Synergistic inhibition of tumor growth and overcoming resistance in Lung Cancer by combining novel dual-targeting DNA-alkylating/HDAC inhibitor with Tumor Suppressor NPRL2- and p53-nanoparticles

Shaoyu Yan, Jing Lin, Kai Xu, Gitanjali Jayachandran, Yuichi Watanabe, Qiufo Ge, Yaodong Wu, Dianwu Guo, Yi Chen, Jack A. Roth, and Lin Ji

Department of Thoracic & Cardiovascular Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX

INTRODUCTION

DNA alkylating agents such as platinum and nitrogen mustard are effective cancer chemotherapeutics. They kill proliferating tumor cells by inducing high levels of DNA damage leading to cell-cycle arrest and cell death. However, their highly toxic side effects and the common drug resistance exhibited in tumors limit their anticancer efficacy and clinical benefits. Here we describe a novel anticancer therapeutic strategy using a new class of rationally designed dual DNA alkylating/HDAC inhibitors combined with nanoparticle-mediated gene therapy targeting the DNA damage/repair pathway in human NSCLC and SCLC cells.

RESULTS

Molecular Docking and Inhibition of HDAC Enzymatic Activities by NL-101, a Potent pan-

Sensitivity/Profiles of NL101, Bendamustine, Cisplatin, Carboplatin, and Paclitaxel in Lung Cancer Cell Lines

Pan-DAC Inhibition Interferes with the Multiple Hallmarks of Human Cancer

Enhanced inhibition on the tumor cell-induced clonogenicity by combination treatment with NL101 and DC-NPRL2 and DC-p53 Nanoparticles in H1299 Cells

Synergistic inhibition on tumor cell growth in SCLC H69 and GL16 cells by Combination Index (CI) plot analysis

MATERIALS AND METHODS

Rational Design of Novel Dual-targeting DNA-alkylating Nitrogen Mustard/HDAC Inhibitor NL101

DNA Damage/Repair Pathway-Targeted Therapeutic Strategy with NL101 and DC-NPRL2- and p53-Nanoparticles

We evaluated the therapeutic effects of NL101 on tumor cell proliferation in a panel of more than 50 human NSCLC and SCLC cell lines.

We analyzed the NL101-induced DNA damage by Comet assay and DNA-damage-induced apoptosis by an anti-ssDNA antibody-based apoptosis assay by FACS in NSCLC cells.

We explored treatment strategies of combining NL101 with tumor suppressor genes NPRL2, a regulator of the DNA damage checkpoint pathway, and p53, a regulator of apoptosis and drug resistance in the DNA damage/repair pathway, on tumor cell proliferation and tumor cell-induced clonogenesis in lung cancer cells.

We analyzed the effect of NL101 on enzymatic activities and protein expression of HDACs and the correlation of NL101 sensitivity phenotype with expression of HDAC and cancer stem cell ALDH1 biomarker in lung cancer cell lines.

CONCLUSION

A combination treatment using a novel dual targeting DNA alkylating /HDAC inhibitor with pro-apoptotic tumor suppressor genes in the DNA damage/repair signaling pathway will enhance chemotherapeutic sensitivity, promote anti-cancer therapeutic synergism, overcome drug resistance, and block tumor progression and relapse by targeting potential cancer stem cells.

* Supported by grants P50CA78970, RO1 CA-116322, and W81XWH0920139