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NFKB signaling pathway as a therapeutic target in chemoresistant ovarian cancer

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Despite advances in surgical debulking and chemotherapy regimens, epithelial ovarian cancer (EOC) has exhibited marginal improvement in survival. Although the majority of patients with EOC achieve a clinical remission after induction therapy, over 80% relapse due to resistance to chemotherapies. In this regard, it is of paramount importance to devise novel therapeutics aimed at quelling the signaling pathways responsible for chemotherapeutic resistance in EOC. NFKB signaling pathway plays important roles in different hallmarks of cancer including chemoresistance, tumor growth and dissemination in human malignancies. In the EOC cells, enhanced phosphorylation and activation of NFKB correlates with tumor cell survival, proliferative and invasive capacities of these cells. Altogether, these seminal studies suggest that NFKB is an attractive preventive and therapeutic target in EOC. Cell proliferation, colony formation and anoikis resistance assay were performed to evaluate the effects of Bay11-7082 on cell viability. ELISA assay was carried out to measure phospho-NFKB in EOC cells. Quantitative reverse transcription-PCR was conducted to measure the effects of Bay11-7082 on expression of *Il6, Il6R, BIRC2, BCL2L1, CCND1, BIRC5, FOXO3, BAX, CDKN1A, PUMA, VEGFC, ICAM-1, CDH-1* and *MMP2*. Propidium iodide (PI)/ Annexin V was performed to measure the effects of Bay11-7082 on induction of apoptosis. Zymo-analysis was done to explore the effects of Bay11-7082 treatment on MMP2 activity of the chemoresistant ovarian carcinoma cells. All data were evaluated in triplicate against untreated control cells and collected from three independent experiments. Data were graphed and analyzed using GraphPad Prism Software 6.0 using one-way ANOVA and the unpaired two-tailed Student's t test. All data are presented as mean±standard deviation (SD). In this report, we showed that phosphorylation of the NFKB factor is higher in therapy-resistant EOC cells compered to sensitive ones. Constitutive activation of NFKB correlated with drug resistance and Bay11-7082, an inhibitor of NFKB, strongly inhibit the proliferation of the chemoresistant EOC cells through an induction of apoptosis. Synergistic activity of Bay11-7082 with Taxane-based and Platinum-based drugs suppressed proliferation, migration and clonogenicity abilities of OVCAR3, SKOV3 and A2780CP cells via inhibition of activation of NFKB. Furthermore, Bay11-7082 reduced invasive potentials of the EOC cells through reduction of matrix metalloproteinase-2 (MMP2) and suppression of anoikis resistance. These results suggest that Bay11-7082 is a potential anti- cancer drug to overcome chemoresistance and inhibit proliferative and invasive characteristics of the EOC cells that exhibit platinum based chemoresistance.

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