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J Cancer Sci Ther 2017, 9:11 (Suppl)
DOI: 10.4172/1948-5956-C1-118

EGFR blockade reverses chemo resistance in human ovarian carcinoma cells

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Epithelial ovarian cancer (EOC) is the most fatal gynecological malignancy worldwide. Despite improvements in cytoreductive surgery and primary chemotherapy, the majority of patients with advanced disease relapse and exhibit cross-resistance to chemotherapeutic drugs. Recurrent EOC is currently an incurable disease and overcoming drug resistance is the key to successful treatment. There is therefore an urgent need for effective treatments to circumvent chemo resistance in the EOC. In this report, we showed that treatment of the EOC cells with a wide range of chemotherapeutics including cisplatin, carboplatin, gemcitabine, vincristine and doxorubicin as well as monoclonal antibodies such as bevacizumab induces EGFR ligands such as heparin-binding epidermal growth factor (HB-EGF). Amphiregulin (AREG) and Epiregulin (EREG) is a phenomenon which was abrogated when the cells were pre-treated with the anti-EGFR mAb cetuximab. Moreover, these findings show that pre-treatment of the cells with gefitinib (EGFR small molecule inhibitor), Buparlisib (a pan-PI3K inhibitor), Trametinib (a MEK1/2-specific inhibitor) and bay 11-7082 (inhibitor of NF- κB) hindered chemotherapy-mediated EGF-like growth factors induction and synergistically re-sensitized the chemo resistant cells to cisplatin. Altogether, these data suggest that EGFR mediates stress-induced expression of its ligands and thereby chemo resistance in the EOC cells via activation of its down-stream pathways such as ERK1/2, AKT and NF-κB.

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