA-MB-231, MDA-MB-157 and HCC1937 cells were infected with an OAd expressing the red fluorescent protein mCherry (OAdmCherry), or with a replication-defective adenovirus expressing green fluorescent protein (AdGFP) as a control to evaluate its infectivity and oncolysis effect. The sensitivity of these cells for OAds infection and TSA treatment was evaluated by determining the IC50 using an alamarBlue viability cell assay. After individual therapies, we tested a combined treatment to attempt to increase viral potency and oncolysis.

RESULTS

TNBC cell lines showed partial resistance to OAd therapy. TSA decreased cells viability in a dose-dependent manner. After combining both therapies we could identify an additive toxicity effect over TNBC cells. This increased OAd efficacy can be partially explained by and increase of viral infectivity over the cells, related with an upregulation of the Coxsackie adenovirus receptor as TSA concentration was increased.

CONCLUSIONS

Our data suggests that TSA can be used to enhance oncolytic virotherapy on TNBC, overcoming the natural resistance of these cells to adenoviral infection which may be applied as a complementary approach to destroy TNBC tumors in patients.

RESULTS

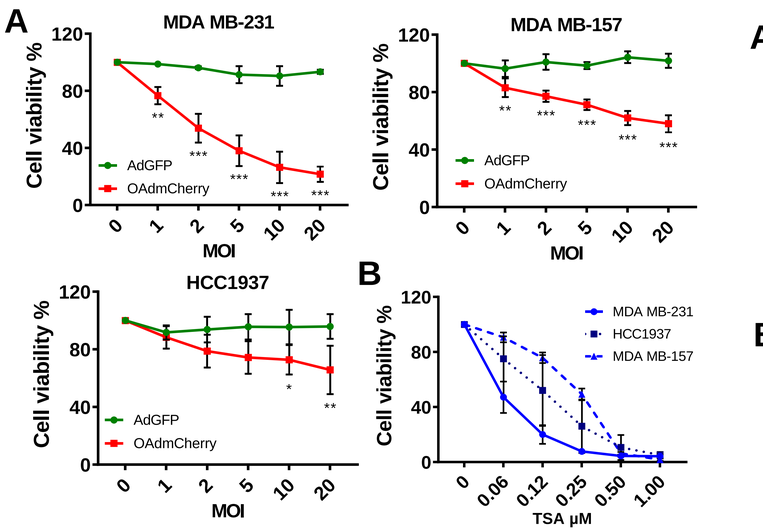

Fig. 1 Viability of TNBC cell lines after treatment with OAd's or TSA. A) Effect over TNBC cell's viability after treatment with the control (non-oncolytic) AdGFP and the oncolytic OAdmCherry . **B)** Decrease of viability at increasing doses of TSA on the TNBC cells. AlamarBlue assay.

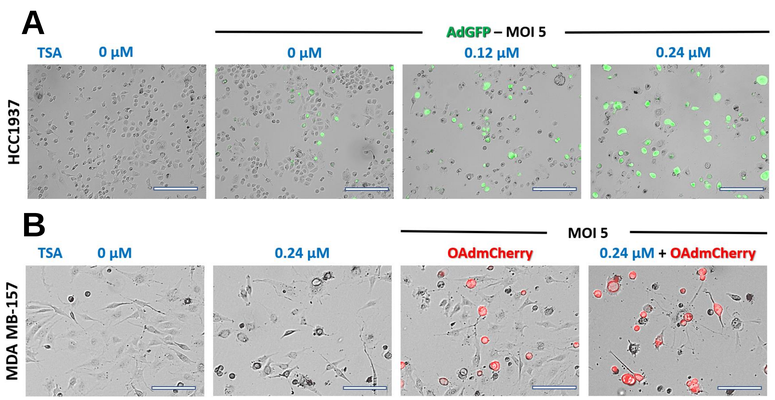

Fig. 3 Fluorescent detection of increased viral infection after TSA treatment. A) Increasing concentrations of TSA allow for more internalization of the AdGFP. **B)** Morphological changes attributed to cellular death is more noticeable in the combination of TSA + OAdmCherry than the single therapy.

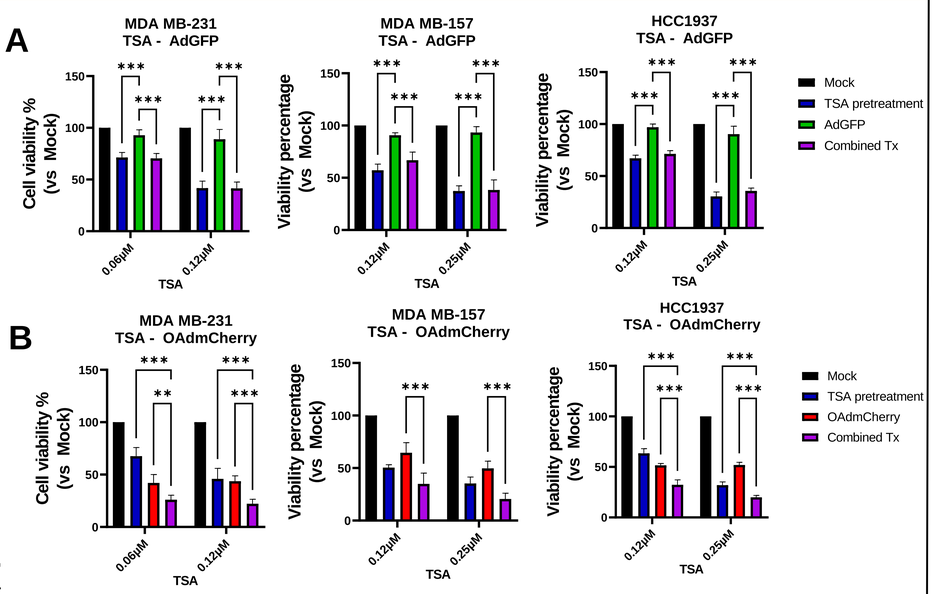

Fig. 2 The combined therapy with TSA + Oncolytic virus overcomes the resistance of TNBC to treatment. A) The control AdGFP has not increased toxic effect over TSA-pretreated cells. **B)** Pretreatment with TSA potentiates the oncolytic effect of the OAdmCherry. AlamarBlue assay.

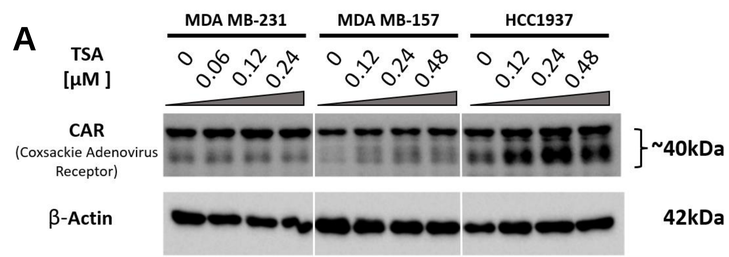

Fig. 4 Coxsackie adenovirus receptor is upregulated by TSA in a dose-dependent manner. A) WB showing a higher detection of the CAR protein as the dose of TSA is increased in the individual TNBC cell lines. β-Actin was used as housekeeping.

ACKNOWLEDGEMENTS

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