IDENTIFICATION OF CISPLATIN-RESISTANCE RELATED GENES IN OVARIAN CLEAR CELL CARCINOMA USING 3D CELL CULTURE SYSTEM

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INTRODUCTION: Ovarian clear cell carcinoma (OCCC) is well known for its higher prevalence in Asian women and poorer prognosis as compared with other histotypes of epithelial ovarian cancer (EOC) due to higher rate of resistance to platinum based chemotherapy. However, the underlying mechanism has not been fully understood. Three-dimensional (3D) cell culture system with extracellular matrix components mimics the in vivo microenvironment and provides more accurate drug responses than two-dimensional (2D) monolayer cell culture. In this study, we adopted 3D cell culture system to study drug responses and to identify cisplatin-resistance associated genes.

MATERIAL AND METHOD: 3D cell culture system utilizing Geltrex® Matrix was developed to test cisplatin responses in a panel of OCCC cell lines and advanced serous ovarian cancer cell lines and compare with conventional 2D system. To further delineate the cell signaling associated with this drug response,the gene profiling analysis (Human Transcriptome Array 2.0) of OCCC cell line TOV-21G cells cultured in 2D and 3D system has been adopted.

RESULTS AND DISCUSSION: Ovarian cancer cell lines underwent morphologic changes in 3D cell culture system and showed remarkable higher cell survival ability upon cisplatin treatment than 2D cell culture system. Western Blot analysis using cleaved PARP and cleaved Caspase3 as well as TUNEL assay demonstrated that ovarian cancer cells including both OCCC and advanced serous cancer cells exhibited lower

apoptotic rates in 3D cell culture system than 2D system against cisplatin treatment. Gene expression analysis revealed 120 up-regulated (>2.0-fold) genes and 323 down-regulated (>2.0-fold) genes in OCCC cells cultured in 3D cell culture system. The involved signaling pathways including regulation of cell cycle, DNA damage response, cell metabolism, autophagy, ErbB signaling and G Protein-Coupled Receptors signaling were significantly altered.

CONCLUSION: These results demonstrated that 3D spheroids of OCCC and advanced serous cell lines exhibited higher cisplatin-resistance than 2D system through dysregulation of numerous signaling pathways concerning different aspects of cell survival. This dysregulation may be generated by intrinsic modification and interaction with extracellular matrix. To study the underlying molecular mechanisms of matrix-mediated cellular changes, further studies to analyze the putative targets of the related signaling are warranted.