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Blood MicroRNAs: Novel 'Omics' Biomarkers for Ovarian Cancer Early Detection

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Five-year survival rates of ovarian cancer will be over 90%, if the cancer is found at an early localized stage. However, from the American Cancer Society's data, only 20% of ovarian cancers are early diagnosed because there are often no obvious symptoms, until the disease has spread. Therefore, ovarian cancer is still the leading cause of death among gynecological cancers. Identification of novel biomarkers for early diagnosis could significantly improve clinical outcomes of ovarian cancer.

Recent studies have suggested that blood microRNA might serve as novel noninvasive biomarkers for ovarian cancer diagnosis. Blood samples are more easily accessible than solid organs, such as ovaries [1]. MicroRNA is a class of small (about 22 nucleotide long) non-coding RNAs. These small molecules negatively regulate the translation of messenger RNAs (mRNA) to target proteins by base pairing. Aberrant microRNA expressions were observed in many cancer types, including ovarian cancer, suggesting microRNA could be involved in the pathogenesis of cancer. Rosenfeld et al. [2] demonstrated that cancer-related microRNA is tissue-specific, which could identify the origin of cancer. Another important feature of microRNA is their biological stability [3]. MicroRNA are still stable, even in formalin-fixed, paraffin-embedded (FFPE) tissue samples. These features make blood microRNA particularly attractive as biomarkers for cancer diagnosis.

Recent advances in whole-genome RNA profiling techniques, such as expression microarray enable us to comprehensibly detect expression levels of microRNA on a genome-wide scale. A variety of blood microRNA differentially expressed in one specific types of cancer patients have been identified. The human disease miRNome project [4,5] (http://genetrail.bioinf.uni-sb.de/wholemirnomeproject/) is a good example. Häusler et al. [5] applied the microarray technique to determine microRNA expression levels in blood cells from 24 ovarian cancer patients and 15 healthy controls. 147 significantly differentially expressed microRNA were identified using the unpaired t-test at $P<0.05$. Seven microRNAs among them such as miR-191, miR-155 and miR-16 have been reported to be related to ovarian cancer. Using a set of 60 microRNA, ovarian cancer patients and healthy controls were discriminated with an accuracy of 76.3% (specificity was 83.0% and sensitivity was 69.7%). Additionally, more than 300 human blood cell samples from patients with other cancer types, including lung cancer, melanoma, prostate cancer, wilms tumors, tumor of stomach and pancreatic cancer were collected and analyzed in the human disease miRNome project. This project may allow us to develop specific blood microRNA biomarkers for ovarian cancer.

Human serum also contains a large amount of stable microRNA [6]. Some studies were performed to test whether the microRNAs directly from serum could have potential to diagnose ovarian cancer. Lodes et al. [7] analyzed genome-wide serum microRNA expression profiles of ovarian, prostate, colon, breast and lung cancer patients, and healthy controls using oligo nucleotide microarrays. It was shown that one milliliter of human serum was enough for microRNA expression level detection, without the PCR amplification. Hierarchical clustering of serum microRNA expression pattern could well separate cancer patients from normal controls. In another example, Resnick et al. [8] applied the TaqMan Array Human MicroRNA Panel, a type of real-time PCR-based microarray, to detect the expression levels of serum microRNA from 28 ovarian cancer patients and 15 healthy controls. Statistical analysis and RT-PCR validations showed that eight microRNA were significantly differentially expressed between patients and healthy controls. Five microRNA, mir-21, 29a, 92, 93 and 126 were up-regulated and three microRNA, mir-99b, 155 and 127 were down-regulated in cancer patients, compared to controls. Most of these eight microRNA have been proved to be oncomirs, microRNA with a role in cancer. The two projects showed that biologically meaningful microRNA expression patterns existed in the serum from ovarian cancer patients.

Conclusions and Prospective

There is an increasing interest to develop novel blood microRNA biomarkers for the noninvasive ovarian cancer diagnosis at the early stage. Many microRNA from blood cells or serum were shown to be associated with ovarian cancer, and these molecules could be molecular finger prints for cancer diagnosis. These results will be validated by larger patient cohort studies in the future. Positive data will pave the way for new ovarian cancer detection kits in clinical practice. On the other hand, the investigations of microRNA and their target genes might significantly enhance our understanding of the molecular mechanism of ovarian cancer, and identify new therapeutic strategies against the disease.

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