ABSTRACT

Methylomic deep sequencing of ovarian cancer reveals diagnostic and prognostic signatures

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Background: The heterogeneity of ovarian cancer requires biomarkers for personalized medicine. DNA methylation aberration is a hallmark of cancer. The attempt of using DNA methylation as biomarkers for prognosis prediction is appealing. Methylomic analysis using next generation sequencing technology has never been applied in ovarian cancer research. The present study for the first time is to explore the methylomics of ovarian cancer using this cutting edge technology.

Materials and Methods: With the advancement of high throughput technology, we are now able to assess global DNA methylation of ovarian cancer using methyl-DNA capture coupled with next-generation sequencing (MethylCap-seq) technology. Logistic regression, Cox regression and Kaplan–Meier survival function were used to estimate the clinical relevance of differential methylation signature (DMS) in ovarian cancer.

Results: We analyzed the methylomic landscapes of malignant (N=75), benign (N=20) ovarian tumors and normal ovarian tissues (N=6). We identified 577 tumor differential methylation signatures (t-DMS) between malignant and benign/normal ovarian tissues. Stringent criteria filtration of these 577 DMRs resulted in 67 DMRs which can discriminate tumorous from non-tumorous patients with 91% accuracy. These 577 DMRs were subjected to survival analysis using Kaplan–Meier method and Cox proportional hazard model. A prognostic differential methylation signatures (p-DMS) constituted by 55 DMRs significantly correlates with progression free survival (PFS). The high and low p-DMS confer the probability of PFS of 87.3% and 17.5%, respectively at 80 months (P < 0.001).

Conclusion: This comprehensive methylomic analysis provides a methylomic signature for prognosis prediction, which will be of great help for the personalized chemotherapy especially the use of demethylation agents of ovarian cancer patients. Further investigation of the functional relevance of candidate genes may lead to novel therapeutics for ovarian cancer.