Identification of key genes associated with cervical cancer by comprehensive analysis of transcriptome microarray and methylation microarray

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Abstract. Cervical cancer is the second most commonly diagnosed type of cancer and the third leading cause of cancer-associated mortality in women. The current study aimed to determine the genes associated with cervical cancer development. Microarray data (GSE55940 and GSE46306) were downloaded from Gene Expression Omnibus. Overlapping genes between the differentially expressed genes (DEGs) in GSE55940 (identified by Limma package) and the differentially methylated genes were screened. Gene Ontology (GO) enrichment analysis was subsequently performed for these genes using the ToppGene database. In GSE55940, 91 downregulated and 151 upregulated DEGs were identified. In GSE46306, 561 overlapping differentially methylated genes were obtained through the differential methylation analysis at the CpG site level, CpG island level and gene level. A total of 5 overlapping genes [dipeptidyl peptidase 4 (DPP4); endothelin 3 (EDN3); fibroblast growth factor 14 (FGF14); tachykinin, precursor 1 (TAC1); and wingless-type MMTV integration site family, member 16 (WNT16)] between the 561 overlapping differentially methylated genes and the 242 DEGs were identified, which were downregulated and hypermethylated simultaneously in cervical cancer samples. Enriched GO terms were receptor binding (involving DPP4, EDN3, FGF14, TAC1 and WNT16), ameboidal-type cell migration (DPP4, EDN3 and TAC1), mitogen-activated protein kinase cascade (FGF14, EDN3 and WNT16) and cell proliferation (EDN3, WNT16, DPP4 and TAC1). These results indicate that DPP4, EDN3, FGF14, TAC1 and WNT16 may be involved in the pathogenesis of cervical cancer.

Introduction

Among women, cervical cancer is the second most commonly diagnosed type of cancer and the third leading cause of cancer-associated mortality (1). Worldwide, ~500,000 cervical cancer cases are diagnosed and 230,000 mortalities occur due to this disease annually (2). DNA methylation, a type of epigenetic event, may increase the risk of cervical cancer through regulating gene expression and chromatin structure (3). Methylated carcinogenic human papillomavirus (HPV) DNA may be used as a predictive and/or diagnostic biomarker for risk of cervical cancer (4). Sood et al (3) demonstrated that methylation of the genes myogenic differentiation 1, telomerase reverse transcriptase and Ras association domain family member 1 could predict a more favorable outcome in patients with invasive cervical carcinoma treated with standard chemoradiation therapy. Kalantari et al (5) reported that methylation of L2 and L1 genes in HPV16, 18, 31 and 45, and of the cellular death-associated protein kinase gene were considered biomarkers of the progression of cervical neoplasia. Furthermore, Nye et al (6) revealed that infection with high-risk HPV types was associated with differentially methylated regions in the paternally expressed 3 (PEG3) gene, and that PEG3 methylation status may have potential as a molecular marker for screening of cervical intraepithelial neoplasia. Numerous studies have reported that methylation of certain genes is associated with the pathogenesis of cervical cancer, while the mechanisms of development and progression of cervical cancer remain unclear (7,8).

Recently, microarray analyses have been performed to identify gene methylation, gene expression and RNA regulation in cervical cancer. Sun et al (9) analyzed differentially expressed long non-coding RNAs (lncRNAs) and mRNAs in the microarray data set GSE55940, and revealed that the enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) gene and EZH2-binding lncRNA in cervical cancer (lncRNA-EBIC) may play roles in the repression of E-cadherin, which could contribute to the metastasis of cervical cancer. Ye et al (10) also analyzed the data in GSE55940, and determined that microRNA-145 expression was decreased in cervical cancer tissues, and was associated with advanced cancer stages and moderate/poor differentiation. In addition, Burris et al (11)
analyzed GSE46306 and revealed that cervical DNA methylation of the prostaglandin E receptor 2 and long interspersed nuclear element-1 Homo sapiens-specific genes was associated with the length of gestation in humans. Although many genes are associated with the progression of cervical cancer, comprehensive analyses of transcriptome microarrays and methylation microarrays have rarely been reported.

It is of interest to further explore the mechanisms of cervical cancer in a comprehensive manner. In the current study, a comprehensive analysis of the GSE55940 and GSE46306 data sets was performed to identify genes involved in the pathogenesis of cervical cancer. Overlapping differentially expressed genes (DEGs) in GSE55940 and differentially methylated genes in GSE46306 were identified, and Gene Ontology (GO) enrichment analysis for these genes was performed.

Materials and methods

**Data preprocessing.** GSE55940 was downloaded from the Gene Expression Omnibus database (GEO; http://www.ncbi.nlm.nih.gov/geo/); this data set included 5 separate cervical cancer tissues and 5 paired non-tumor samples. The platform of GSE55940 was GPL16238: [hGlue_3.0_v1] Glue Grant Human Transcriptome Array version 3.0 (GG-H) [transcript-level]. GSE46306 was also downloaded from the GEO database. In this study, 20 normal cervical samples (HPV-negative) and 6 cervical cancer tissues (HPV-positive) were included in the subsequent analysis. GPL13534 Illumina HumanMethylation450 BeadChip (HumanMethylation450_15017482) was used to detect the methylation level of the CpG sites in GSE46306.

GSE55940 was preprocessed using affy package (www.bioconductor.org/packages/release/bioc/html/affy.html) in R language. Background correction, quantile normalization and probe summarization were performed using the Robust Multi-array Average algorithm. For the data set GSE4306, the CpG sites with \( \beta > 0.05 \) and the samples [CpG sites \( P > 0.05 \) and the samples [CpG sites \( P > 0.05 \)] were excluded. Peak standardization was then performed for the remaining CpG sites and samples using the Illumina Methylation Analyzer (IMA) package (12).

**Identification of DEGs and differentially methylated genes.** The normalized data GSE55940 were further analyzed by Limma package (13), and genes with \( P < 0.05 \) and \( \log[\text{fold change (FC)}] > 0.5 \) were defined as DEGs.

For the data GSE46306, the differentially methylated genes were identified based on three levels: CpG site level, CpG island level and gene level. For CpG site level, the average \( \beta \) value (\( \beta_e \)) in normal cervical and cervical cancer samples was calculated for every CpG site. Limma method in IMA was used to identify differentially methylated CpG sites that met the criteria \( |\Delta \beta| > 0.2 \) and \( P < 0.05 \). Genes containing the differentially methylated sites were obtained based on the annotation file of the microarray platform.

For CpG island level, the \( \beta \) values of five region categories [CpG islands, upstream 2,000 bp of CpG islands (N-shore), upstream 2,001-4,000 bp of CpG islands (N-shelf), downstream 2,000 bp of CpG islands (S-shore), and upstream 2,001-4,000 bp of CpG islands (S-shelf)] were calculated based on the \( \beta \) value of the CpG sites in those regions, and opensea referred to the annotations associated with UCSC islands. Additionally, Limma method in IMA was used to identify differentially methylated regions with the cut-off of \( \Delta \beta > 0.2 \) and \( P < 0.05 \). The genes located in the differentially methylated regions were obtained based on the annotation file of the microarray platform.

For the gene level, the \( \beta \) values of the upstream 200 bp of genes (TSS200), the upstream 201-1,500 bp of genes (TSS1500), 5' untranslated region (UTR), the first exon region, the gene body regions and 3’-UTR were calculated using a \( t \)-test, and the gene regions with \( |\Delta \beta| > 0.2 \) and \( P < 0.05 \) were considered to be differentially methylated.

**Comprehensive analysis of DEGs and differentially methylated genes.** For GSE46306, the overlapping genes that were identified based on CpG site level, CpG island level and gene level were screened. Subsequently, the overlapping genes of the overlapping differentially methylated genes in GSE46306 and the DEGs in GSE55940 were also screened, and GO enrichment analysis was performed for these genes using the ToppGene database (toppgene.cchmc.org/).

**Results**

**Analysis of DEGs.** In the analysis of GSE55940, a total of 242 DEGs between the cervical cancer group and the adjacent non-tumor group were identified, including 91 downregulated and 151 upregulated DEGs. The distribution of DEGs is shown in Fig. 1.

**Analysis of differentially methylated genes.** For GSE46306, 15,515 differentially methylated CpG sites were identified, involving 3,064 genes, 2,772 differentially methylated CpG island regions containing 1,082 genes, and 1,857 differentially methylated gene regions that related to 1,012 genes, between
the cervical cancer group and the control group (Table I). Distribution locations and percentages of differentially methylated regions at the CpG island level and differentially methylated regions at the gene level between the cervical cancer group and the control group.

Table I. Number of differentially methylated CpG sites, differentially methylated regions at the CpG island level and differentially methylated regions at the gene level between the cervical cancer group and the control group.

| Type                | Region        | Count | Gene count |
|---------------------|---------------|-------|------------|
| CpG sites           | Whole genome  | 15,515| 3,064      |
| Gene region         | TSS1500       | 259   | 1,012      |
|                     | TSS200        | 497   |            |
|                     | 5' UTR        | 382   |            |
|                     | 3' UTR        | 91    |            |
|                     | Gene body     | 121   |            |
|                     | Exon 1        | 507   |            |
| CpG island region   | Island        | 1,505 | 1,082      |
|                     | N-shore       | 607   |            |
|                     | N-shelf       | 78    |            |
|                     | S-shore       | 520   |            |
|                     | S-shelf       | 62    |            |

Table II. Overlapping genes between the 561 overlapping differentially methylated genes in GSE46306 and 242 differentially expressed genes in GSE55940.

| Gene      | logFC | CpG ID                  | ∆β   |
|-----------|-------|-------------------------|------|
| DPP4      | -0.567| cg09601770               | 0.210|
|           |       | cg10112391               | 0.208|
|           |       | cg12335708               | 0.212|
|           |       | cg18892517               | 0.234|
|           |       | cg19350270               | 0.274|
|           |       | cg25912827               | 0.248|
| EDN3      | -1.227| cg04048259               | 0.345|
|           |       | cg08318212               | 0.238|
|           |       | cg09005679               | 0.286|
|           |       | cg13919285               | 0.213|
|           |       | cg16205854               | 0.226|
|           |       | cg17146570               | 0.231|
|           |       | cg20910807               | 0.233|
|           |       | cg21163415               | 0.395|
|           |       | cg21512644               | 0.325|
| FGF14     | -0.558| cg02491276               | 0.202|
|           |       | cg05210258               | 0.377|
|           |       | cg08597761               | 0.410|
|           |       | cg09896622               | 0.277|
|           |       | cg16398329               | 0.259|
|           |       | cg20335672               | 0.244|
|           |       | cg22583065               | 0.245|
|           |       | cg22809871               | 0.292|
|           |       | cg23809442               | 0.215|
|           |       | cg24172416               | 0.280|
|           |       | cg25317585               | 0.370|
| TAC1      | -0.648| cg01287975               | 0.359|
|           |       | cg09236284               | 0.253|
|           |       | cg10997627               | 0.244|
|           |       | cg11873482               | 0.333|
|           |       | cg16288089               | 0.297|
|           |       | cg17437939               | 0.387|
|           |       | cg19212224               | 0.276|
| WNT16     | -0.728| cg05470554               | 0.273|
|           |       | cg14448169               | 0.265|
|           |       | cg16868298               | 0.274|
|           |       | cg18579879               | 0.223|
|           |       | cg25608490               | 0.235|
|           |       | cg26690075               | 0.280|

logFC, log₂(fold change) between the cervical cancer and normal samples; ∆β, difference of average β value of the CpG sites in cervical cancer and normal samples; DPP4, dipeptidyl peptidase 4; EDN3, endothelin 3; FGF14, fibroblast growth factor 14; TAC1, tachykinin, precursor 1; WNT16, wingless-type MMTV integration site family, member 16.

(FGF14); tachykinin, precursor 1 (TAC1); and wingless-type MMTV integration site family, member 16 (WNT16). All of the 5 genes were downregulated and hypermethylated in cervical cancer samples.
The genes **DPP4**, **EDN3**, **FGF14**, **TAC1** and **WNT16** were enriched in 86 GO terms. The top ten GO enrichment terms are shown in Table III. In particular, these genes were predominantly enriched in cell migration and cell proliferation, including receptor binding (**DPP4**, **EDN3**, **FGF14**, **TAC1** and **WNT16**), ameboidal-type cell migration (**DPP4**, **EDN3** and **TAC1**), mitogen-activated protein kinase (MAPK) cascade (**FGF14**, **EDN3** and **WNT16**), and cell proliferation (**EDN3**, **WNT16**, **DPP4** and **TAC1**).

**Table III. Top ten GO terms of DPP4, EDN3, FGF14, TAC1 and WNT16.**

| Category ID | Terms                                      | P-value       | Count | Genes                                      |
|-------------|--------------------------------------------|---------------|-------|--------------------------------------------|
| GO: MF      | Receptor binding                           | 2.63x10⁻⁶     | 5     | **FGF14**, **EDN3**, **WNT16**, **DPP4**, **TAC1** |
| GO: BP      | Ameboidal-type cell migration               | 2.66x10⁻⁵     | 3     | **EDN3**, **DPP4**, **TAC1**               |
| GO: BP      | Regulation of heart rate                    | 1.79x10⁻⁴     | 2     | **EDN3**, **TAC1**                        |
| GO: BP      | Endocrine process                           | 2.22x10⁻⁴     | 2     | **EDN3**, **TAC1**                        |
| GO: BP      | Positive regulation of hormone secretion    | 3.73x10⁻⁴     | 2     | **EDN3**, **TAC1**                        |
| GO: BP      | Mitogen-activated protein kinase cascade     | 4.16x10⁻⁴     | 3     | **FGF14**, **EDN3**, **WNT16**            |
| GO: BP      | Behavior                                   | 4.84x10⁻⁴     | 3     | **FGF14**, **EDN3**, **TAC1**             |
| GO: BP      | Signal transduction by phosphorylation      | 4.96x10⁻⁴     | 3     | **FGF14**, **EDN3**, **WNT16**            |
| GO: BP      | Cell proliferation                          | 4.98x10⁻⁴     | 4     | **EDN3**, **WNT16**, **DPP4**, **TAC1**   |
| GO: BP      | Positive regulation of transport            | 5.42x10⁻⁴     | 3     | **FGF14**, **EDN3**, **TAC1**             |

GO, Gene Ontology; **DPP4**, dipeptidyl peptidase 4; **EDN3**, endothelin 3; **FGF14**, fibroblast growth factor 14; **TAC1**, tachykinin, precursor 1; **WNT16**, wingless-type MMTV integration site family, member 16; MF, molecular function; BP, biological process.

Enrichment analysis of DEGs. The genes **DPP4**, **EDN3**, **FGF14**, **TAC1** and **WNT16** were enriched in 86 GO terms. The top ten GO enrichment terms are shown in Table III. In particular, these genes were predominantly enriched in cell migration and cell proliferation, including receptor binding (**DPP4**, **EDN3**, **FGF14**, **TAC1** and **WNT16**), ameboidal-type cell migration (**DPP4**, **EDN3** and **TAC1**), mitogen-activated protein kinase (MAPK) cascade (**FGF14**, **EDN3** and **WNT16**) and cell proliferation (**EDN3**, **WNT16**, **DPP4** and **TAC1**).

**Discussion**

DNA methylation is one of the most common epigenetic events and can regulate the expression of certain genes through preventing the binding of transcription factors with the genes (14). A number of studies have investigated the relationship between the occurrence and development of cervical cancer and DNA methylation or gene expression (15,16). However, comprehensive studies of DNA methylation and gene expression are rare.

In the current study, 5 genes (**DPP4**, **EDN3**, **FGF14**, **TAC1**, and **WNT16**) that were overlapping between the 561 overlapping differentially methylated genes and the 242 DEGs were identified; these genes were downregulated and hypermethylated simultaneously in cervical cancer samples. The predominant enriched GO terms included receptor binding, ameboidal-type cell migration, MAPK cascade and cell proliferation.
proliferation. The comprehensive analysis of transcriptome and methylation microarrays indicated that DPP4, EDN3, FGF14, TAC1 and WNT16 may contribute to the development of cervical cancer.

DPP4 [also known as cluster of differentiation (CD) 26], is a membrane-bound enzyme that serves functions in metabolism, the immune and endocrine systems, cancer growth and cell adhesion (17). DPP4 has been shown to act as a tumor suppressor or activator by associating with fibroblast activation protein α, adenosine deaminase, CD45 and C-X-C motif chemokine receptor 4, and could be considered as a potential therapeutic target in cancers expressing DPP4 (18,19). In addition, Buffon et al (20) demonstrated that DPP4 was involved in processes of cervical cancer by regulating cell migration and adhesion. In the current study, DPP4 was identified as a differentially methylated gene and DEG associated with the pathogenesis of cervical cancer and involved in receptor binding, ameboidal-type cell migration and cell proliferation. Taken together, these findings indicate that DPP4 is closely associated with the development of cervical cancer by regulating cell migration and adhesion.

EDN3 is a member of endothelin family, and the EDN3 pathway has been shown to be essential for the proliferation, survival and migration of melanocyte precursor cells (21,22). Garcia et al (23) demonstrated that EDN3 exhibited a tumor-angiogenic response in a melanoma mouse model. Furthermore, EDN3 may be a target of epigenetic inactivation, affecting the endothelin signalling pathway in human breast cancer, and hypermethylation of the EDN3 promoter could lead to gene silencing (24). In addition, Espinosa et al (25) revealed that the expression of EDN3 was downregulated in cervical cancer, and Chen et al (26) revealed that DNA methylation of EDN3 could be considered a cancer biomarker in cervical cancer. The current findings were consistent with these previous reports; EDN3 was identified as differentially methylated gene and DEG related to cervical cancer, and was indicated to be involved in ameboidal-type cell migration, MAPK cascade and cell proliferation. Based on these findings, it may be speculated that EDN3 is involved in the development of cervical cancer.

FGF14 is a member of the fibroblast growth factor (FGF) family, which includes four homologous factors: FGF11, FGF12, FGF13 and FGF14 (27). Upregulated expression of FGF13 has been demonstrated to mediate the resistance to platinum-based drugs in cervical cancer cells (28). Thus, as a homolog of FGF13, it is possible that FGF14 is involved in cervical cancer development. However, few studies have reported on the correlation between FGF14 and cervical cancer (28,29). In the current study, using a comprehensive analysis of microarray data, EDN3 was identified to be a differentially methylated gene and DEG associated with cervical cancer. These findings suggest that FGF14 may be involved in the development of cervical cancer.

Previously, methylation of TAC1 has been demonstrated to have a potential correlation with prognosis in cervical cancer (2). Consistently, the results of the current study implied that TAC1 was associated with the pathogenesis of cervical cancer. In addition, WNT16 is important in oncogenesis, and the WNT signalling pathway is related to β-catenin signaling and prostate cancer development (30,31). However, few studies have reported on the participation of WNT16 in the development of cervical cancer. In the current study, TAC1 and WNT16 were identified as differentially methylated genes and DEGs in cervical cancer. Taken together, it may be speculated that TAC1 and WNT16 are involved in cervical cancer development.

In summary, the present study identified 91 downregulated and 151 upregulated DEGs in the GSE55940 data set. In GSE46306, 561 overlapping differentially methylated genes based on a differential methylation analysis at the CpG site level, CpG island level and gene level were screened. A total of 5 overlapping genes (DPP4, EDN3, FGF14, TAC1 and WNT16) of the 561 overlapping differentially methylated genes and 242 DEGs were identified, which were downregulated and hypermethylated in cervical cancer samples. DPP4, EDN3, FGF14, TAC1 and WNT16 may be involved in the pathogenesis of cervical cancer. However, the results must be confirmed by further experiments.

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