RESEARCH ARTICLE

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Alterations in *miRNA* Expression and Their Role in the Pathogenesis of Cervical Cancer

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Abstract

Background: Cervical cancer has a high incidence and mortality rate, affecting more than half a million women in 2018. Its development is strongly related to high-risk HPV infection. After infection, several cellular molecules are affected, including microRNAs (*miRNAs*), which are the focus of our study. We aimed to investigate changes in microRNA expression associated with cervical cancer and analyze the biological significance of these changes induced by HPV proteins. **Methods:** We analyzed transcriptome data retrieved from the NCBI website to investigate *miRNA* and gene expression in cervical cancer. We evaluated the alteration in expression of *miRNAs* and genes (between normal tissues and cervical cancer) using the GEO2R tool and selected those with significantly altered expression (p-value < 0.05). The target genes of *miRNAs* were predicted using the *miRNA* Pathway Dictionary Database. Subsequently, we created a network of biological pathways affected by *miRNA* deregulation using Cytoscape software and associated the altered *miRNAs* with the Hallmarks of Cancer using COSMIC v84. **Results:** We identified 10 *miRNAs* and 82 target genes with significantly altered expression levels in cervical cancer that matched the predicted results. In addition, the deregulation of these genes causes changes in 52 biological pathways. These *miRNAs* affected pathways such as interferon signaling (miR-106b-5p and miR-1183), signaling by interleukins (miR-557, miR-106b-5p, miR-15a-5p, and miR-21-5p), oxidative stress-induced senescence (miR-557 and miR-15a-5p), cell cycle checkpoints (miR-557), transcriptional regulation by P53 (miR-557 and miR-15a-5p), and the exchange of oxygen and carbon dioxide in erythrocytes (miR-15a-5p). **Conclusion:** Alterations in *miRNA* expression play an important role in the pathogenesis of cervical cancer, affecting several biological pathways and Hallmarks of Cancer, such as immune system regulation, cell cycle regulation, and energy metabolism. Thus, their analysis can contribute to the development of diagnostic and prognostic biomarkers and more effective treatments for cervical cancer.

Keywords: MicroRNAs- Uterine Cervical Neoplasms- Human Papillomavirus Viruses

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Introduction

Cervical cancer is the fourth most common cancer in women worldwide [1]. With large global variations in mortality rates, it is the leading cause of cancer-related death among women in 36 countries. In 2020, 604.127 new cases were diagnosed, with 341.831 deaths projected [2]. The development of cervical squamous cell carcinomas occurs through well-recognized premalignant precursor lesions, known as cervical intraepithelial neoplasia (CIN), graded 1-3, while the precursor stages preceding cervical adenocarcinomas are less well understood [3].

The pathogenic mechanisms of cervical cancer are initiated by high-risk human papillomavirus (hrHPV) infection. The HPV genome contains genes such as E1, E2, and E4-E7, which encode viral oncoproteins. Among these viral oncoproteins, E5, E6, and E7 deserve special mention. The E5 protein can act by activating the epidermal growth factor receptor (EGFR). The hr-HPV E6 protein binds to a component of the E3 family of ubiquitin ligases, called E6-AP (E6-associated protein ligase), and induces the formation of a complex with the p53 tumor suppressor protein, leading to genetic instability. E7 binds to and promotes the proteasomal degradation of

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the pRb protein (retinoblastoma protein), resulting in the stimulation of the G1/S phase transition of the cell cycle [4]. In addition to these well-known processes, these oncoproteins are also involved in other mechanisms, such as telomere maintenance and chromosomal stability [5].

In addition to these cellular alterations caused by oncoproteins, other pathophysiological mechanisms are also involved. For example, the infection can promote epigenetic alterations, such as modifications in the expression of noncoding RNAs [6]. MicroRNAs, also known as *miRNAs* or miRs, are small noncoding RNA molecules (approximately 18–22 nucleotides) that can regulate gene expression at the post-transcriptional level by inhibiting translation or promoting the degradation of target RNAs (mRNAs).

Mature microRNAs can target and bind to the 3′-untranslated regions (3′-UTR) of mRNA and then modulate their expression. It has been predicted that microRNAs may modulate up to 90% of mammalian genes and therefore play fundamental roles in cellular functions [7].

It is known that *miRNAs* are involved in many important intracellular processes in cervical cancer, such as cell proliferation, invasive capacity [8], differentiation, and chemoresistance [9]. Alterations in microRNAs can stimulate tumor progression by inducing mRNA degradation or suppressing translation in pathways related to tumor suppressors at the post-transcriptional stage [10].

Alterations in the expression of many *miRNAs* have been associated with the development of cervical cancer. For example, high levels of miR-21 have been detected in cervical cancer, as well as in other malignant neoplasms such as glioblastomas, breast cancer, and pancreatic cancer [11]. Other *miRNAs*, such as *miRNA*-15, are found at low levels in cervical cancer and other tumors, such as chronic colorectal cancer, pituitary adenomas, and prostate carcinoma. Therefore, *miRNA*-15 has been classified as a Tumor Suppressor *miRNA* [12].

In recent years, many studies have detected changes in these molecules in various pathologies, highlighting the importance of these molecules in understanding numerous diseases. Despite this, few studies have conducted a comprehensive analysis of the pathophysiology of *miRNAs* in cervical cancer.

Therefore, this study aimed to organize and provide biological context to all this information, as a way of contributing to the development of tools and biomarkers for the early diagnosis of cancer, assisting health professionals in choosing more individualized treatments, validating drug targets, predicting treatment responses, and proposing biomarkers for assessing disease propensity. The study also explored direct targeting of *miRNAs*, with potential implications for future therapeutic interventions. The last-mentioned strategy involved two approaches for modulating *miRNAs*: introducing molecules that mimic the expression of downregulated *miRNAs* in cancer and introducing antagomiRs, which are synthetic *miRNAs* complementary to the *miRNAs* of interest, to inhibit those overexpressed in tumors [13].

Materials and Methods

Transcriptome studies

An in silico evaluation of changes in *miRNA* and mRNA expression levels between normal and cancerous cervical samples was performed. Transcriptome studies in GEO DataSets [14] were searched using the keywords "HPV" and "cervical cancer." This search yielded 251 transcriptome files, and only those that allowed for the comparison of alterations in mRNA and *miRNA* expression levels between healthy cervical tissues and cervical cancer tissues infected by high-risk HPV were selected (Table 1 and Table 2).

Comparison between normal and cancerous tissues

These files were submitted to the GEO2R tool [14] to analyze the comparative expression of *miRNAs* and mRNAs between normal cervical tissues and cervical cancer tissues infected by HPV. Using the GEO2R tool, we selected 250 molecules (*miRNAs* and mRNAs) with the most significantly altered expression between healthy and diseased tissues. Additionally, only differentially expressed molecules with a p-value of <0.05 were selected. To increase the reliability of the results, only *miRNAs* and mRNAs that were altered in at least two studies, as suggested by Chen et al. [15], were selected.

Prediction of targets

After identifying altered *miRNAs* and mRNAs, we aimed to predict target genes using miRPathDB. However, since the data provided does not represent cells from specific organs or body parts [16], it is crucial to identify which predicted genes are altered by *miRNA* dysregulation specifically in cervical tissues. Therefore, the intersection between *miRNAs* provided by miRPathDB and transcriptome studies is important. This approach verifies that these *miRNAs* are specifically altered in cervical tissues and, more importantly, in the context relevant to our study—cervical cancer tissues infected by HPV.

We considered the RNA-*miRNA* relationship to be valid when two criteria were met: a) the prediction software (miRPathDB) indicated the relationship, and b) the molecules involved in the prediction showed altered expression in transcriptome studies comparing normal and cervical cancer tissues.

Network development and association with Hallmarks of Cancer

By analyzing the functions of each gene altered by *miRNA* deregulation, we constructed networks to visualize the affected processes. To build these networks linking *miRNAs* to genes, we utilized the Cytoscape tool [17]. Additionally, we associated genes and their pathways with the Hallmarks of Cancer, using the COSMIC tool, based on their roles in carcinogenesis [18].

Results

In our analysis, we identified 10 *miRNAs* that exhibited significant alterations. These *miRNAs* target 82 genes,

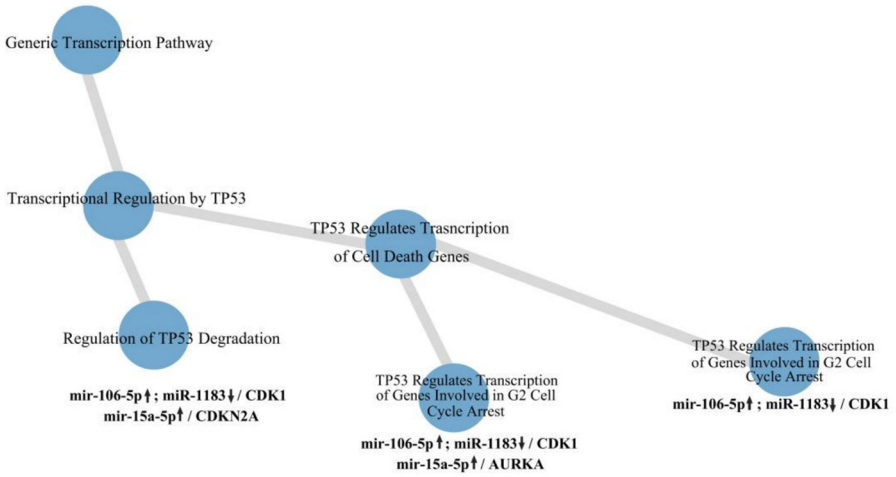

Figure 1. Network Showing an Example of Dysregulation in Pathways Related to P53 Protein Transcription. TP53, tumor protein p53; CDK1, cyclin dependent kinase 1; CDKN2A, cyclin-dependent kinase inhibitor 2A; AURKA, aurora kinase A

which, in turn, affect 52 biological pathways, including the AKT and interleukin pathways both of which play crucial roles in cellular regulation and immune response. The details of these findings are presented in Tables 1 and 2.

The alterations observed in these *miRNAs* disrupt signal transduction in various ways, interfering with essential macromolecular functions. We noted significant effects on processes such as protein and RNA metabolism, immune system regulation, small molecule transport, cell cycle progression, keratinization, cell-cell junction organization, cellular senescence, and the metabolism of lipids, carbohydrates, amino acids, and cobalamin. Additionally, signaling pathways involving NOTCH, ERBB, and GPCR genes were also impacted, as illustrated in Figure 1 and Supplementary Figure 1-9. These findings suggest a complex network of molecular interactions that may play a fundamental role in the progression of cervical cancer.

Using the COSMIC database [18] and performing a search in PubMed with the term "cancer" combined with descriptors associated with each cancer hallmark, we were able to link the deregulation of these *miRNAs* to all known cancer hallmarks (Figure 2). Particularly, the proliferative signaling pathway emerged as the most quantitatively altered pathway, indicating a significant shift in cellular proliferation mechanisms. This pathway

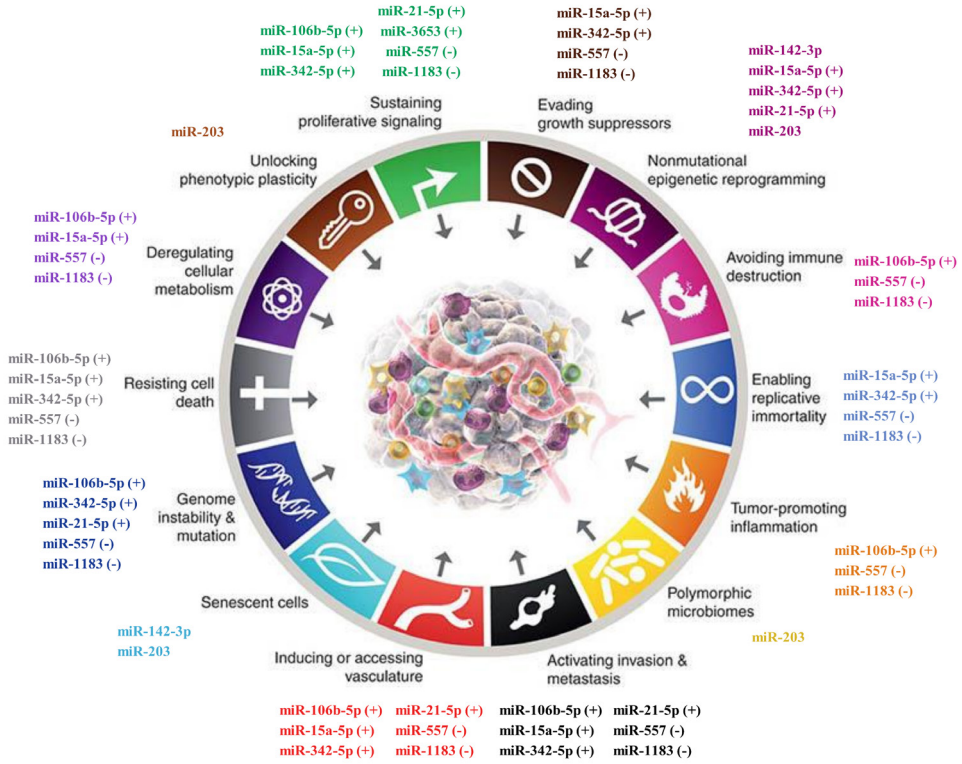

Figure 2. Association between Hallmarks of Cancer and miRNAs according to Their Function.

Table 1. miRNAs with Increased Expression in Cervical Cancer, Their Corresponding Target mRNAs, and the Biological Pathways that are Affected

microRNA		mRNA (target genes)	Main altered biological pathways
Name	Expression in Cervical Cancer		
miR-106b-5p	Increased	*DUSP1, EYA1, SLC18A2, SOSTDC1, ECT2, TGM3, TTK, E2F7, DTL, ESR1, TIMELESS, ATAD2, ACPP, DPP4, KANK2, BIRC5, CDK1, MCM2, TYMS, FGF7, EDNRB, EGR1, DSG1, TGFBR3, ANK2, LDB2, IGF1, CLDN1, ADAMTS1, EPHA3, FUT6.*	* PIP3 activates AKT signaling * Signaling by Tho GTPases * Signaling by receptor tyrosine kinases * Signaling by ERBB4 * MAPK family signaling cascades * Regulation of insulin-like Growth Factor (IGF) transport and uptake by insulin-like Growth Factor Binding Proteins (IGFBPs) * Peptide hormone metabolism (GLP-1, GIP and Ghrelin pathways) * Post-translational protein modification (deubiquination and neddylation) * SUMOylation of DNA replication proteins * Interferon alpha/beta signaling * Interleukin 4 and 13 signaling * Neutrophil degranulation * Cell cycle (G2/M checkpoints, nuclear envelope breakdown, condensation of prometaphase chromosomes, separation of sister chromatids, phosphorylation of proteins involved in the G2/M transition by Cyclin: CDC2 complexes, regulation of DNA replication, OCR1 removal from chromatin) * Platelet activation, signaling and aggregation (response to elevated platelet cytosolic Ca2+) * Norepinephrine neurotransmitter release, serotonin, neurotransmitter release * Anchoring of the basal body to the plasma membrane * PI3/AKT signaling in cancer * Formation of the cornified envelope * Tight junction interactions * Regulation of TP53 degradation, TP53 regulates transcription of genes involved in G2 cell cycle arrest
miR-142-3p	Increased	*FOXF2, FAM83D, ZEB2.*	* Wnt pathway * Hedgehog pathway * Notch pathway * PI3K/AKT/mTOR pathway
miR-15a-5p	Increased	*NUP210, GAS7, ECT2, DSG2, CELSR3, ASPM, RHCG, CA4, BIRC5, HPSE2, CEP55, NUSAP1, ABCA8, PRSS3, SLC6A8, CDKN2A, SLC5A1, KIF2C, ALOX12.*	* Signaling by Tho GTPases * Post-translational protein modification (neddylation) * SUMOylation of DNA replication proteins * SUMOylation of transcriptional factors * Metabolism of noncoding RNA * tRNA processing in the nucleus * Transport of mature transcript to cytoplasm * Neutrophil degranulation * Alpha-defensins * MHC class II antigen presentation * Interleukin 4 and 13 signaling * ISG15 antiviral mechanism * O2/CO2 exchange in erythrocytes * ABC-family proteins mediated transport * Hexose transport * Oncogene induced senescence * Oxidative stress induced senescence * Kinesins * Cell cycle (nuclear envelope breakdown separation of sister chromatids, regulation of DNA replication and amplification of signal from unattached kinetochores via a MAD2 inhibitory signal) * Formation of the cornified envelope * Oxidative stress induced senescence * Cobalamin (CBL, vitamin B12) transport and metabolism * Reversible hydration of carbon dioxide * Creatine metabolism * Regulation of glucokinase regulatory protein * Transcriptional regulation by small RNAs * Regulation of TP53 degradation

DUSP1, Dual Specificity Phosphatase 1; EYA1, Transcriptional Coactivator and Phosphatase 1; SLC18A2, solute carrier family 18 member A2; SOSTDC1, sclerostin domain containing 1; ECT2, epithelial cell transforming 2; TGM3, transglutaminase 3; TTK, TTK protein kinase; E2F7, E2F transcription factor 7; DTL, denticleless E3 ubiquitin protein ligase homolog; ESR1, estrogen receptor 1; TIMELESS, timeless circadian regulator; ATAD2, ATPase family AAA domain containing 2; ACPP, prostatic acid phosphatase; DPP4, dipeptidyl peptidase 4; KANK2, KN Motif and Ankyrin Repeat Domains 2; BIRC5, Baculoviral IAP Repeat Containing 5; CDK1, Cyclin Dependent Kinase 1; MCM2, Minichromosome Maintenance Complex Component 2; TYMS, Thymidylate Synthetase; FGF7, Fibroblast Growth Factor 7; EDNRB, Endothelin Receptor Type B; EGR1, Early Growth Response 1; DSG1, Desmoglein 1; TGFBR3, Transforming Growth Factor Beta Receptor III; ANK2, Ankyrin 2; LDB2, LIM Domain Binding 2; IGF1, Insulin Like Growth Factor 1; CLDN1, Claudin 1; ADAMTS1, A Disintegrin and Metalloproteinase with Thrombospondin Motifs 1; EPHA3, EPH Receptor A3; FUT6, Fucosyltransferase 6; ; PIP3, Phosphatidylinositol-4,5-bisphosphate 3-kinase; AKT, Protein kinase B; ERBB4, erb-b2 receptor tyrosine kinase 4; MAPK, Mitogen-activated protein kinase; GLP-1, Glucagon-like peptide 1; GIP, Glucose-dependent insulinotropic peptide; DNA, Deoxyribonucleic Acid; CDC2, Cell division control protein 2; OCR1, Ovarian cancer-related protein 1; PI3, Phosphatidylinositol 3-kinase; TP53, Tumor protein p53; FOXF2, Forkhead box protein F2; FAM83D, Family with sequence similarity 83 member D; ZEB2, Zinc finger E-box-binding homeobox 2; WNT, Wingless-related integration site; PI3K, Phosphoinositide 3-kinase; mTOR, Mechanistic target of rapamycin; NUP210, Nuclear pore complex protein Nup210; GAS7, Growth arrest-specific protein 7; DSG2, Desmoglein-2; CELSR3, Cadherin EGF LAG seven-pass G-type receptor 3; ASPM, Abnormal spindle-like microcephaly-associated protein; RHCG, Rh family C glycoprotein; CA4, Carbonic anhydrase 4; HPSE2, Heparanase 2; CEP55, Centrosomal protein of 55 kDa; NUSAP1, Nucleolar and spindle-associated protein 1; ABCA8, ATP binding cassette subfamily A member 8; PRSS3, serine protease 3; SLC6A8, solute carrier family 6 member 8; CDKN2A, Cyclin-dependent kinase inhibitor 2A; SLC5A1, solute carrier family 5 member 1; KIF2C, kinesin family member 2C; ALOX12, arachidonate 12-lipoxygenase, 12S type; MHC, major histocompatibility complex; ISG15, ISG15 ubiquitin like modifier; MAD2, Mitotic arrest deficient 2; CBL, Cbl proto-oncogene; SPRY1, Sprouty homolog 1; VIM, Vimentin; BUB1, BUB1 Mitotic Checkpoint Serine/Threonine Kinase; MSX1, Msh Homeobox 1; PTGER2, Prostaglandin E Receptor 2; MELK, Maternal Embryonic Leucine Zipper Kinase; TACC3, Transforming Acidic Coiled-Coil Containing Protein 3; PLPP3, Phospholipid Phosphatase 3; TIMELESS, timeless circadian regulator; FOXM1, Forkhead Box M1; FOSB, FosB proto-oncogene; PRC1, Protein Regulator of Cytokinesis 1; SMC4, Structural Maintenance of Chromosomes 4; CDKN3, Cyclin-dependent kinase inhibitor 3; TSPAN1, Tetraspanin 1; AURKA, Aurora Kinase A; KLK6, Kallikrein Related Peptidase 6; MAP1LC3B, Microtubule Associated Protein 1 Light Chain 3 Beta; DNMT1, DNA Methyltransferase 1; NFAT1, Nuclear Factor of Activated T-Cells 1; Wnt3A, Wnt Family Member 3A.

Table 1. Continued

microRNA		mRNA (target genes)	Main altered biological pathways
Name	Expression in Cervical Cancer		
miR-21-5p	Increased	*SPRY1, VIM, BUB1, MSX1, PTGER2.*	* Signaling by Tho GTPases * Prostanoid ligand receptors * Interleukin 4 and 13 signaling * Cell cycle (separation of sister chromatids, amplification of signal from unattached kinetochores via a MAD2 inhibitory signal)
miR-342-5p	Increased	*LDB2, MELK, TACC3, GAS7, CELSR3, PLPP3, CENPA, TIMELESS, FOXM1, FOSB, HPSE2, PRC1, SMC4, CDKN3, TSPAN1, AURKA, SLC6A8, KLK6, MAP1LC3B, DNMT1.*	* Signaling by Tho GTPases * SUMOylation of DNA replication proteins cell cycle (separation of sister chromatids, amplification of signal from unattached kinetochores via a MAD2 inhibitory signal and condensation of prometaphase chromosomes) * Creatine metabolism * TP53 regulates transcription of genes involved in G2 cell cycle arrest * miR-342-3p promoter methylation
miR-3653	Increased	*TSPAN1.*	* Moderately decreased NFAT1 nuclear translocation * Downregulation of Wnt pathway after Wnt3A stimulation

DUSP1, Dual Specificity Phosphatase 1; EYA1, Transcriptional Coactivator and Phosphatase 1; SLC18A2, solute carrier family 18 member A2; SOSTDC1, sclerostin domain containing 1; ECT2, epithelial cell transforming 2; TGM3, transglutaminase 3; TTK, TTK protein kinase; E2F7, E2F transcription factor 7; DTL, denticleless E3 ubiquitin protein ligase homolog; ESR1, estrogen receptor 1; TIMELESS, timeless circadian regulator; ATAD2, ATPase family AAA domain containing 2; ACPP, prostatic acid phosphatase; DPP4, dipeptidyl peptidase 4; KANK2, KN Motif and Ankyrin Repeat Domains 2; BIRC5, Baculoviral IAP Repeat Containing 5; CDK1, Cyclin Dependent Kinase 1; MCM2, Minichromosome Maintenance Complex Component 2; TYMS, Thymidylate Synthetase; FGF7, Fibroblast Growth Factor 7; EDNRB, Endothelin Receptor Type B; EGR1, Early Growth Response 1; DSG1, Desmoglein 1; TGFBR3, Transforming Growth Factor Beta Receptor III; ANK2, Ankyrin 2; LDB2, LIM Domain Binding 2; IGF1, Insulin Like Growth Factor 1; CLDN1, Claudin 1; ADAMTS1, A Disintegrin and Metalloproteinase with Thrombospondin Motifs 1; EPHA3, EPH Receptor A3; FUT6, Fucosyltransferase 6; ; PIP3, Phosphatidylinositol-4,5-bisphosphate 3-kinase; AKT, Protein kinase B; ERBB4, erb-b2 receptor tyrosine kinase 4; MAPK, Mitogen-activated protein kinase; GLP-1, Glucagon-like peptide 1; GIP, Glucose-dependent insulinotropic peptide; DNA, Deoxyribonucleic Acid; CDC2, Cell division control protein 2; OCR1, Ovarian cancer-related protein 1; PI3, Phosphatidylinositol 3-kinase; TP53, Tumor protein p53; FOXF2, Forkhead box protein F2; FAM83D, Family with sequence similarity 83 member D; ZEB2, Zinc finger E-box-binding homeobox 2; WNT, Wingless-related integration site; PI3K, Phosphoinositide 3-kinase; mTOR, Mechanistic target of rapamycin; NUP210, Nuclear pore complex protein Nup210; GAS7, Growth arrest-specific protein 7; DSG2, Desmoglein-2; CELSR3, Cadherin EGF LAG seven-pass G-type receptor 3; ASPM, Abnormal spindle-like microcephaly-associated protein; RHCG, Rh family C glycoprotein; CA4, Carbonic anhydrase 4; HPSE2, Heparanase 2; CEP55, Centrosomal protein of 55 kDa; NUSAP1, Nucleolar and spindle-associated protein 1; ABCA8, ATP binding cassette subfamily A member 8; PRSS3, serine protease 3; SLC6A8, solute carrier family 6 member 8; CDKN2A, Cyclin-dependent kinase inhibitor 2A; SLC5A1, solute carrier family 5 member 1; KIF2C, kinesin family member 2C; ALOX12, arachidonate 12-lipoxygenase, 12S type; MHC, major histocompatibility complex; ISG15, ISG15 ubiquitin like modifier; MAD2, Mitotic arrest deficient 2; CBL, Cbl proto-oncogene; SPRY1, Sprouty homolog 1; VIM, Vimentin; BUB1, BUB1 Mitotic Checkpoint Serine/Threonine Kinase; MSX1, Msh Homeobox 1; PTGER2, Prostaglandin E Receptor 2; MELK, Maternal Embryonic Leucine Zipper Kinase; TACC3, Transforming Acidic Coiled-Coil Containing Protein 3; PLPP3, Phospholipid Phosphatase 3; TIMELESS, timeless circadian regulator; FOXM1, Forkhead Box M1; FOSB, FosB proto-oncogene; PRC1, Protein Regulator of Cytokinesis 1; SMC4, Structural Maintenance of Chromosomes 4; CDKN3, Cyclin-dependent kinase inhibitor 3; TSPAN1, Tetraspanin 1; AURKA, Aurora Kinase A; KLK6, Kallikrein Related Peptidase 6; MAP1LC3B, Microtubule Associated Protein 1 Light Chain 3 Beta; DNMT1, DNA Methyltransferase 1; NFAT1, Nuclear Factor of Activated T-Cells 1; Wnt3A, Wnt Family Member 3A.

was followed by changes related to "inducing or accessing vasculature," which are crucial for enabling tumors to develop their own blood supply and support further growth. Additionally, alterations in pathways associated with "activating invasion and metastasis" were also prominent, reflecting the tumor's increased potential to spread to distant sites. The prominence of these pathways underscores their critical role in driving tumor progression, highlighting their importance not only in the initial stages of tumor development but also in the subsequent phases of metastasis and disease advancement. This detailed analysis emphasizes the pivotal role of these signaling pathways in the progression of cancer, providing valuable insights into potential therapeutic targets and areas for further research.

The association of specific *miRNAs* with clinical features highlights their potential as diagnostic and prognostic biomarkers. For example, *miR-3653* expression was correlated with FIGO stage and lymph node metastasis, indicating its potential use as a biomarker for cervical cancer. Additionally, *miRNAs* such as miR-203 and miR-557, which are associated with tumor suppression, showed reduced expression in tumor tissues, providing significant insights into the pathophysiology of cervical cancer. In contrast, *miRNAs* related to cell and tumor proliferation, such as miR-106b-5p and miR-142-3p, exhibited increased expression, suggesting their potential role in promoting tumor progression.

Discussion

The high-risk HPV infection is fundamental to the pathogenesis of cervical cancer and it occurs in 99.7% of patients with this disease, furthermore, the prevalence of high-risk HPV was significantly increased from 2015 to 2021 [19, 20]. After this infection, cells start to lose their stability. This instability is orchestrated by disorders in many pathways, which were already established as important for malignancy [21]. Our study brings significant findings in pathways altered by dysregulation in *miRNAs*.

There are several processes that a cell goes through in order to achieve a malignant state and, as scientific studies advance, more information are available. We found that all Hallmarks of cancer are affected by deregulation in *miRNAs*, which is a significant finding for the understanding of cervical cancer, since the hallmarks of cancer are a summarization of all biological pathways that leads a cell to malignancy [22].

Ten deregulated *miRNAs* were identified as highly associated to cervical cancer, generating disorders in biological pathways by post-transcriptional mechanisms and, consequently, generating alterations in carcinogenesis. For example, it is known that continuous stimulation to cell proliferation is fundamental for tumor progression [22], and it was found as quantitatively most affected pathways by *miRNA* alterations in our study. However, we cannot yet affirm whether sustaining proliferative signaling is the main Hallmark affected in vivo, indeed, or whether the databases are further enriched with sustaining

Table 2. miRNAs with Decreased Expression in Cervical Cancer, Their Corresponding Target mRNAs, and the Biological Pathways that are Affected

microRNA		mRNA (target genes)	
Name	Expression in Cervical Cancer		Main altered biological pathways
miR-1183	Decreased	*GINS1, ASPM, KNTC1, ECT2, CELSR3, SPRY1, ESR1, E2F7, TTK, MITF, ATAD2, CENPA, EYA1, DUSP1, EGR1, EREG, EDNRB, FGF7, MCM2, CDK1, EDN3, ANK2, MCM5, CDKN3, OSR2, CLDN1, IGF1, TGFBR3, CYR61, FBN1, ADAMTS1, EPHA3, EMP1, FOXF2.*	* PIP3 activates AKT signaling * Signaling by receptor tyrosine kinases * MAPK family signaling cascades * Regulation of insulin-like Growth Factor (IGF) transport and uptake by insulin-like Growth * Post-translational protein modification (deubiquination, post-transcriptional protein phosphorylation) * SUMOylation of DNA replication proteins and transcriptional factors * Interferon alpha/beta signaling * Platelet activation, signaling and aggregation (response to elevated platelet cytosolic Ca2+) * Integrin cell surface interactions and elastic fibers formation * Cell cycle (separation of sister chromatids, phosphorylation of proteins involved in the phosphorylation of proteins involved in the G2/M transition by Cyclin: CDC2 complexes, regulation of DNA replication, OCR1 removal from chromatin, G2/M checkpoints, amplification of signal from unattached kinetochores via a MAD2 inhibitory signal) * Anchoring of the basal body to the plasma membrane * PI3/AKT signaling in cancer * Tight junction interactions * Regulation of TP53 degradation * TP53 regulates transcription of genes involved in G2 cell cycle arrest
miR-557	Decreased	*MELK, DLGAP5, TACC3, ECT2, DSG2, CENPF, DTL, VIM, MITF, FOXM1, PLPP3, SOSTDC1, SLC18A2, COL14A1, OGN, EDN3, SMC4, APOD, CYR61, FBN1, CDKN2A, IL1RN.*	* Notch3 intracellular domain regulates transcriptional * Signaling by Tho GTPases * Regulation of insulin-like Growth Factor (IGF) transport and uptake by insulin-like Growth Factor Binding Proteins (IGFBPs) * Post-translational protein modification (neddylation and Post-transcriptional protein phosphorylation) * SUMOylation of transcriptional factors * Signaling by interleukin 38 * Transport of fatty acids * Oxidative stress induced senescence * Oncogene induced senescence * Elastic fibers formation * Collagen chain trimerization * Integrin cell surface interactions * Collagen degradation * Cell cycle (separation of sister chromatids, amplification of signal from unattached kinetochores via a MAD2 inhibitory signal and condensation of prometaphase chromosomes) * Norepinephrine neurotransmitter release * Serotonin neurotransmitter release * Formation of the cornified envelope * Oxidative stress induced senescence
miR-601	Decreased	*MITF.*	* SUMOylation of transcriptional factors
miR-203	Decreased	*FOSB, SNAI1, E2F3, NEDD9, Hakai, DKK1.*	* IL-1 Family Signaling Pathways * DNA transcription factor activity * Wnt sinaling

GINS1, GINS complex subunit 1; ASPM, Abnormal spindle-like microcephaly-associated protein; KNTC1, Kinetochore-associated protein 1; ECT2, epithelial cell transforming 2; CELSR3, Cadherin EGF LAG seven-pass G-type receptor 3; SPRY1, Sprouty homolog 1; ESR1, estrogen receptor 1; E2F7, E2F transcription factor 7; TTK, TTK protein kinase; MITF, Microphthalmia-associated transcription factor; ATAD2, ATPase family AAA domain containing 2; CENPA, Centromere protein A; EYA1, Transcriptional Coactivator and Phosphatase 1; DUSP1, Dual Specificity Phosphatase 1; EGR1, Early Growth Response 1; EREG, Epiregulin; EDN3, Endothelin-3; EDNRB, Endothelin Receptor Type B; FGF7, Fibroblast Growth Factor 7; MCM2, Minichromosome Maintenance Complex Component 2; CDK1, Cyclin Dependent Kinase 1; ANK2, Ankyrin 2; MCM5, Minichromosome maintenance complex component 5; CDKN3, Cyclin-dependent kinase inhibitor 3; OSR2, Odd-skipped related transcription factor 2; CLDN1, Claudin 1; IGF1, Insulin Like Growth Factor 1; TGFBR3, Transforming Growth Factor Beta Receptor III; CYR61, Cysteine-rich angiogenic inducer 61; FBN1, Fibrillin-1; ADAMTS1, A Disintegrin and Metalloproteinase with Thrombospondin Motifs 1; EPHA3, EPH Receptor A3; EMP1, Epithelial membrane protein 1; FOXF2, Forkhead box protein F2; PIP3, Phosphatidylinositol-4,5-bisphosphate 3-kinase; AKT, Protein kinase B; MAPK, Mitogen-activated protein kinase; GLP-1, Glucagon-like peptide 1; GIP, Glucose-dependent insulinotropic peptide; CDC2, Cell division control protein 2; OCR1, Ovarian cancer-related protein 1; MAD2, Mitotic arrest deficient 2; PI3, Phosphatidylinositol 3-kinase; TP53, Tumor protein p53; MELK, Maternal Embryonic Leucine Zipper Kinase; DLGAP5, DLG Associated Protein 5; TACC3, Transforming Acidic Coiled-Coil Containing Protein 3; DSG2, Desmoglein-2; CENPF, Centromere Protein F; DTL, denticleless; VIM, Vimentin; FOXM1, Forkhead Box M1; PLPP3, Phospholipid Phosphatase 3; SOSTDC1, sclerostin domain containing 1; SLC18A2, solute carrier family 18 member A2; COL14A1, Collagen Type XIV Alpha 1 Chain; OGN, Osteoglycin; SMC4, Structural Maintenance of Chromosomes 4; APOD, Apolipoprotein D; CDKN2A, Cyclin-dependent kinase inhibitor 2A; IL1RN, Interleukin 1 Receptor Antagonist; Notch3, Notch receptor 3; FOSB, FosB proto-oncogene; SNAI1, Snail Family Transcriptional Repressor 1; E2F3, E2F Transcription Factor 3; NEDD9, Neural Precursor Cell Expressed, Developmentally Down-Regulated 9; Hakai, E3 ubiquitin-protein ligase; DKK1, Dickkopf WNT Signaling Pathway Inhibitor 1; IL-1, Interleukin 1 Alpha.

proliferative signaling information. Therefore, our results show that, quantitatively, this pathway is the most altered, but it is necessary to perform more analysis to affirm that this pathway are the main Hallmark to cervical cancer development.

Some *miRNAs* have most well-defined biological functions by others studies, such as miR-21-5p, miR-15a-5p and miR-342-5p. MiR-21-5p is elevated in cancers and targets VIM gene that is active in apoptosis [23]. Another altered molecule is miR-1883 (decreased in cervical cancer), probably determining EREG gene overexpression and thereby stimulating cell proliferation, through tyrosine kinase receptors pathways [24]. Additionally, energy metabolism dysregulation is known

to be one of the essential steps in tumor progression [23], and miR-15a-5p and miR-342-5p are involved in this process by targeting the ALOX12 [25] and SLC6A8 [26] genes, which play roles in critical cellular energy metabolism pathways, including lipid, carbohydrate, and creatine metabolism.

It is challenging to determine a specific role or even the pathways affected by *miRNA* deregulation in cancer pathophysiology, as these molecules can simultaneously affect many genes. For example, although miR-106 is involved in the P53 protein pathway, classically associated with cancer, since its dysregulation is linked to the loss of DNA damage repair and cell death, this *miRNA* is involved in numerous biological pathways and cancers. It has been described in other studies as important in the pathophysiology of ovarian, breast, gastric, and renal cancer cells [27]. In our study, miR-106 targets 31 genes (Tables 1 and 2) and affects eight cancer hallmarks in biological pathways, including cell proliferation, apoptosis, cell cycle, invasion, metastasis, and involvement in drug resistance.

Furthermore, we found that miR-557 deregulation affects all cancer hallmarks. Studies show that miR-557 acts as a cancer suppressor by negatively regulating LEF1 gene expression [28]. The knockdown of miR-557 and, consequently, the elevation of LEF1 expression in Glioblastoma Multiforme cells inhibits invasion, migration, proliferation, and the self-renewal potential of stem-like cells [29]. Among chronic lymphocytic leukemia cases, patients exhibiting higher expression levels of LEF1 have increased proliferation and decreased apoptosis of cancer cells [30]. Moreover, they show a poorer prognosis with lower overall survival compared to patients with low LEF1 expression [31]. Consequently, LEF1 has been considered an ideal target for therapeutic treatment in addressing cancer proliferation [32], suggesting that miR-557 could also act as a biological protector in cervical cancer. Additionally, one of the genes affected by this *miRNA* is the NOTCH gene. Notch signaling balances the differentiation of certain cells, ensuring that their neighbors do not follow the same path. The deregulation of this function may contribute to carcinogenesis due to the loss of control over the differentiation process [33].

An increase in miR-15a-5p expression was observed in CC tissue. MicroRNA-15a-5p down-regulation inhibits cervical cancer by targeting TP53INP1 in vitro, functioning as a tumor-promoting gene and indicating that this *miRNA* might be a potential treatment target for cervical cancer patients [34].

MiR-3653 was found to be highly expressed in cervical cancer tissue. Results of the association analysis of *miR-3653* with clinicopathological characteristics of cervical cancer patients indicated that *miR-3653* expression was related to HPV infection, tumor diameter, FIGO stage, and lymph node metastasis. Furthermore, a low level of *miR-3653* is associated with poor prognosis in patients with hepatocellular carcinoma [35]. Therefore, *miR-3653* can be used as a diagnostic and prognostic biomarker for patients with cervical cancer [35].

MiR-142-3p (increased) targets the FOXF2 gene. Deregulation of this gene has been linked to tumorigenesis and metastasis development. Studies show that deficient expression of this gene accelerates visceral metastasis of breast cancer [30]. Additionally, DNA methylation has been strongly associated with certain cancers, such as gastric cancer (GC). Therefore, identifying genes suppressed by methylation is essential for understanding the pathogenesis of GC. Through genome-wide methylation analysis, FOXF2 (a target of miR-142-3p) transcription was found to be suppressed by methylation. Ectopic expression of FOXF2 inhibits proliferation, G1-S cell cycle transition, and induces apoptosis in mice cells, while FOXF2 knockdown had the opposite effect [36]. Moreover, miR-142-3p has been reported to induce the proliferation of non-small cell lung cancer cells through the repression of TGFbR1 and has been identified as a biomarker for aggressive and recurrent forms of lung adenocarcinomas [37].

The MITF gene (Melanocyte Inducing Transcription Factor) is targeted by miR-601, which was found to be decreased in our study. MITF operates across a broad range of activity levels, and melanoma cells that express high levels of this gene can differentiate and proliferate [38]. Additionally, miR-601 is reduced in advanced colorectal cancer compared to healthy controls [39]. Furthermore, there is evidence suggesting a possible association of miR-601 with the prognosis of this cancer, indicating its potential as a therapeutic target [40].

Another *miRNA* highly associated with cervical cancer in our study was miR-203. Its strong relationship with carcinogenesis is well documented in various cancers, such as non-small cell lung cancer, where it inhibits cell proliferation, invasion, and migration [41]. MiR-203 also inhibits ovarian tumor metastasis by targeting BIRC5 and attenuating the TGFβ pathway [42]. Specifically in cervical cancer, this *miRNA* is known to suppress tumor growth and angiogenesis by targeting VEGFA [43].

Based on our findings, we can assert that the reported dysregulation occurs specifically in cervical tissues. This is particularly important as we observed a significant reduction in the pool of *miRNAs* from transcriptomic analyses of cervical tissues, compared to the initially predicted *miRNAs*, suggesting that only *miRNAs* specific to cervical tissues were retained. The study of non-coding *miRNAs* in cancer development is relatively new and represents a critical step in understanding the pathogenesis of the disease. This research may eventually provide a foundation for developing more advanced diagnostic and therapeutic tools for cervical cancer.

MiRNAs represent just one class of non-coding RNA molecules, but they can interact with other classes of non-coding RNAs, such as long noncoding RNAs (lncRNAs), Piwi-associated RNAs (piRNAs), antisense RNAs (asRNAs), and enhancer RNAs (eRNAs) [44]. Therefore, further studies addressing these other classes of non-coding RNAs could provide complementary insights for this research and potentially answer unresolved questions about *miRNAs*.

The analysis of these biological pathways reveals that alterations in *miRNAs* are associated with key steps in the pathogenesis of cervical cancer. By affecting all Hallmarks of Cancer, we propose that *miRNAs* play a significant role

in the pathophysiology of cervical cancer, impacting many signaling pathways that are crucial for the establishment of this disease. Therefore, in addition to contributing to the understanding of the mechanisms underlying this pathology, the *miRNAs* described in this study may, in the future, pave the way for more personalized treatments, thereby reducing patient morbidity and mortality.

Author Contribution Statement

PSFF was involved in the conception of the study, literature review and drafting the manuscript. FLF was involved in the conception of the study, literature review and drafting the manuscript. TPP was involved in the conception of the study, literature review and drafting the manuscript. DRQA was involved in drafting the manuscript. AEC was involved in revising the manuscript critically for important intellectual content. VDA was involved in literature review. GAC was involved in literature review. JASJ was involved in literature review. TDR was involved in literature review. EGCN was involved in revising the manuscript critically for important intellectual content. ITO was involved in revising the manuscript critically for important intellectual content. CMB was involved in literature review. JVF was involved in revising the manuscript critically for important intellectual content. TAAMF was involved in the conception of the study, literature review and drafting the manuscript. All authors read and approved the final manuscript.

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Conflict of Interests

There is no Conflict of Interest

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