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Research Article

Potential Novel Biomarkers Identification in Cervical Cancer Specific to DNA Methylation Using Analytical Pathways

Bikash Ranabhat[1]*, Madan Baral[1]

[1]School of Engineering, Faculty of Science and Technology, Pokhara University, Nepal

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***Corresponding author**
Bikash Ranabhat,
School of Engineering, Faculty of Science and Technology, Pokhara University, Nepal
Email: bikashranabhat72@gmail.com

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Abstract

Background: Cervical cancer is a major global health burden, especially in low- and middle-income countries with limited access to screening and treatment. DNA methylation, an epigenetic modification, critically regulates gene expression and cancer progression. This study investigates the relationship between DNA methylation and gene expression in cervical cancer to identify potential biomarkers and therapeutic targets.
Objective: To identify potential novel biomarkers in cervical cancer specific to DNA methylation using analytical pathways.
Methods: We performed a comprehensive bioinformatics analysis using GEO datasets (GSE122697, GSE63514, GSE46306, GSE168841) and TCGA data. Differentially methylated and expressed genes were identified, followed by functional pathway enrichment, validation, survival analysis, and evaluation of their therapeutic potential.
Results: We identified 3 Hypo-HE oncogenes, including PDZK1IP1, TGM3, and S100A7 and 3 Hyper-LE TSGs such as THBS1, TMEFF1, and GREM1, emerged as potential biomarkers for cervical cancer.
Conclusion: Our integrative bioinformatics analysis identified six key genes PDZK1IP1, TGM3, S100A7, GREM1, THBS1, and TMEFF1 as promising biomarkers and therapeutic targets in cervical cancer. These genes play critical roles in cancer progression through abnormal methylation and expression patterns. Targeting them may enable more precise, personalized treatment strategies to improve patient outcomes.

Keywords: methylation; expression; epigenetic; biomarkers; hypomethylated; hypermethylated.

Introduction

Cervical cancer, which begins in the female reproductive system, ranks as the fourth leading cause of cancer-related deaths among women (Cai *et al*., 2020), 90% of these fatalities take place in nations with low and moderate incomes (Gültekin *et al*., 2020). Over 348,189 deaths and roughly 661,021 new cases were reported in 2022 (Bray *et al*., 2024). Every year, many women in low status countries succumb to this preventable and treatable disease (Farghaly, 2019). In response to this significant global health issue 194 nations joined the World Health Organization (WHO) in launching a historic campaign called the Global Strategy to Accelerate the Elimination of Cervical Cancer. This policy lays forth aggressive targets to be met by 2030, such as 90% access to treatment for the cervical illness that has been diagnosed, 70% screening coverage for women aged 35 years and 45 years, and 90% HPV vaccination rates for adolescents by the age of 15 years. By 2050, this all-encompassing strategy seeks to avoid 5 million deaths and cut the number of new cervical cancer cases by more than 40% (World Health Organization, 2022).

HPV is the most significant risk factor for cervical cancer and is found in nearly all cases (Walboomers *et al*., 1999). However, cervical cancer cannot be caused by HPV infection alone (Hausen, 2001). Promoter hypermethylation is a common feature in cervical cancer, detected in 79% of cervical carcinoma cases. This encompasses 71% of cases involving squamous cell carcinoma (SCC) and 91% of case related to adenocarcinoma (AC). HPV E7 DNA is present in 91% of these cancer cases, with HPV-16 prevalent in 81% of SCC and HPV-18 common place in 59% of AC (Dong *et al*., 2001). The human papillomavirus (HPV) vaccine's ultimate objective is to shield women against invasive cervical cancer by avoiding infections with the primary HPV strains that cause cancer (Lei *et al*., 2020).

Epigenetic alterations, such as histone modifications and DNA methylation, are important in cancer development and can cause heritable gene silence. DNA methylation is a biochemical modification in which a methyl group (CH3) is added to the 5th carbon of the cytosine base within DNA, regulating gene activity and maintaining normal cellular functions (Kulis and Esteller, 2010). Using S-adenosylmethionine SAM as a methyl giver, DNA methyltransferases (DNMTs) catalyze this process, which can change gene expression without altering the underlying DNA sequence (Bhat *et al*., 2016).

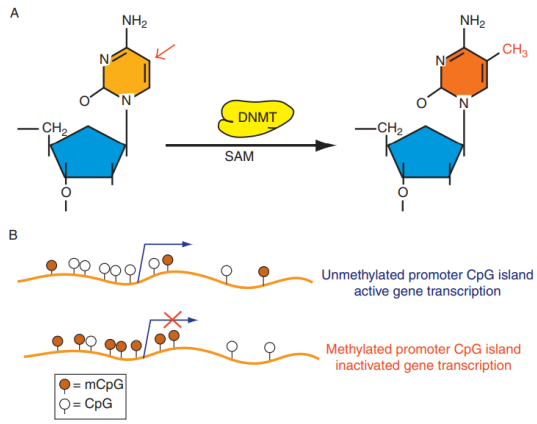


Fig. 1: DNA Methylation

(A) Cytosine methylation is the process in which methyl group is added to the 5th carbon of the cytosine base, a reaction driven by DNMTs with SAM acting as the methyl donor. (B) When CpG sites within a gene's promoter region are unmethylated, the gene remains active and can be transcribed and expressed. Conversely, methylation of these CpG sites leads to gene silencing, effectively switching off its expression (Kulis and Esteller, 2010).

It has been discovered that DNA methylation inactivates a growing number of genes throughout the formation of tumors, particularly those that function as tumor suppressors in healthy tissues (Feinberg *et al*., 2006). 92% of individuals with cervical cancer who receive an early diagnosis survive for five years (Xu *et al*., 2019).

Despite advancements in diagnostic methods predicting drug sensitivity and achieving early, accurate diagnosis remains challenging (Li *et al*., 2009) (Banno *et al*., 2007). There is a chance for improved prognostic and diagnostic methods because current research indicates that different DNA methylation of genes acts a dangerous role in cervical carcinogenesis (Xie *et al*., 2019). In order to identify novel genes, we intend to perform a genome-wide differential study of the methylation status of cervical cancer using microarray data. Despite our growing understanding of cancer, there is a pressing need for new, effective clinical tools. This research aims to fill that gap by providing a Novel Biomarker in Cervical Cancer Specific to DNA Methylation for enhanced diagnostic precision.

Methods

Data Acquisition

The GEO database was utilized to download the gene expression dataset, methylation profile dataset, and clinical data of cervical cancer patients for modelling. Two methylation datasets (GSE46306 using Illumina 450K and GSE168841 using Illumina 850K) and two mRNA expression datasets (GSE122697 and GSE63514, based on different microarray platforms) were selected. All eligible samples were included in the analysis.

Inclusion criteria:

- Invasive cervical cancer samples
- HPV-positive cervical cancer tissues
- Tumor samples
- Normal cervical samples (including HPV-negative)

Exclusion criteria:

- Cell lines (SiHa, HeLa, C33A)
- CIN1, CIN2, and CIN3 lesions

From the GSE122697 dataset (19 samples), only 11 invasive cervical cancer samples and 5 HPV-negative normal controls were used. In GSE63514, 24 normal and 28 cancer samples (out of 128) were selected. For GSE46306 (44 samples), 24 healthy and 6 cancerous samples were included. All 15 samples from GSE168841 (5 normal, 10 tumors) were used.

Data Processing and DEG and DMG Identification

For our study, we used R biopackages such as GEOquery for data retrieval and limma for identifying differentially expressed genes (DEGs). Samples were grouped into "Normal" and "Cervical Cancer," followed by log2 transformation, normalization, and linear modeling with empirical Bayes methods. For differentially methylated genes (DMGs), we used minfi and limma, applying similar grouping and statistical approaches to detect key methylation differences.

The criteria $|logFc| > 2$ and adjusted. P-value, which represents the P-value modified by the Benjamini–Hochberg technique < 0.05 were used to identify DEGs, whereas $|logFc| > 0.2$ and adjusted-P-value < 0.05 were used to identify DMGs. Prior to establishing criteria, we looked

over previously published literature (Xu *et al*., 2019) (Liu *et al*., 2020). Following that, a list of TSG and oncogenes was brought from two internet databases. An application called Venn diagram was used to show how DEGs, DMGs, oncogenes, and TSGs cross (Chen and Boutros, 2011). This led to the identification of hypermethylated downregulated TSGs and hypomethylated upregulated oncogenes.

Pathways Analysis of Abnormally Methylated DEGs

We used an online program called DAVID to assess KEGG pathway and the GO function for the genes we chose (Dennis *et al*., 2003). A P-value of below than 0.05 indicates statistical appropriate.

Validation of the Selected Genes

Online software UALCAN was utilized to further validate the expression profiles of TSGs and oncogenes (Chandrashekar *et al*., 2022). Similarly, the TCGA database was used to validate the genes that were differentiated and expressed with aberrant methylation. The Human Protein Atlas database was used to assess the immunohistochemical staining results from the normal and malignant cervical samples in order to validate the translational level of certain oncogenes/TSGs. Based on the gene expression status, survival analysis was carried out utilizing GEPIA (Tang *et al*., 2017) and TISIDB (Ru *et al*., 2019) for the hub genes.

GSEA

Using GSEA 4.3.3 software, Gene Set Enrichment Analysis was carried out to determine the hub gene's underlying activities and increased biological processes (Subramanian *et al*., 2007). Annotated gene sets of c5.go.v2024.1.Hs.symbols are collected. The reference gene sets were chosen to be Gene Matrix Transpose (GMT).

Therapeutic Values

We used STRING to find potential therapeutic values related to cervical cancer for our hub genes. An additional web-based utility GeneCards (Safran *et al*., 2010) was employed to learn about drugs that are directly linked to the gene from various sources, the source includes DrugBank, ApexBio, DGIdb, ClinicalTrials.gov, and PharmGKB, which consists organized information according to each drug's approval status, quality of the source, number, and group.

Results

Analysis of Differentially Expressed Genes (DEGs)

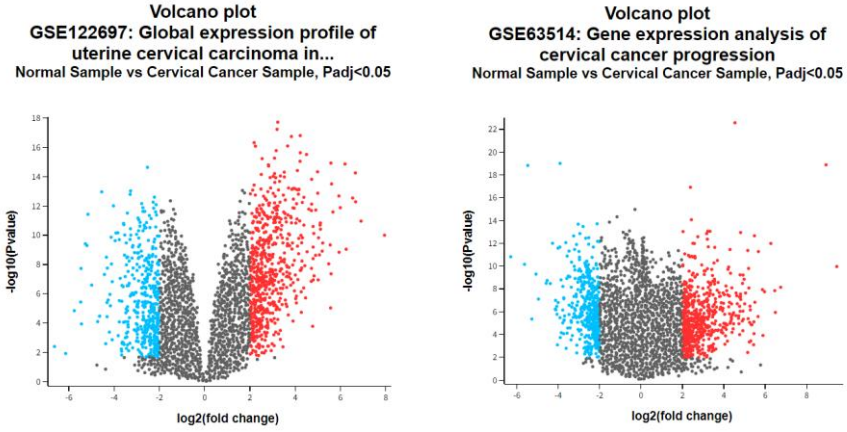
665 downregulated and 977 upregulated DEGs were among the 1,642 DEGs between the normal and cervical cancer groups found in the analysis of GSE122697 and GSE63514. The distribution of DEGs is shown in (Fig. 2).

Analysis of Differentially Methylated Genes (DMGs)

Within the normal and cervical cancer groups, 23,453 DMGs were found in the study of GSE46306 and GSE168841, comprising 10,068 hypermethylated and 13,385 hypomethylated DMGs. The DMG distribution is depicted in (Fig. 3).

Aberrantly Methylated DEGs

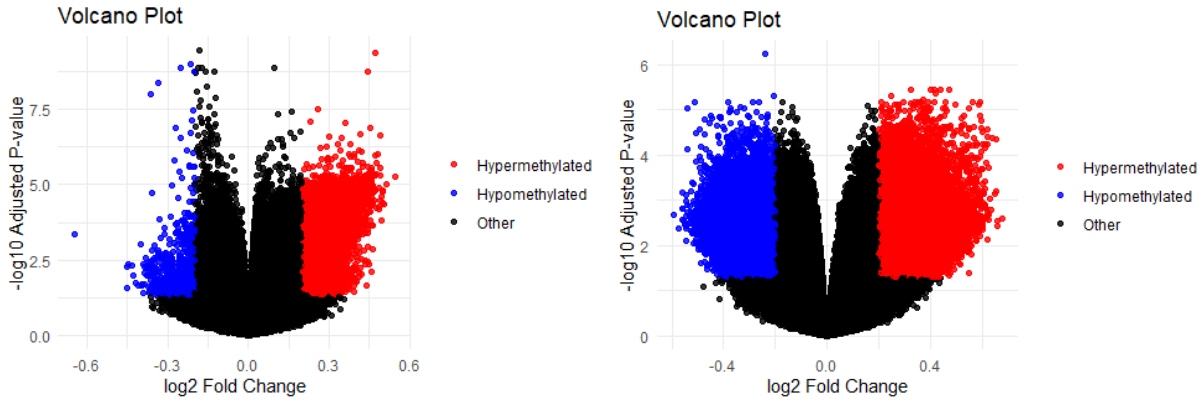
92 hypermethylated low-expression genes (Hyper-LEGs) and 317 hypomethylated high-expression genes (Hypo-HEGs) were found. Hypo-HEGs were compared to known oncogenes and Hyper-LEGs to tumor suppressor genes (TSGs) in order to identify abnormally methylated DEGs. Eleven hypomethylated oncogenes were found to be increased in this study (Fig. 4 A), indicating that hypomethylation may increase the expression of genes and so cause cancer. Furthermore, we identified six hypermethylated TSGs that were downregulated (Fig. 4 B), suggesting that abnormal hypermethylation may aid in carcinogenesis by reducing the expression.



GSE122697 GSE63514

Fig. 2: Expression for GSE122697 and GSE63514

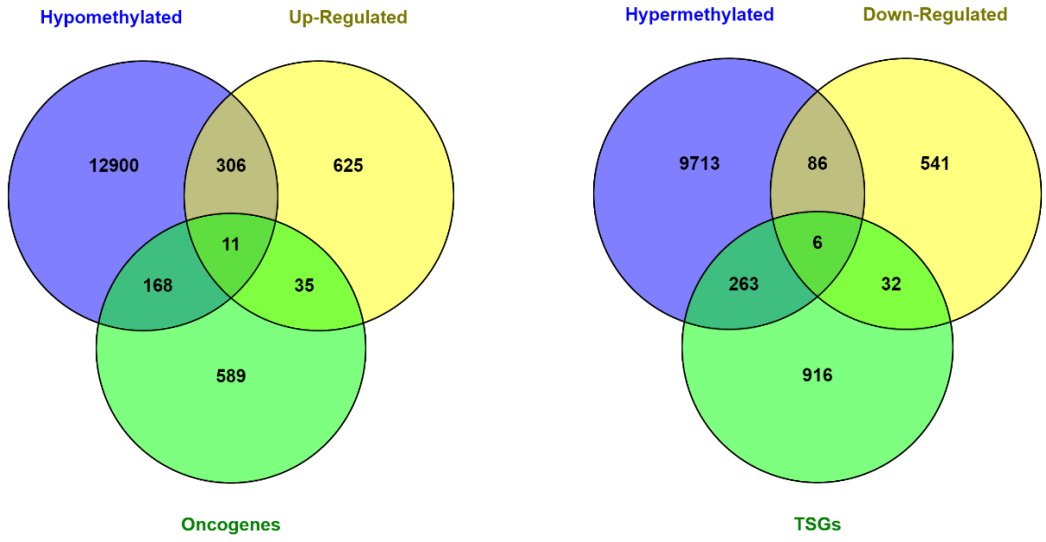
All the DEGs between the groups with cervical cancer and those without are depicted in the volcano plot. Genes that do not exhibit differential expression are represented by black colored dots, down-regulated genes by blue colored dots, and up-regulated genes by red colored dots.



GSE46306 GSE168841

Fig. 3: Expression for GSE46306 and GSE168841

All the DMGs between the cervical cancer and normal groups are shown in the volcano plot. Black colored dots in this plot indicate genes without differential methylation, blue colored dots represent genes with hypomethylation, and red colored dots represent genes with hypermethylation.



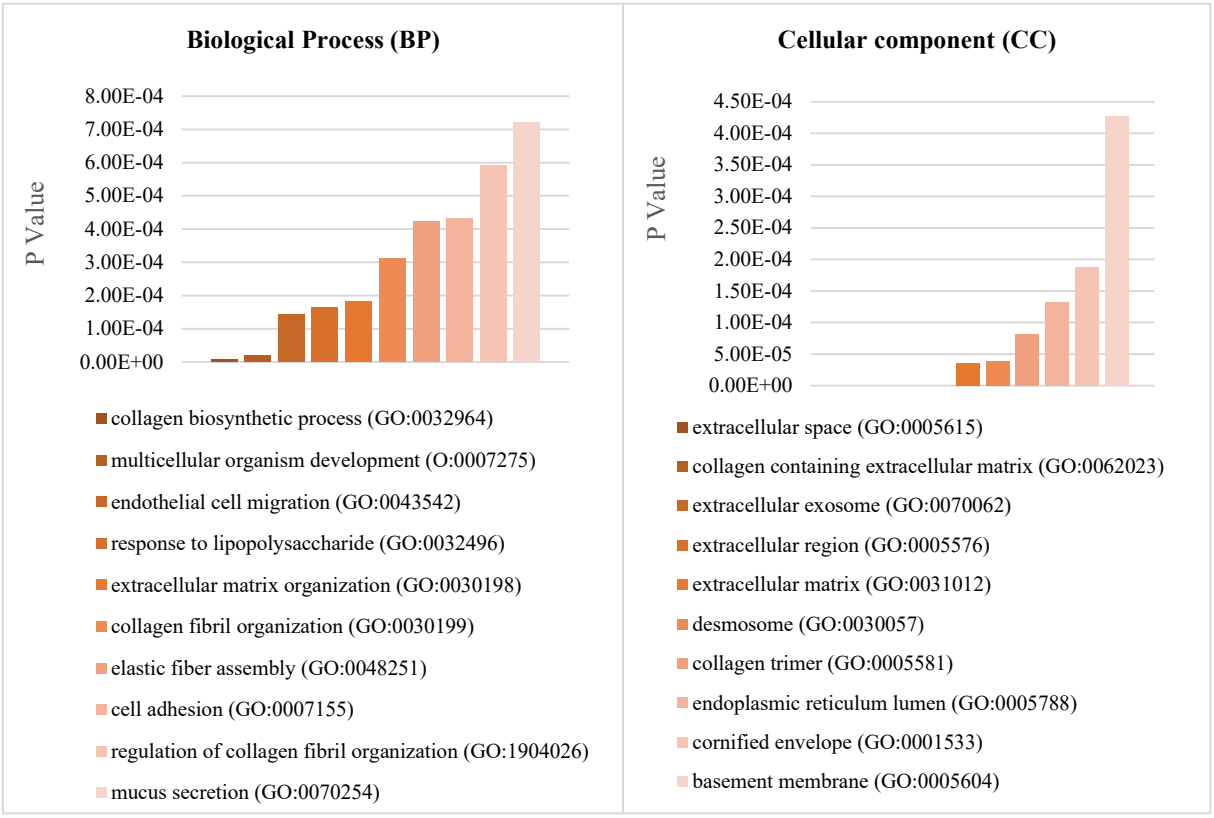
(A) (B)

Fig. 4: Aberrantly methylated oncogenes and tumor suppressor genes (TSGs)

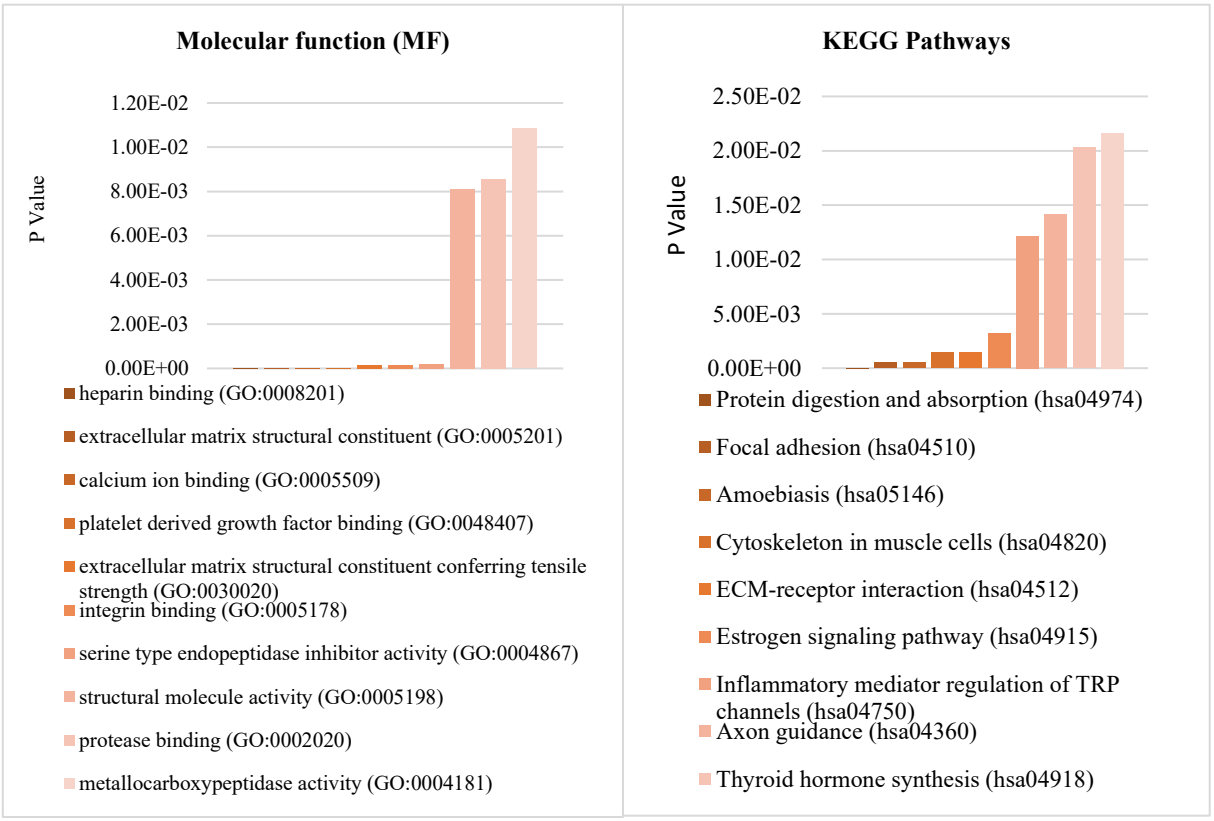
(A) A total of 317 genes, including 11 oncogenes, were found to be elevated and hypomethylated.
(B) 6 TSGs were among the 92 down-expressed and highly methylated genes found.

Analysis of KEGG and GO Pathways for Abnormally Methylation DEGS

The Gene Ontology (GO) enrichment analysis, encompassing Molecular Function (MF), Cellular Component (CC), and Biological Process (BP), was performed on the identified gene sets. The findings for 317 hypomethylated high expression genes (Hypo-HEGs) (A, B, C, D) and 92 hypermethylated low expression genes (Hyper-LEGs) (E, F, G, H) are illustrated in the figure 5, highlighting the significantly enriched GO terms associated with each group.


Biological Process (BP)
P Value
8.00E-04
7.00E-04
6.00E-04
5.00E-04
4.00E-04
3.00E-04
2.00E-04
1.00E-04
0.00E+00
collagen biosynthetic process (GO:0032964)
multicellular organism development (O:0007275)
endothelial cell migration (GO:0043542)
response to lipopolysaccharide (GO:0032496)
extracellular matrix organization (GO:0030198)
collagen fibril organization (GO:0030199)
elastic fiber assembly (GO:0048251)
cell adhesion (GO:0007155)
regulation of collagen fibril organization (GO:1904026)
mucus secretion (GO:0070254)
Cellular component (CC)
P Value
4.50E-04
4.00E-04
3.50E-04
3.00E-04
2.50E-04
2.00E-04
1.50E-04
1.00E-04
5.00E-05
0.00E+00
extracellular space (GO:0005615)
collagen containing extracellular matrix (GO:0062023)
extracellular exosome (GO:0070062)
extracellular region (GO:0005576)
extracellular matrix (GO:0031012)
desmosome (GO:0030057)
collagen trimer (GO:0005581)
endoplasmic reticulum lumen (GO:0005788)
cornified envelope (GO:0001533)
basement membrane (GO:0005604)

(A) (B)


Molecular function (MF)
P Value
1.20E-02
1.00E-02
8.00E-03
6.00E-03
4.00E-03
2.00E-03
0.00E+00
heparin binding (GO:0008201)
extracellular matrix structural constituent (GO:0005201)
calcium ion binding (GO:0005509)
platelet derived growth factor binding (GO:0048407)
extracellular matrix structural constituent conferring tensile strength (GO:0030020)
integrin binding (GO:0005178)
serine type endopeptidase inhibitor activity (GO:0004867)
structural molecule activity (GO:0005198)
protease binding (GO:0002020)
metallocarboxypeptidase activity (GO:0004181)
KEGG Pathways
P Value
2.50E-02
2.00E-02
1.50E-02
1.00E-02
5.00E-03
0.00E+00
Protein digestion and absorption (hsa04974)
Focal adhesion (hsa04510)
Amoebiasis (hsa05146)
Cytoskeleton in muscle cells (hsa04820)
ECM-receptor interaction (hsa04512)
Estrogen signaling pathway (hsa04915)
Inflammatory mediator regulation of TRP channels (hsa04750)
Axon guidance (hsa04360)
Thyroid hormone synthesis (hsa04918)

(C) (D)

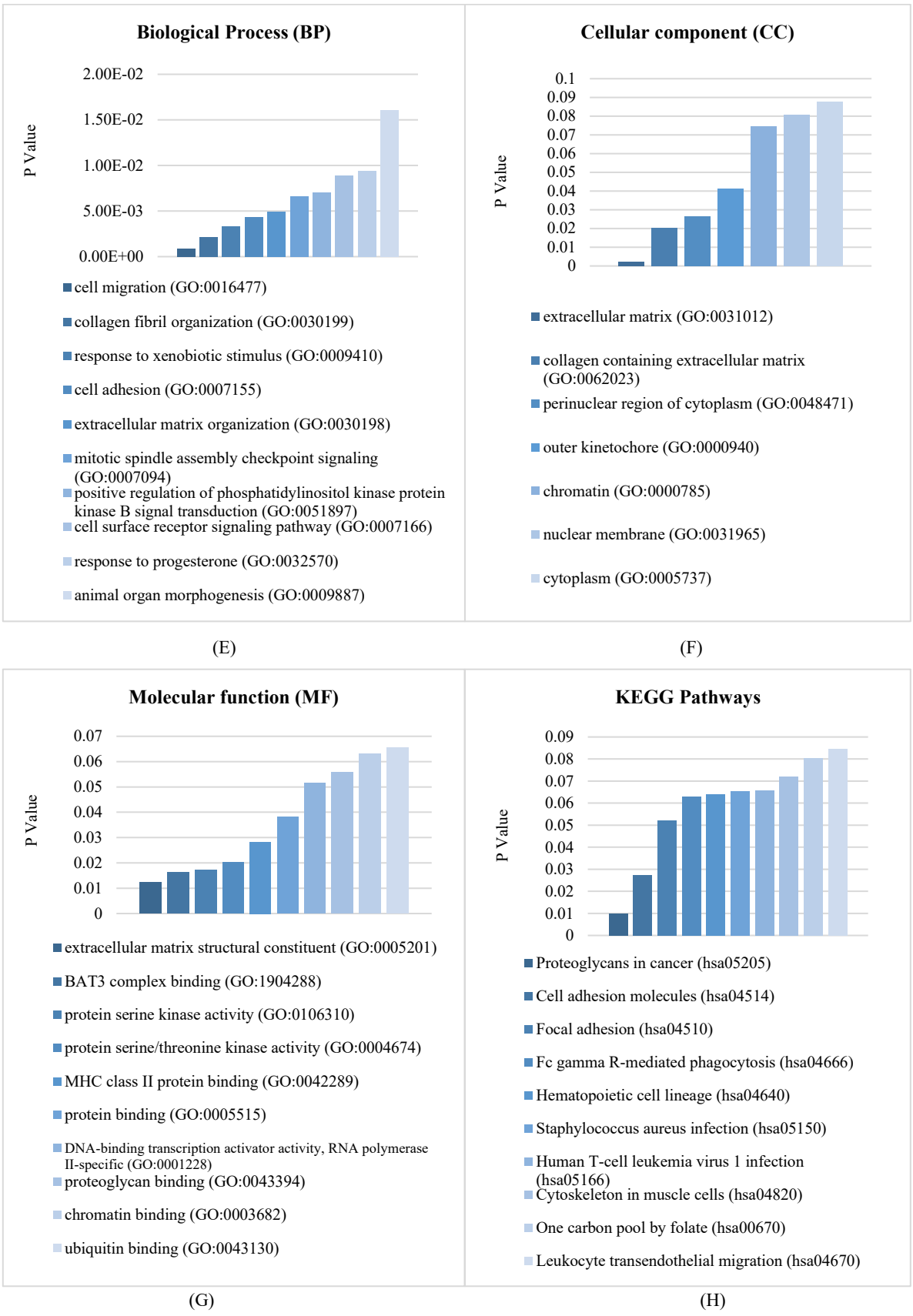


Fig. 5: GO functional annotation of aberrantly methylated DEGs.

Validation of the Selected Genes

We verified the involvement of methylation and differentially expressed genes in cervical cancer condition using UALCAN data. Three down-expressed, highly methylated tumor TSGs and three up-expressed, low methylated oncogenes were found to have variable expression between normal and malignant tissues. Furthermore, by analyzing TCGA CESC data, we identified 5 DMGs including PDZK1IP1, TGM3, GREM1, THBS1, and TMEFF1 (methylation information of S100A7 was not

found in UALCAN). Furthermore, the Human Protein Atlas database's immunohistochemistry staining photos showed that the genes PDZK1IP1, TGM3, and S100A7 were up-regulated while THBS1 and TMEFF1 were down-regulated. Also, GREM1 expression did not significantly differ between tumor and normal tissues.

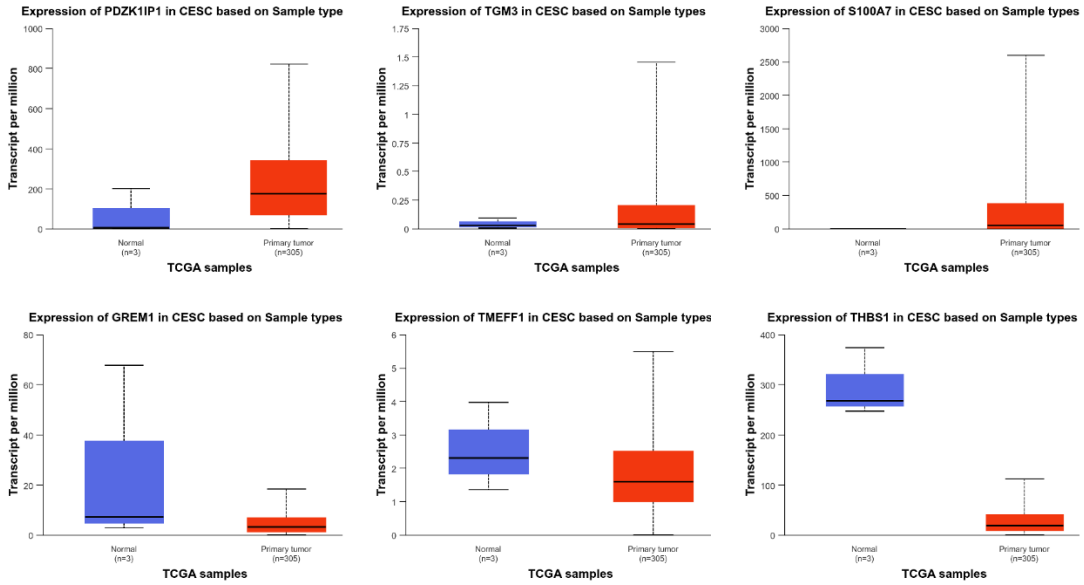


Fig. 6: UALCAN data used to validate the six hub genes.

Using data from the TCGA database in UALCAN, box plots illustrating gene expression levels revealed that six genes expression patterns matched those found in our investigation.

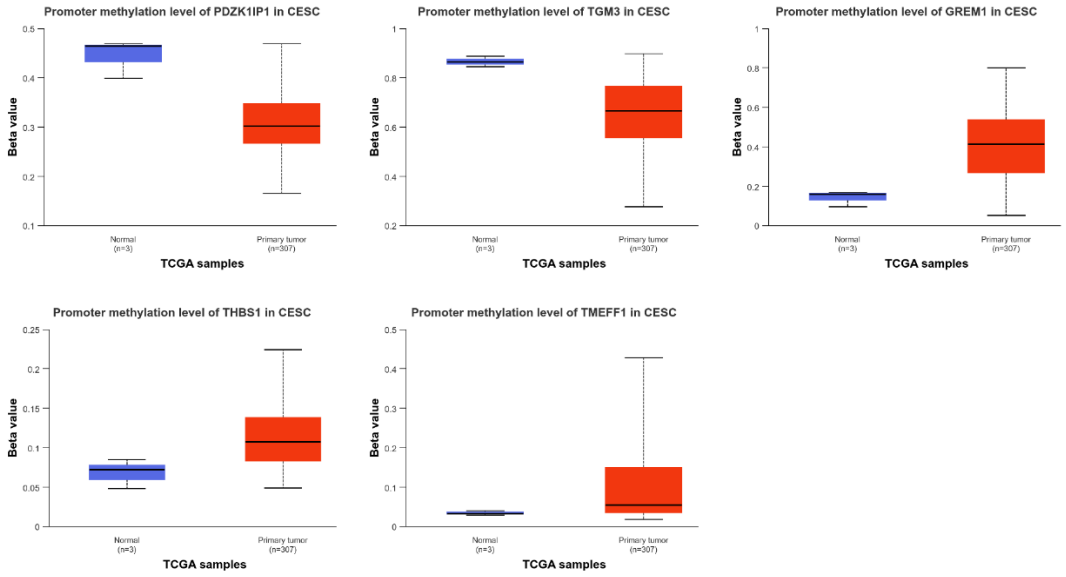


Fig. 7: TCGA CESC data used to validate the hub genes.

BOX plots displaying the methylation condition of the five genes utilizing TCGA database were the same as in our study.

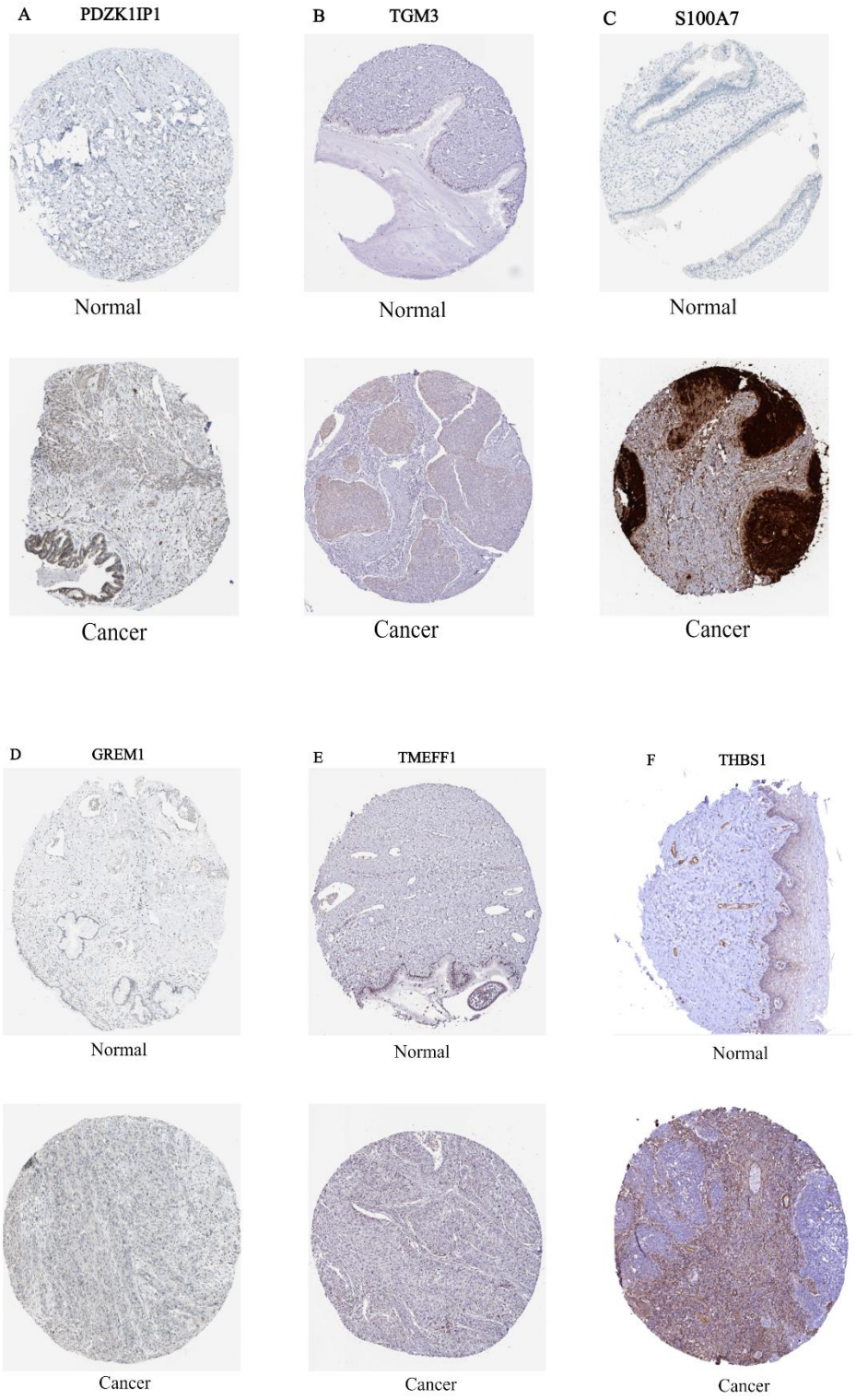


Fig. 8: Immunohistochemistry images of the six genes according on The Human Protein Atlas

(A) The protein condition of PDZK1IP1 in normal tissues showed weak staining, a quantity of 75%–25%, and low staining. Medium staining, moderate intensity, and a comparable quantity of 75%–25% were seen in cancer tissues by PDZK1IP1.
(B) In terms of TGM3, cancerous tissues exhibited low staining, weak intensity, and a quantity ranging from 75% to 25%, whereas normal tissues showed no staining at all, with a quantity of less than 25% and weak intensity.
(C) S100A7's protein level in healthy tissues was medium stained, strongly intensity, and less than 25%; In cancerous tissues, however, it was highly stained, strongly intensity, and more than 75% in quantity.
(D) GREM1 protein levels in both normal and cancer tissues were undetectable, with negative staining intensity and no measurable quantity.
(E) TMEFF1 protein levels were undetectable in cancer tissues, exhibiting negative staining, no intensity and no amount of quantity, but in normal tissues they displayed mediumly staining, moderately intensity, and a quantity between 75% and 25%.
(F) THBS1 protein levels in cancer tissues were undetectable, with negative intensity and no quantifiable amount, but in normal tissues they showed lowerly staining, weak intensity, and a quantity between 75% and 25%.

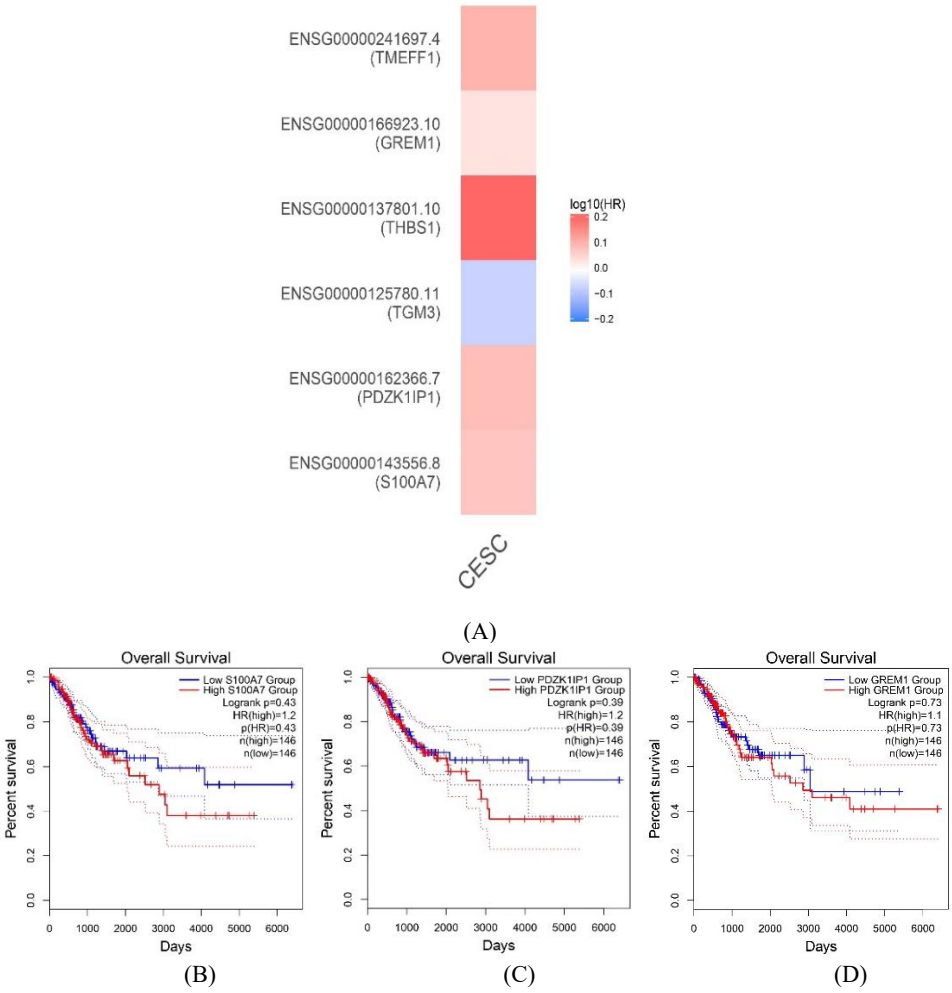


Fig. 9: Survival analysis of hub genes.

(A) According to the heat map **THBS1** has the strongest association with poor survival, while **TGM3** shows a protective effect**. TMEFF1, GREM1, PDZK1IP1,** and **S100A7** are also associated with poorer survival but with less pronounced effects. (B, C, D) The role of hub genes in cervical cancer prognosis. Poorer overall survival time was linked to higher degrees of expressiveness of S100A7 and PDZK1IP1 and lower degree of expressiveness levels of GREM1, respectively.

Survival Analysis and Function Analysis of the Hub Genes

Furthermore, the survival map visualizes the log10 hazard ratios (HR) for six hub genes TMEFF1, GREM1, THBS1, TGM3, PDZK1IP1, and S100A7 in cervical squamous cell carcinoma (CESC). Red indicates a positive HR (worse prognosis), while blue indicates a negative HR (better prognosis). THBS1 has the strongest association with poor survival, while TGM3 shows a protective effect. TMEFF1, GREM1, PDZK1IP1, and S100A7 are also associated with poorer survival but with less pronounced effects. This map highlights key genes potentially linked to prognosis in cervical cancer (Fig. 9 A). Additionally, the GEPIA survival examination based on the expression status of the multi-gene signature was obtained using the database, and a K-M curve plot was produced to evaluate the prognostic importance of the genes that were differently expressed and aberrantly methylated. Analysis showed that shorter survival times were associated with higher degrees of expressiveness of PDZK1IP1 and S100A7 and lower degrees of expressiveness of GREM1. (Fig. 9 B, C, D).

GSEA

To determine the activity of six specific genes in cervical cancer, we performed GSEA to determine which pathways are noticeably more abundant in human samples. Three down-expressed hypermethylated TSGs and three up-expressed hypomethylated oncogenes were examined separately. The upregulated hypomethylated oncogenes were associated with the development of skin, epidermis, keratinocytes, epithelial cells, epithelium, and epidermal cells are the six enriched routes (Fig. 10). Likewise, six negatively enriched pathways in the downregulated hypermethylated TSGs included amoeboid type cell migration, anatomical structure formation involved in morphogenesis, apoptotic process, blood, vessel morphogenesis, cellular stress response and blood vessel endothelial cell migration (Fig. 11).

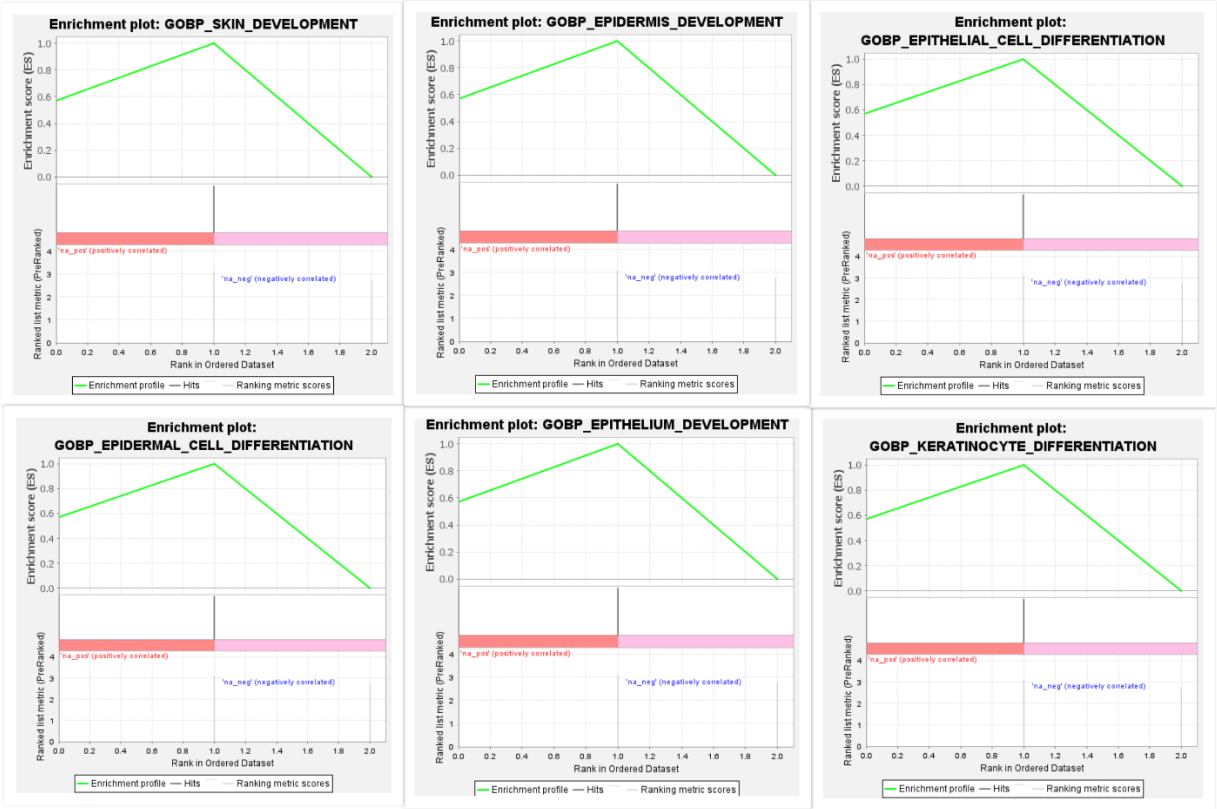


Fig. 10: Six enriched pathways in the Upregulated hypomethylated oncogenes.

All the gene sets showed strong positive enrichment.

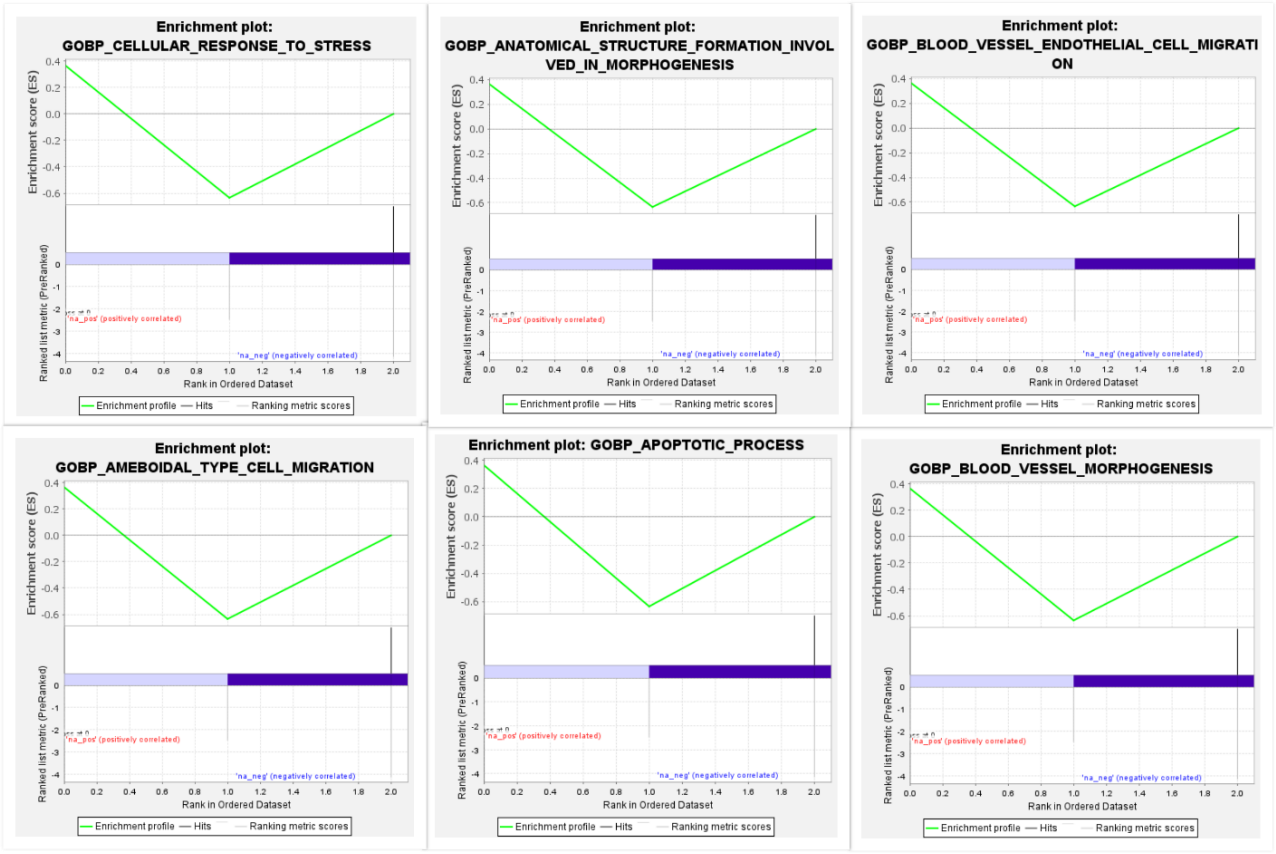


Fig. 11: Six negatively enriched pathways in the downregulated hypermethylated TSGs.

All the gene sets listed showed negative enrichment.

Therapeutic Values

The therapeutic values of the six genes were analyzed with the STRING online database. We also used GeneCards: the human gene database to examine hub genes in order to list out small molecule medications. In contrast, we found that S100A7, targeted by drugs such as Ibuprofen and Dexibuprofen, plays a role in cancer progression, particularly in inflammation-driven cancers, due to its involvement in inflammatory responses. THBS1, linked to Simvastatin and Camptothecin possesses antiangiogenic properties, meaning it can stop the growth of tumors by inhibiting the development of fresh blood vessels that provide the tumor with nutrients. TGM3, associated with L-Glutamine and other experimental compounds, is crucial for keratinocyte differentiation, which may influence cancer cell survival and behavior. Lastly, GREM1 interacts with Dexamethasone, an anti-inflammatory glucocorticoid, and acts as a BMP (Bone Morphogenetic Protein) antagonist, playing a key role in processes that drive cancer progression. Together, these genes and their interactions with specific drugs suggest potential therapeutic avenues for targeting cancer growth and progression. No drugs and compound related data available for PDZK1IP1 and TMEFF1 genes.

Discussion

Cervical cancer progression is driven by complex genetic, environmental, and lifestyle factors. Identifying novel DNA methylation-based biomarkers is crucial for improving diagnosis, treatment, and prognosis. In this study, we used public datasets (GSE122697, GSE63514, GSE46306, GSE168841) and R biopackages to analyze differentially methylated and expressed genes (DMGs and DEGs) in cervical cancer. We identified 11 upregulated hypomethylated oncogenes and 6 downregulated hypermethylated tumor suppressor genes (TSGs). From TCGA-CESC data, we highlighted three key oncogenes (PDZK1IP1, TGM3, S100A7) and three TSGs (GREM1, THBS1, TMEFF1) with significant differential expression between normal and cancer tissues. Functional enrichment analysis revealed critical pathways and hub genes involved in carcinogenesis. Validation using UALCAN and TCGA supported our findings, and immunohistochemical labeling further confirmed gene dysregulation. This integrative bioinformatics approach provides valuable insights into cervical cancer mechanisms and potential therapeutic targets

Upregulated hypomethylated oncogenes were found to be strongly associated with a number of processes, including differentiation of keratinocyte, skin development, epidermal cell differentiation, epidermis development, formation of epithelium and differentiation of epithelial cells, according to the GSEA analysis. As aging and cancer develop, these particular mechanisms of gene expression become dysregulated, supporting the growing notion that aberrant DNA methylation during cell differentiation contributes to carcinogenesis. For downregulated hypermethylated TSGs in cervical cancer amoeboid type cell migration, anatomical structure formation involved in cellular response to stress, apoptosis process, morphogenesis, morphogenesis of blood vessel, and migration of endothelial cell were negatively enriched. Amoeboid cell migration is characterized by rapid, shape-changing movement, which can occur in a low-adhesion, protease-independent manner (Lämmermann and Sixt, 2009). In addition, the flexibility of amoeboid movement allows cancer cells to move through porous environments without needing to degrade them, aiding in their invasive capacity. Morphogenesis refers to the process through which tissues, organs, and entire organisms take shape during development. It is an essential concept in developmental biology, focusing on how cells organize and create the structure and form of various biological systems (Davies, 2023), further disruption in morphogenetic processes can lead to abnormal tissue architecture, which is often seen in tumors, facilitating cancer progression.

Importantly, it was observed that reduced levels of both THBS1 and GREM1 were associated with worse survival outcomes, underlining their crucial roles as tumor suppressors in cancer. THBS1 is recognized for its antiangiogenic properties, effectively hindering tumor growth by obstructing the formation of new blood vessels that provide crucial nutrients to the tumor. Similarly, GREM1 disrupts Bone Morphogenetic Protein (BMP) signaling in cancer cells, which helps slow down cancer progression. On the other hand, PDZK1IP1 and S100A7 exhibited elevated expression levels that were strongly associated with shorter survival times. S100A7 is particularly well-known for its role in promoting cancer, especially in inflammation-driven cancers, where inflammation can accelerate tumor growth and progression. However, the precise mechanisms of PDZK1IP1 remain unclear and require further investigation to fully understand its role. All things considered, these discoveries show how therapeutic approaches that target these hubs genes may enhance patient outcomes and more successfully treat cancer in those who are impacted.

Conclusion

To conclude, our comprehensive bioinformatics analysis has effectively identified a wide array of differentially expressed and abnormally methylated oncogenes and TSGs within cervical cancer tissues. This study not only pinpointed these genetic alterations but also elucidated the associated pathways and functional roles they play in the context of the disease. By employing a meticulous approach to data analysis, we explored how these genes contribute to the intricate biological mechanisms underlying cervical cancer progression. Further validation through the TCGA database underscored the significance of six crucial genes

PDZK1IP1, TGM3, S100A7, GREM1, THBS1, and TMEFF1 which exhibit notable potential as both biomarkers and therapeutic targets. By focusing on these key genes, we can pave the way for more effective interventions that are specifically designed to address the unique genetic profiles of individual patients. This personalized approach is crucial in the realm of oncology, where treatments can often be generalized rather than customized to meet the specific needs of patients.

Author's Contribution

Both authors designed the research plan & analyzed the data; Bikash Ranabhat collected the data & prepared the manuscript. Madan Baral revised and finalized the manuscript. Final form of manuscript was approved by all authors.

Conflict of Interest

The author(s) declare(s) that there is (are) no conflict(s) of interest regarding the publication of this paper.

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References

Banno K, Yanokura M, Kawaguchi M, Kuwabara Y, Akiyoshi J, Kobayashi Y, Iwata T, Hirasawa A, Fujii T, Susumu N and Tsukazaki K (2007) Epigenetic inactivation of the CHFR gene in cervical cancer contributes to sensitivity to taxanes. *Int J Oncol* **31**(4): 713–720. DOI: 10.3892/ijo.31.4.713

Bhat S, Kabekkodu SP, Noronha A, Satyamoorthy K (2016) Biological implications and therapeutic significance of DNA methylation regulated genes in cervical cancer. *Biochimie*, **121**: 298–311. DOI: 10.1016/j.biochi.2015.12.018

Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A (2024) Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* **74**(3): 229–263. DOI: 10.3322/caac.21834

Cai S, Yu X, Gu Z, Yang Q, Wen B, Sheng J, Guan R (2020) A 10-gene prognostic methylation signature for stage I–III cervical cancer. Arch Gynecol Obstet **301**: 1275–1287. DOI: 10.1007/s00404-020-05524-3

Chandrashekar DS, Karthikeyan SK, Korla PK, Patel H, Shovon AR, Athar M, Netto GJ, Qin ZS, Kumar S, Manne U, Creighton CJ (2022) UALCAN: an update to the integrated cancer data analysis platform. *Neoplasia* **25**: 18–27. DOI: 10.1016/j.neo.2022.01.001

Chen H, Boutros PC (2011) VennDiagram: a package for the generation of highly-customizable Venn and Euler diagrams in R. *BMC Bioinformatics* **12**: 35. DOI: 10.1186/1471-2105-12-35

Davies JA (2023) Mechanisms of Morphogenesis. Elsevier. DOI: 10.1016/B978-0-323-99965-6.00020-8

Dennis Jr G, Sherman BT, Hosack DA, Yang J, Gao W, Lane HC, Lempicki RA (2003) DAVID: database for annotation, visualization, and integrated discovery. *Genome Biol* **4**: P3. DOI: 10.1186/gb-2003-4-5-p3

Dong SM, Kim HS, Rha SH, Sidransky D (2001) Promoter hypermethylation of multiple genes in carcinoma of the uterine cervix. *Clin Cancer Res* **7**(7): 1982–1986. https://aacrjournals.org/clincancerres/article/7/7/1982/288755/Promoter-Hypermethylation-of-Multiple-Genes-in

Farghaly SA (2019) Uterine Cervical Cancer: Clinical and Therapeutic Perspectives. Springer. DOI: 10.1007/978-3-030-02701-8

Feinberg AP, Ohlsson R, Henikoff S (2006) The epigenetic progenitor origin of human cancer. *Nat Rev Genet* **7**(1): 21–33. DOI: 10.1038/nrg1748

Gultekin M, Ramirez PT, Broutet N, Hutubessy R (2020) World Health Organization call for action to eliminate cervical cancer globally. *Int J Gynecol Cancer* **30**(4). DOI: 10.1136/ijgc-2020-001285

Hausen HZ (2001) Cervical carcinoma and human papillomavirus: on the road to preventing a major human cancer. *J Natl Cancer Inst* **93**(4): 252–253. DOI: 10.1093/jnci/93.4.252

Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P (2020) HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med* **383**(14): 1340–1348. DOI: 10.1056/NEJMoa1917338

Li M, Balch C, Montgomery JS, Jeong M, Chung JH, Yan P, Huang TH, Kim S, Nephew KP (2009) Integrated analysis of DNA methylation and gene expression reveals specific signalling pathways associated with platinum resistance in ovarian cancer. *BMC Med Genomics* **2**: 34. DOI: 10.1186/1755-8794-2-34

Liu J, Wan Y, Li S, Qiu H, Jiang Y, Ma X, Zhou S, Cheng W (2020) Identification of aberrantly methylated differentially expressed genes and associated pathways in endometrial cancer using integrated bioinformatic analysis. *Cancer Med* **9**(10): 3522–3536. DOI: 10.1002/cam4.2956

Lämmermann T, Sixt M (2009) Mechanical modes of amoeboid cell migration. *Curr Opin Cell Biol* **21**(5): 636–644. DOI: 10.1016/j.ceb.2009.05.003

Kulis M, Esteller M (2010) DNA methylation and cancer. *Adv Genet* **70**: 27–56. DOI: 10.1016/B978-0-12-380866-0.60002-2

Ru B, Wong CN, Tong Y, Zhong JY, Zhong SS, Wu WC, Chu KC, Wong CY, Lau CY, Chen I, Chan NW (2019) TISIDB: an integrated repository portal for tumor–immune system interactions. *Bioinformatics* **35**(20): 4200–4202. DOI: 10.1093/bioinformatics/btz210

Safran M, Dalah I, Alexander J, Rosen N, Iny Stein T, Shmoish M, Nativ N, Bahir I, Doniger T, Krug H, Sirota-Madi A (2010) GeneCards Version 3: the human gene integrator. Database **2010**: baq020. DOI: 10.1093/database/baq020

Subramanian A, Kuehn H, Gould J, Tamayo P, Mesirov JP (2007) GSEA-P: a desktop application for Gene Set Enrichment Analysis. *Bioinformatics* **23**(23): 3251–3253. DOI: 10.1093/bioinformatics/btm369

Tang Z, Li C, Kang B, Gao G, Li C, Zhang Z (2017) GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic Acids Res* **45**(W1): W98–W102. DOI: 10.1093/nar/gkx247

Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Muñoz N (1999) Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* **189**(1): 12–19. DOI: 10.1002/(SICI)1096-9896

World Health Organization (2022) Accelerating the elimination of cervical cancer as a public health problem: Towards achieving 90-70-90 targets by 2030. WHO Regional Office for South-East Asia. https://pesquisa.bvsalud.org/portal/resource/pt/who-361138

Xie F, Dong D, Du N, Guo L, Ni W, Yuan H, Zhang N, Jie J, Liu G, Tai G (2019) An 8-gene signature predicts the prognosis of cervical cancer following radiotherapy. *Mol Med Rep* **20**(4): 2990–3002. DOI: 10.3892/mmr.2019.10535

Xu W, Xu M, Wang L, Zhou W, Xiang R, Shi Y, Zhang Y, Piao Y (2019) Integrative analysis of DNA methylation and gene expression identified cervical cancer-specific diagnostic biomarkers. *Signal Transduct Target Ther* **4**(1): 55. DOI: 10.1038/s41392-019-0081-6