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Abstract 4525: Hypoxia signaling pathway plays a role in ovarian cancer chemoresistance

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Abstract

Hypoxia-inducible factor 1 (HIF-1) is a basic helix-loop-helix transcription factor that when induced regulates the expression of many genes involved in cytoprotective stimuli, which attenuates apoptosis and improves survival.. Increased expression of HIF-1 α gene (HIF1A) has been found in several carcinomas, including ovarian cancer. Ovarian cancers are generally refractory to platinum-based chemotherapy. Despite the large number of studies, molecular events that govern the emergence of aggressive therapy-resistant cells after chemotherapy are poorly defined. Genomic instabilities, such as copy number variation(CNV), may play an important role in chemoresistance and have been implicated in many complex diseases, like cancer.. We analyzed CNV data that is publically available through the Cancer Genome Atlas and others. Of particular interest was the transcription factor HIF1A which plays an integral role in oxidative stress response such as those induced by chemotherapy reagents. The present study provides evidence for the rare escape of tumor cells from drug-induced cell death by entering a non-cycling senescent state. We report the adaptive response of human ovarian surface epithelium cells to CoCl₂, a chemical hypoxia-mimicking agent resulting in a senescent-like state of chemoresistant cells. The effect of the treatment was evaluated on CNV of HIF-1 α gene expression, cell proliferation, survival, and tumor invasiveness. We show here that CNV duplication events of HIF1 α results in an oxidative stress response in cells leading to chemoresistance through the induction of cellular senescence. Understanding the molecular events associated with chemoresistance will ultimately lead to better patient treatment and outcomes.

Note: This abstract was not presented at the meeting.