

IMMUNE MODULATION BY TARGETED THERAPIES INCREASES ONCOLYTIC VIRAL THERAPEUTIC ACTIVITY IN LUNG CANCER

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INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide, and non-small cell lung cancer (NSCLC) accounts for 85% of its diagnoses [1]. Despite paradigm shifting targeted (personalized/precision) opportunities for a select group of patients, current treatments have failed to improve the five-year survival rate of only 16.3% [2]. Enhancing the host immune systems' ability to combat NSCLC has been an unrealized goal for decades.

Conventional radiotherapy and chemotherapy have a low therapeutic window, causing detrimental effects to both tumor and healthy cells alike. Furthermore, an increasing level of immunosuppressive regulatory cells in the tumor microenvironment and inadequate cytotoxic T-lymphocytes mediated anti-tumor activity characterize tumor progression, making the enhancement of the host immune system's ability to combat NSCLC crucial [3]. With recent studies indicating sunitinib's role in inhibiting immunosuppressive cells in the tumor microenvironment and reovirus' oncolytic, immunostimulating properties in targeting tumor cells, this investigation aims to explore the potential of combining reovirus and sunitinib as a novel therapy for NSCLC [4].

METHODS

Reovirus and sunitinib effective dose 50 (ED50) were determined for human NSCLC cell lines A549, H460, H1299, and H1975 by exposing each to varying concentrations of reovirus or sunitinib for 48 hours, and quantifying absorbance with WST-1 reagent at 450nm. % viability was used to generate dose response curves, and CalcuSyn software was utilized to calculate ED50. Each cell line was then exposed to reovirus, sunitinib, or combination at ED50, ½ ED50, or ¼ ED50 for 48 hours. 20µM was used as ED50 for sunitinib resistant cell lines. Absorbance at 450nm upon WST-1 exposure was read, and combination index (CI) was calculated using CalcuSyn. Each experiment contained at least 3 replicates and was repeated 3 times. CI<1 indicates synergistic effects, CI=1 indicates additive effects, and CI>1 indicates antagonistic effects.

RESULTS

Reovirus and sunitinib ED50 values for A549, H460, H1299, and H1975 cells were 15.29±0.99MOI and 17.12±2.62µM, 238.02±41.29MOI and 11.27±1.52µM, 6.85±2.39MOI and resistant, and 19.80±20.35µM and not determinable, respectively. CI values for all cell lines were < 1 at ED50.

DISCUSSION AND CONCLUSIONS

In the present *in vitro* study, we have demonstrated that sunitinib and reovirus combination therapy results in synergy in NSCLC cells. This promising investigation establishes the preclinical foundation for further investigations into reovirus and sunitinib as a novel combination therapy to treat NSCLC. Following *ex vivo* and *in vivo* investigations, it is anticipated that this study will culminate into a human clinical trial.

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