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ELUCIDATING THE UNDERLYING MECHANISM OF CSC ENRICHMENT BY PLATINUM TREATMENT IN EPITHELIAL OVARIAN CANCER CELLS: A STORY JUST BEGINS TO UNFOLD

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High grade serous epithelial ovarian cancer (HGSOC) is notoriously known for high recurrence and mortality due to acquirement of chemoresistance. Both chemonaive and platinum sensitive relapse cases of HGSOC patients are treated with cisplatin/carboplatin with or without other drugs as a standard therapy regime for last two decades. Unfortunately, both cases eventually develop platinum resistance and succumb to the disease. Whether and how repetitive exposure of platinum drugs in cancer cells creates enriched drug resistant cancer stem cells like fate has not been explored in detail. To decipher this molecular mechanism, we looked into IGF1R-PIK3CA-AKT signalling pathway alteration during acquirement of platinum resistance in indigenously developed chemoresistant cellular models. Increased CSC-marker expression, side population, spheroid formation were observed during the course of resistance acquirement. Interestingly, CSC like SP cells which are in early phase of resistance development demonstrated faster tumorigenic potential than CSC like SP cells isolated from late resistant phases (Singh et al, Scientific Reports, 2016). This late resistant cells contain maximal percentage of CSCs and other characteristics of stem cells. Using a DNA-protein pull down assay, we identified NF- B as a prime transcriptional regulator of PIK3CA-Akt signalling in these late cisplatin resistant cells and their corresponding SP cells after cisplatin treatment. Along with PIK3CA, NF-κB also escalated TNFα expression specifically in SP fraction upon cisplatin treatment. Our data conclusively showed that this CSC-specific NF-κB-TNFα-PIK3CA bi-modal loop, on one hand, maintains persistent activation of NF-κB through TNFα- NF-κB autocrine loop, while NF-κB-PIK3CA loop nurtures CSC population under cisplatin treatment. Overall, activation of PI3K/AKT and NF-κB signaling in resistant cells favours survival and enrichment of CSCs by acquiring anti-apoptotic, quiescent state (Thakur and Ray, J. of Exp. Clin. Cancer Res., 2017). In order to explore a mode to inhibit enrichment of CSC with progression of resistance, we developed chemoresistant cellular model treated with platinum-taxol along with Metformin, a known anti-diabetic drug. Intriguingly, concurrent treatment of metformin with platinum-taxol significantly reduced the CSC like side population (32% vs. 10%) and the resistance properties (92% to 70%) of these cells. Further studies are ongoing to understand the alleviating effect of Metformin on platinum resistance with a special emphasis on NF-B-TNFα-PIK3CA bi-modal loop present in platinum resistant ovarian cancer cells.

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