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ADVANCES IN CELLULAR AND MOLECULAR PATHOLOGY: MECHANISTIC INSIGHTS INTO DISEASE ETIOLOGY AND THERAPEUTIC TARGETS

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ABSTRACT

Molecular changes in the gynecological cancers are complex and play a pivotal role in disease onset, progression and drug resistance. Transcriptomics is a powerful tool to discover the altered genes and pathways in cervical cancer. The present study aimed to identify differentially expressed genes and enriched molecular pathways associated with cervical cancer and to highlight potential mechanistic and therapeutic targets. A secondary transcriptomic dataset comprising cervical, endometrial, and vulvar cancer and normal tissue samples was analyzed, with a focused comparison between cervical cancer and normal cervical tissues. Genes with low variance were filtered, probe identifiers were mapped to gene symbols, and differential expression analysis was performed using a threshold of $p < 0.01$ and $|\log2 \text{ fold change}| \geq 1$. Functional interpretation was carried out using Gene Ontology and KEGG pathway enrichment analyses for both upregulated and downregulated gene sets. A total of 628 differentially expressed genes were identified, including 323 upregulated and 305 downregulated genes. Upregulated genes were primarily enriched in DNA replication, DNA metabolic processes, mitotic spindle organization, cell cycle regulation, p53 signaling, and homologous recombination, with key candidates including *MCM4*, *MCM2*, *FEN1*, *CDK1*, *CCNB1*, and *PCNA*. In contrast, downregulated genes were associated with extracellular matrix assembly, epithelial development, muscle contraction, Wnt signaling, and focal adhesion, including *ZFP36L2*, *LTBP4*, *MYL9*, and *TAGLN*. These findings indicate a transcriptional shift toward enhanced proliferative and genome-maintenance activity alongside suppression of structural and differentiation-related processes. The results provide mechanistic insight into cervical cancer etiology and identify candidate molecular targets for further validation and therapeutic exploration.

KEYWORDS: cervical cancer, transcriptomics, differential gene expression, pathway enrichment, molecular targets

1. INTRODUCTION

Cancer continues to be a major burden of disease and death globally, with many cases linked to preventable and non-preventable risk factors. A recent global cancer burden assessment suggests that the disease burden continues to rise across different populations, reflecting demographic changes, environmental and lifestyle risk factors (Tran et al., 2022). Time trends analysis also reveals that cancer incidence and mortality rates have continued to increase in 204 countries and territories, highlighting the need for a better understanding of the disease and potential interventions (Wu et al., 2024). Gynecological cancers, such as cervical, endometrial, and vulvar cancers, are a major burden in low- and middle-income regions, including cervical cancer.

Cervical cancer, in particular, remains highly burdensome despite screening and vaccination measures. Attempts at global eradication have shown the potential and challenges of population-level control of this disease (Brisson & Drolet, 2019). On a clinical level, cervical cancer has a multifactorial origin with persistent infection by high-risk human papillomavirus (HPV) playing a key role, alongside host genetic and environmental factors (Cohen et al., 2019). While screening has led to marked reductions in incidence in some countries, early detection and health care access are still key obstacles (Eun & Perkins, 2020). On a molecular scale, cervical cancer development involves intricate changes in gene expression, signaling networks, and cellular mechanisms such as disruption of cell cycle regulation, apoptosis and immune responses (Vallejo-Ruiz et al., 2024). Modern high-throughput technologies have allowed detailed mapping of gene expression, offering key insights into cancer biology. In particular, transcriptomic approaches are pivotal in the discovery of biomarkers and therapeutic targets, facilitating the assessment of gene expression across different disease conditions (Yang et al., 2020a). Such studies have enabled the identification of potential RNA-based biomarkers for diagnosis and prognosis of gynecological cancers, underscoring the importance of changes in gene expression patterns in cancer development (Hulstaert et al., 2021). Moreover, the analysis of specific molecular regulators, such as Polo-like kinase 1, has shown their involvement in tumor growth and progression in cervical cancer, highlighting the significance of gene-specific

analyses (Gao et al., 2020). In addition to single genes, transcriptomic analyses have also shed light on regulatory networks and pathway-level changes in cancer. For example, the p53 pathway and its interaction with non-coding RNAs have been shown to play a role in tumor formation and progression, highlighting the intricate regulatory mechanisms involved in gynecological cancers (Pal et al., 2020). Likewise, the refinement of cancer subtype definitions using transcriptomic profiling has enabled a more precise categorization of tumors to better inform treatment approaches and understand heterogeneity (Cook & Vanderhyden, 2019). In cervical cancer, gene expression profiling has revealed the dysregulation of genes implicated in DNA replication and cell proliferation, further highlighting the importance of transcriptional changes in tumor development (Liang et al., 2024). However, there are some gaps in the current literature. One issue is the absence of a consensus on the identified biomarkers between studies, which can be due to differences in the study design, sample population, and analysis methods. Furthermore, although a large number of studies have identified differentially expressed genes, few have linked these to functional and pathway analysis to gain a holistic view of disease biology. There is also a need for a better understanding of the overlap and tissue-specificity of molecular signatures among gynecological cancers to facilitate the translation of findings across multiple cancer types, and to prioritise common therapeutic targets. Further, the integration of transcriptomic data with clinically relevant information is an area that needs to be explored. In this regard, systematic re-analysis of published transcriptomic data sets can help to overcome these limitations by using uniform analytical approaches and linking gene-level and pathway-level data. The current study aims to explore the molecular basis of gynecological cancers, with a particular emphasis on cervical cancer, using gene expression datasets. Through the identification of genes with altered expression in cancerous versus normal tissues, and their functional and pathway associations, the study seeks to reveal important biological pathways in disease development. Furthermore, combined analyses of enrichment aim to identify potential targets for therapy. By doing so, the study aims to provide new insights into cellular and molecular pathology and link mechanistic findings with disease etiology and progression.

2. METHODOLOGY

2.1 Research design

The main aim of this study was to perform a re-analysis of transcriptomic data to detect molecular changes in gynecological cancers, especially the comparison of cervical cancer with normal cervical tissue. A structured bioinformatics approach was used that involved data processing, differential gene expression, gene annotation and functional analysis to gain biologically relevant insights into disease processes.

2.2 Data source

This study used the gene expression dataset published by Pappa et al. (2015). This dataset includes transcriptomic data from cervical, endometrial and vulvar cancers, as well as their respective normal tissues. It was used to study the transcriptional similarities between various gynecological cancers and to detect universal molecular signatures driving tumorigenesis (Pappa et al., 2015).

2.3 Data preprocessing

The gene expression data were structured into a matrix of probe IDs and sample expression values. Metadata were collected to categorise samples according to tissue and disease status. The expression matrix was linked to the metadata to provide sample correspondence. To enhance the analysis, genes of low variance across samples were filtered out using variance filtering. This process eliminated noise and focused on genes with variable expression patterns for further analysis.

2.4 Differential expression analysis

A differential gene expression analysis was conducted between cervical cancer and normal cervical tissues. Genes with statistically significant changes in expression were determined using statistical tests. Genes were considered differentially expressed based on a threshold of $p < 0.01$ and $|\log2 \text{ fold change}| \geq 1$. This identified genes that were up- and down-regulated, corresponding to increased and decreased transcription, respectively, in disease.

2.5 Gene annotation

We used platform-specific annotations to map probe identifiers to gene symbols and Entrez Gene IDs. In cases where multiple probes mapped to the same gene, representative probe values were chosen to yield a single expression value for each gene. This allowed for correct biological interpretation and removal of redundancies.

2.6 Functional enrichment analysis

To understand the biological processes involved with the differentially expressed genes, functional enrichment analysis was performed. We used Gene Ontology (GO) analysis to identify enriched biological processes. Significance of the enrichment was measured by adjusted p-values, and the most informative terms were chosen. Analysis was carried out separately for upregulated and downregulated genes to identify biological processes that are activated and repressed.

2.7 Pathway enrichment analysis

Pathway enrichment analysis was conducted to determine pathways enriched for the differentially expressed genes. Significant pathways were determined by adjusting p-values. The analysis was performed with the sets of up- and down-

regulated genes, allowing us to identify pathways responsible for disease progression and for loss of important cellular functions.

3. RESULTS

3.1 Dataset characteristics and sample distribution

The transcriptomic cohort consisted of 35 samples, representing the cervix, endometrium and vulva, including both diseased and normal states. The breakdown of samples by tissue and condition is detailed in Table 1 to enable balanced comparisons.

Table 1. Sample distribution across tissues and conditions

Tissue	Condition	Sample count
Cervix	Cancer	5
Cervix	Normal	5
Endometrium	Cancer	7
Endometrium	Normal	5
Vulva	Cancer	6
Vulva	Normal	7

In order to assess global transcriptional variation, principal component analysis (PCA) was conducted. Figure 1 also indicates that PC1 had an explanation of 32.7%, with PC2 explaining 15.2%. Separate clusters were created around cancer and normal samples, segregating based on disease status. Moreover, tissue-specific clustering was still observed, meaning that the disease condition and the origin of the tissue are all part of the total variance.

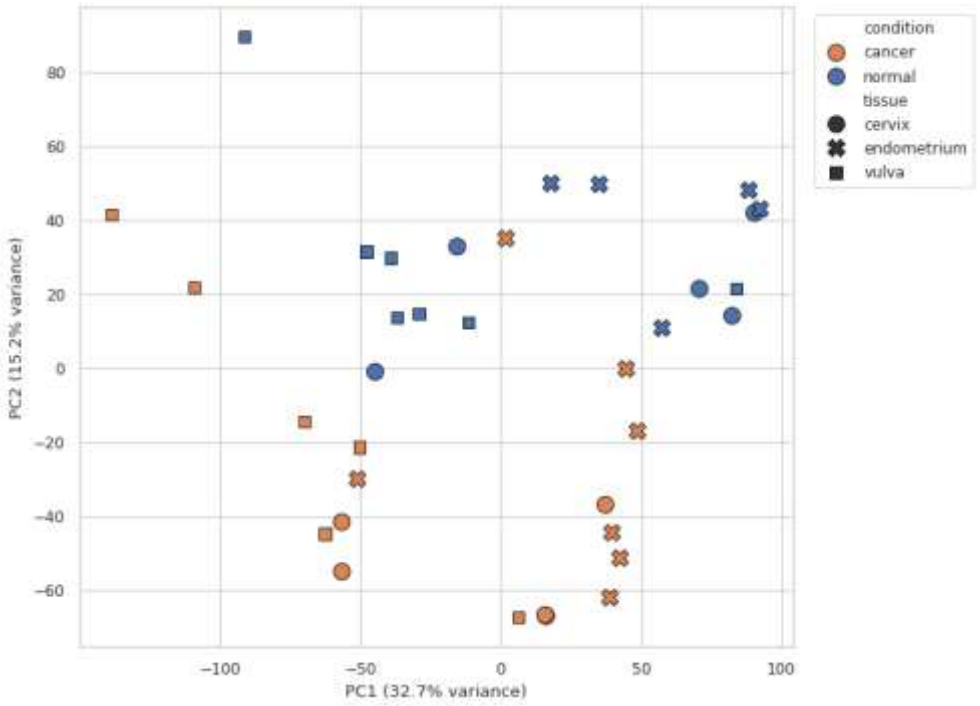

Figure 1. Principal Component Analysis of GSE63678 samples

3.2 Differential gene expression profiling in cervical cancer

Differential expression analysis between cervical cancer and normal cervical tissues identified 628 genes meeting the threshold criteria ($p < 0.01$ and $|\log2FC| \geq 1$), including 323 upregulated and 305 downregulated genes. The general pattern of such transcriptional changes is represented in Figure 2, where the volcano diagram shows that there is a clear distinction between highly upregulated and downregulated genes. The upregulation of genes was highly observed in *MCM4, ECT2* and *FEN1,* but *ZWP36L2* and *LTBP4* were significantly downregulated.

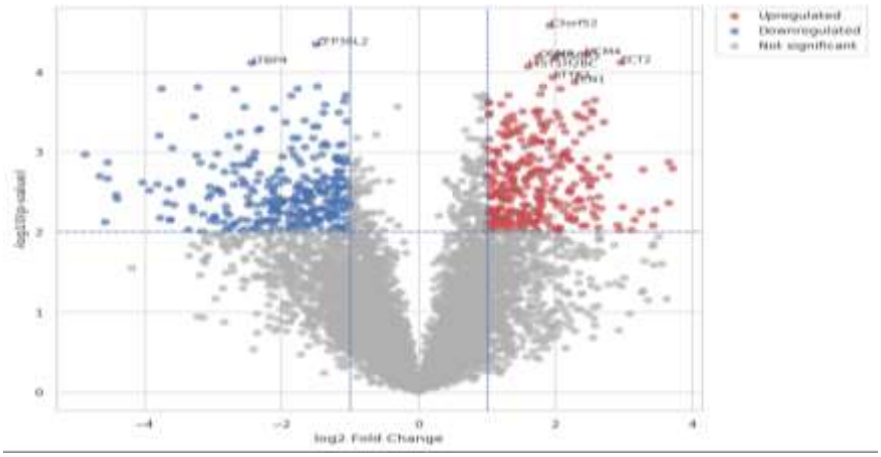

Figure 2. Volcano plot of differential gene expression in cervical cancer versus normal tissue

Table 2 shows the most significant candidate genes obtained as a result of probe-level annotation and gene-level aggregation.

Table 2. Top candidate differentially expressed genes in cervical cancer

Gene Symbol	Gene Title	Entrez ID	log2FC	p-value
C3orf52	Chromosome 3 open reading frame 52	79669	1.93	2.7×10^{-5}
ZFP36L2	ZFP36 ring finger protein-like 2	678	-1.49	4.6×10^{-5}
MCM4	Minichromosome maintenance complex component 4	4173	2.43	6.1×10^{-5}
OSMR	Oncostatin M receptor	9180	1.75	6.5×10^{-5}
PLSCR1	Phospholipid scramblase 1	5359	2.00	6.8×10^{-5}
ECT2	Epithelial cell transforming 2	1894	2.97	7.7×10^{-5}
LTBP4	Latent transforming growth factor beta binding protein 4	8425	-2.43	7.8×10^{-5}
STYK1	Serine/threonine/tyrosine kinase 1	55359	1.97	1.2×10^{-4}
FEN1	Flap structure-specific endonuclease 1	2237	2.29	1.3×10^{-4}
NUP50	Nucleoporin 50kDa	10762	1.83	1.5×10^{-4}

3.3 Expression pattern clustering of differentially expressed genes

Hierarchical clustering of the top DEGs was used to determine the similarity of the expression patterns between samples. The heatmap obtained (Figure 3) indicates a strong segregation of cancer and normal samples. DNA replication and cell cycle-related genes like *MCM2, MCM4, and TYMS* were upregulated consistently in the tumor samples, and genes related to the organization of the extracellular matrix and cytoskeletal functioning, such as *TAGLN, MYL9,* and *LTBP4*, were downregulated consistently.

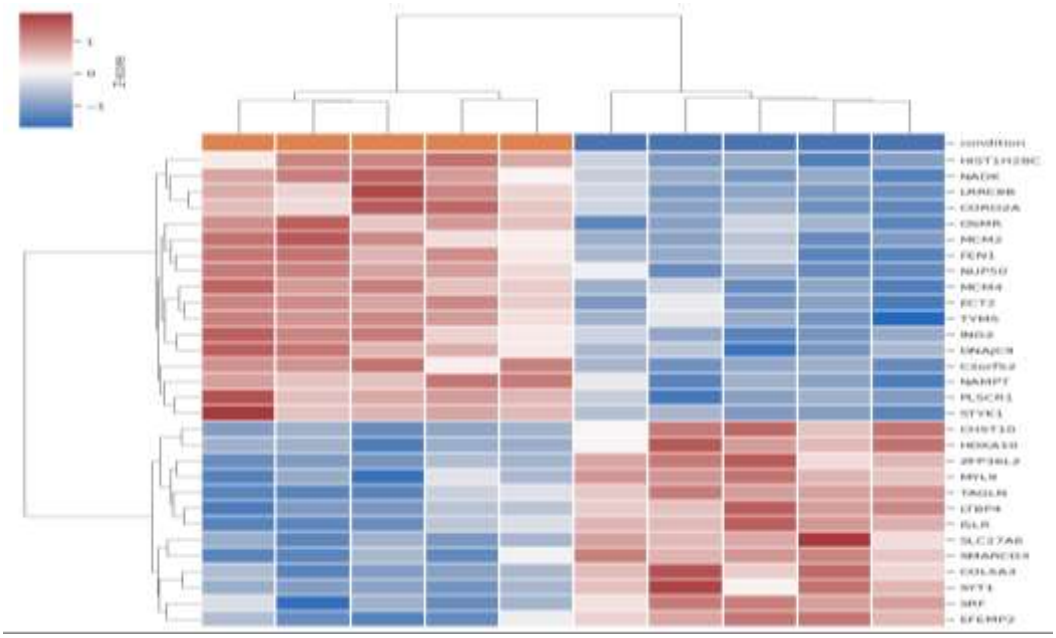

Figure 3. Heatmap of the top differentially expressed genes in cervical cancer

3.4 Functional enrichment analysis of biological processes

Gene Ontology enrichment analysis was conducted to explore the biological meaning of the identified DEGs. Table 3 summarizes the highest enriched biological processes.

Table 3. Top enriched GO biological processes

Regulation	Term	Overlap	Adjusted p-value	Odds Ratio
Upregulated	DNA replication	29/108	3.35×10^{-24}	24.47
Upregulated	DNA metabolic process	40/277	2.09×10^{-23}	11.59
Upregulated	DNA-dependent DNA replication	28/129	5.68×10^{-21}	18.40
Upregulated	Mitotic spindle organization	27/157	1.21×10^{-17}	13.72
Downregulated	Muscle contraction	16/129	2.96×10^{-7}	9.59
Downregulated	Elastic fiber assembly	6/8	3.70×10^{-7}	197.59
Downregulated	Extracellular matrix assembly	8/24	8.99×10^{-7}	33.13
Downregulated	Epithelium development	12/122	1.05×10^{-4}	7.29

As illustrated in Figure 4, upregulated genes were strongly enriched in DNA replication, mitotic processes, and DNA repair pathways, whereas downregulated genes were associated with structural and differentiation-related processes.

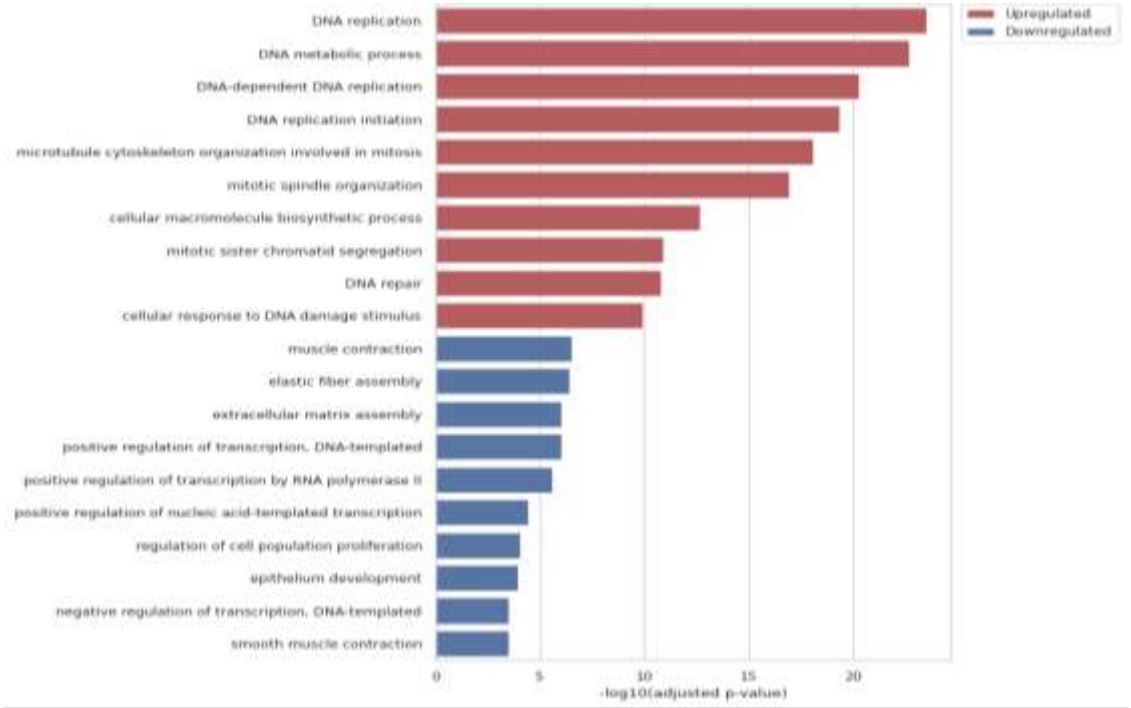

Figure 4. GO Biological Process enrichment analysis

3.5 KEGG pathway enrichment analysis

KEGG pathway enrichment analysis also identified important signaling pathways that relate to cervical cancer. Table 4 shows the best enriched pathways.

Table 4. Top enriched KEGG pathways

Regulation	Pathway	Overlap	Adjusted p-value	Odds Ratio
Upregulated	Cell cycle	27/124	1.05×10^{-20}	18.41
Upregulated	DNA replication	16/36	8.54×10^{-18}	51.22
Upregulated	p53 signaling pathway	8/73	5.26×10^{-4}	7.66
Upregulated	Homologous recombination	7/41	1.60×10^{-4}	12.80
Downregulated	Vascular smooth muscle contraction	13/133	2.91×10^{-5}	7.26
Downregulated	cGMP-PKG signaling pathway	13/167	2.01×10^{-4}	5.65
Downregulated	Pathways in cancer	23/531	5.75×10^{-4}	3.08
Downregulated	Wnt signaling pathway	11/166	2.25×10^{-3}	4.72

Trends in enrichment are further visualized in Figure 5, with upregulated pathways much more commonly associated with cell cycle progression and DNA replication, whereas downregulated pathways are related to cellular signaling and structural integrity.

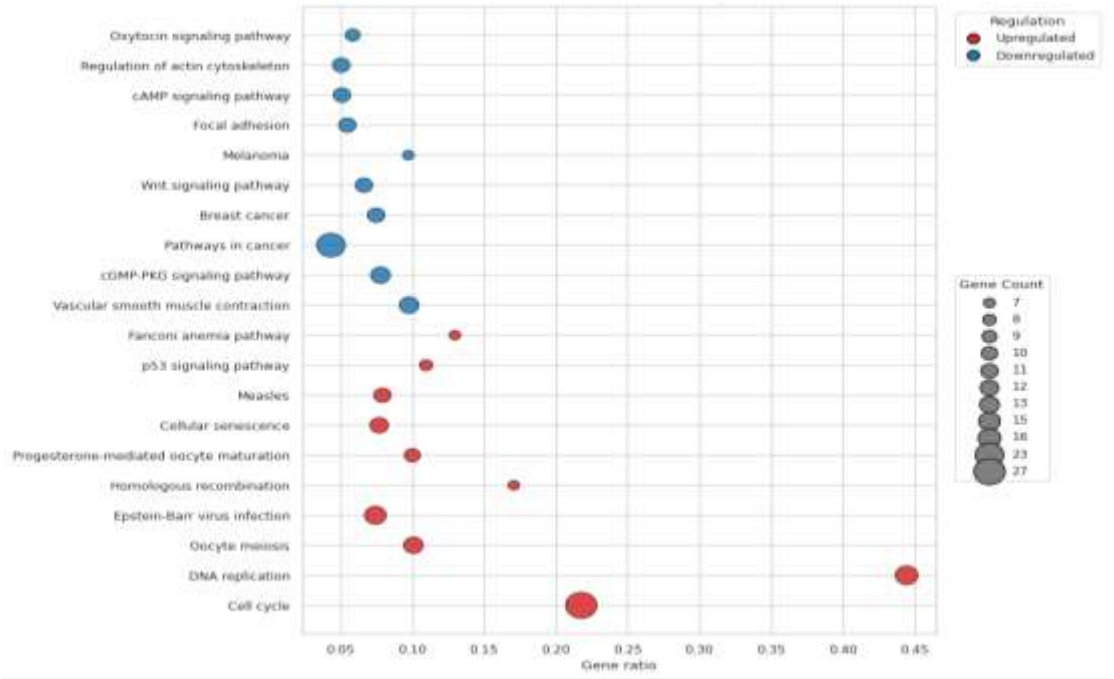

Figure 5. KEGG pathway enrichment analysis

4. DISCUSSION

The transcriptomic analysis of samples of cervical cancer showed a concerted change in the molecular state, which included the up-regulation of proliferative signatures and down-regulation of genes of normal tissue structure. Differential expression analysis revealed that there were 628 genes that had significant changes in their expression, such as 323 upregulated and 305 downregulated genes. The equal representation of up- and down-regulated genes indicates that activation of oncogenic programs is not the sole cause of cervical carcinogenesis, but loss of normal regulatory and structural functions also contributes. The highly upregulated gene set was highly enriched with DNA replication, DNA metabolic processes, mitotic spindle organization, cell cycle progression and pathways of DNA repair. These results suggest that cervical cancer cells have a higher replicative activity and greater maintenance mechanisms of their genomes. Among the notable ones were genes like *MCM4, MCM2, FEN1, CDC7, CCNB1, PCNA* and *CDK1*, indicating active replication licensing, DNA synthesis, and mitotic progression. The p53 signaling and homologous recombination pathway enrichment further implicates the existence of the replication stress and DNA damage response activity, typical of rapidly dividing malignant cells. Conversely, suppressions in genes were overrepresented in the extracellular matrix assembly, muscle contraction, epithelial development, vascular smooth muscle contraction, Wnt signaling, and the focal adhesion pathways. Such a trend indicates that there is a disorganization of tissues, cell adhesion, and cell differentiation functions. The decreased expression of genes like *MYL9, TAGLN, LTBP4* and *IGF1* helps in the interpretation that cervical cancer tissue is subjected to structural remodeling and loss of normal cell identity. Collectively, these findings indicate that there was a two-fold etiology of disease in augmented proliferative pressure and diminished preservation of usual tissue structure. The prevalence of cell cycle and DNA replication pathways is also compatible with their previous bioinformatics results on cervical cancer development, in which mitosis, DNA replication, and cell division genes were over and over again found to be key molecular features of the advancement of the disease (Yi et al., 2020). The identified increase in minichromosome maintenance genes is also consistent with the previous research that indicated that MCM family members, and especially *MCM2*, are linked with cervical cancer progression and growth (Kaur et al., 2019). More evidence of the enrichment of replication-related genes in the current analysis is the literature on the dysregulation of thymidine kinase and DNA synthesis-related genes in cervical squamous cell carcinoma (Liang et al., 2024). Involvement of DNA repair-related genes, such as *FEN1*, is biologically plausible, with structure-specific nucleases playing a role in genome stability, and increasingly regarded as relevant targets in cancer therapy (Sun et al., 2024). The epithelial down-regulation of extracellular matrix and structural genes is consistent with the evidence that epithelial remodeling and epithelial-mesenchymal transition are a major part of cervical cancer progression. Molecular alterations that occur due to HPV have been indicated to stimulate epithelial-mesenchymal transition via pathways that involve TGF-β-related signaling (Han et al., 2022). On the same note, the latent transforming growth factor beta binding proteins have been implicated in the immune-suppressive signaling and metastatic behavior in cervical cancer, and thus, it supports the applicability of the altered LTBP pattern in this case (Gu et al., 2022). Some of the candidate genes that were found in this analysis also agree with independent cancer studies. Upregulated in the current findings, *STYK1* has been reported to facilitate epithelial-mesenchymal transition and tolerance to therapy in ovarian cancer, suggesting the possibility of wider applicability in gynecological cancers (Shi et al., 2019). Similarly, OSMR upregulation can be of biological importance, with OSMR-targeted inhibition having been demonstrated to prevent tumor growth and *STAT3* signaling in ovarian cancer models (Geethadevi et al., 2021). The finding of downregulated candidate *ZFP36L2* also aligns with the fact that miR-520d-3p inhibits cervical cancer growth and epithelial-mesenchymal transition by targeting *ZFP36L2*, suggesting that it may be a component of cervical cancer regulatory pathways (Zhang et al., 2023). Other recent studies also substantiate

the oncogenicity of genes like *TMEM160* in cervical adenocarcinoma cells, which support the expanded significance of transcriptomic techniques in identifying tumor-promoting genes (Herrera-Quiterio et al., 2025). The general trends in the pathways are also similar to other cervical cancer bioinformatics studies, which have found enrichment of cell cycle, DNA replication and cancer signaling pathways among differentially-expressed genes (Wu & Xi, 2021). Other diagnostic and prognostic bioinformatics studies have also identified important genes and pathways that drive cervical cancer development, which, in turn, underscores the translational value of combined gene and pathway analyses (Yang et al., 2020b). Additionally, biomarker and small-molecule screening experiments have highlighted that DEG-based methods can be effective in finding potential therapeutic choices in cervical cancer (Qiu et al., 2020).

The results indicate that cervical cancer is marked by the high activity of DNA replication and cell cycle machinery, which are important mechanistic characteristics and possible therapeutic weaknesses. Candidate biomarkers or therapeutic targets include genes like *CDK1, CCNB1, CDC7, PCNA, MCM2, MCM4,* and *FEN1* due to their role in key processes in proliferation and genome maintenance. The repression of extracellular matrix and differentiation-related genes also suggests that both the loss of structural organisation can play a role in tumor development, invasion, and tissue identity changes. These findings also support the usefulness of re-analysis of transcriptomics in finding mechanistic patterns using available data. Instead of examining individual DEGs, a combination of gene-level changes and GO and KEGG enrichment would give a better biological perspective of disease progression. This method can help in prioritizing biomarkers in the future and inform experimental validation of candidates.

Certain constraints are to be recognized. The small sample size used in the cervical cancer comparison could be a limitation on the statistical power and possibly explain the lack of highly significant results when the sample was corrected by stringent multiple-testing. It was analyzed using expression data through microarray analysis, which has a relatively low dynamic range in comparison to next-generation sequencing methods and might not be capable of completely resolving transcriptomic complexity. Moreover, the results were obtained based on secondary sources and were not confirmed by in vitro and in vivo experimental models.

Future research should aim at validating the identified genes in an independent cohort and larger transcriptomic data to make it robust and reproducible. The functional roles of the main candidates, including *MCM4, FEN1, CDK1, OSMR* and *ZFP36L2*, should be further justified through in vitro cell-based tests and in vivo models. Combination with proteomic, epigenomic, and clinical outcome data can also enhance the biological and translational relevance of those findings and aid in their further use in precision oncology.

5. CONCLUSION

The transcriptomic examination of data on gynecological cancer demonstrated that cervical cancer had a distinctive molecular signature with the activation of proliferative and genome-maintenance signatures, as well as the inhibition of structural and differentiation-related signatures. The results of the identification of 628 differentially expressed genes, such as the major candidates *MCM4, MCM2, FEN1, CDK1, OSMR,* and *ZFP36L2*, demonstrate the significance of cell cycle regulation, DNA replication, DNA repair, and extracellular matrix remodeling in the evolution of diseases. Other enrichment analyses revealed that functional and pathway enrichment of cervical cancer was enriched with elevated cell cycle activity and DNA replication, and decreased normal tissue-related processes of epithelial development, muscle contraction, Wnt signaling, and focal adhesion. The results offer mechanistic understanding of cervical cancer etiology and candidate molecular targets that might be of diagnostic and therapeutic interest. Independent data validation and experimental models will be crucial in proving the biological and clinical relevance of these targets.

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