Marcela Chmelarova et al., Hereditary Genet Curr Res 2018, Volume 7
DOI: 10.4172/2161-1041-C1-003

Role of DNA methylation in resistance to platinum-based chemotherapy in ovarian cancer cells

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Statement of the Problem: Ovarian cancer is the leading cause of death from gynecological tumors. The current standard treatment consists of cyto reductive surgery followed by chemotherapy, alternatively biological treatment. For chemotherapy treatment the combination of platinum derivatives with taxane are used. However, 20-40% of the patients exhibit primary drug resistance. Carcinogenesis includes genetic changes but also epigenetic deregulation. One of the most commonly occurring epigenetic events taking place in the mammalian genome is DNA methylation. Furthermore, DNA methylation in solid tumors has been associated with resistance to therapy and poor prognosis. Hence, hypermethylation is an attractive target for treatment in order to influence tumor biology and potentially to overcome therapy resistance. The objective of our project was to identify DNA methylation changes associated with platinum resistance.

Methodology & Theoretical Orientation: To search for DNA methylation changes in selected genes (*GATA4, HNF1B, CDH13 and CDH1*) we used bisulfite next generation sequencing and then we compare the methylation status in cisplatin sensitive/resistant A2780 ovarian cancer cell lines. Furthermore, we tested the effect of de-methylating agent (zebularine) on reversal of platinum chemoresistance.

Findings: Our experiments detected elevated methylation in selected genes in cisplatin resistant cell line A2780cis compared to cisplatin sensitive cell line A2780, which supports the theory that DNA methylation is connected to chemotherapeutics resistance, especially to cisplatin. Moreover, we found that zebularine affected methylation status and sensitivity to cisplatin.

Conclusion & Significance: Epigenetic deregulation of selected adhesion molecules and transcription factors is involved in chemoresistance of ovarian cancer. These findings could potentially be used in development of new treatment strategies for ovarian cancer and may have implications in prediction of chemotherapy resistance in ovarian cancer patients.

Figure 1: Hypothesis of epigenetic regulation of platinum resistance in ovarian cancer cells and possible prediction of platinum resistance in HGSCO (High-grade serous ovarian cancer)

Recent Publications:

1. Barton C A, Hacker N F, Clark S J and O'Brien P M (2008) DNA methylation changes in ovarian cancer: implications for early diagnosis, prognosis and treatment. Gynecologic Oncology 109(1):129-39.
2. Ferlay J, Steliarova Foucher E, Lortet Tieulent J, Rosso S, Coebergh J W, Comber H, Forman D and Bray F (2013) Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. European Journal of Cancer 49(6):1374-403.
3. Zeller C, Dai W, Steele N L, Siddiq A, Walley A J, Wilhelm Benartzi C S, Rizzo S, van der Zee A, Plumb J A and Brown R (2012) Candidate DNA methylation drivers of acquired cisplatin resistance in ovarian cancer identified by methylome and expression profiling. Oncogene 31(42):4567-76.

4. Lund R J, Huhtinen K, Salmi J, Rantala J, Nguyen E V, Moulder R, Goodlett D R, Lahesmaa R and Carpén O (2017) DNA methylation and transcriptome changes associated with cisplatin resistance in ovarian cancer. Scientific Reports 7(1):1469.
5. Fang F, Cardenas H, Huang H, Jiang G, Perkins S M, Zhang C, Keer H N, Liu Y, Nephew K P and Matei D (2018) Genomic and epigenomic signatures in ovarian cancer associated with resensitization to platinum drugs. Cancer Research 78(3):631-644.

Biography

Marcela Chmelarova has her expertise in cancer epigenetics. Ever since she started her PhD studies, her work has been mainly focused on evaluation of DNA methylation changes primarily in gynecological cancer. She has years of experience in basic research, data evaluation and she actively engages in teaching in her home institutions of University Hospital Hradec Kralove and Charles University-Faculty of Medicine in Hradec Kralove. Recently her team started more vigorously, to explore mechanisms of platinum based resistance in ovarian cancer among other topics of cancer epigenetics.

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