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Differences Expression of miRNAs in Types of Cervical Cancer Based on dbDEMC 3.0 and CCDB

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ABSTRACT

Background: Cervical cancer is one of the main and important causes of death and the fourth most common malignancy in females worldwide. By identifying miRNAs involved in different types and stages of cervical cancer, these miRNAs may be considered potential biomarkers for the early detection of cervical cancer or for targeted therapy, leading to new therapeutic strategies.

Materials and Methods: The dbDEMC database is a collection of differentially expressed miRNAs in human cancers, compiled from microarray and miRNA-seq data. In this study, we selected a number of experiments and listed the miRNAs with increased or decreased expression using dbDEMC. The CCDB contains data on the number of genes found in cervical cancer, classified by molecular class.

Results: By selecting cervical cancer, 10 experiments are displayed. By choosing Experiment EXP00166, in which 42 miRNAs are overexpressed and 32 miRNAs are down-expressed. By choosing the EXP00167 experiment, in which the cervical cancer subtype is cervical squamous cell carcinoma and its design is based on cancer vs. normal, 25 miRNAs were down-expressed and 28 miRNAs were up-expressed. By selecting the EXP00168 trial, which has a cervical adenocarcinoma subtype and is designed to compare high-grade tumors with low-grade tumors, 15 miRNAs have decreased expression, and 24 miRNAs have increased expression. By choosing the EXP00803 experiment, which is designed based on cancer vs. normal, and has 30 miRNAs down-expressed and 43 miRNAs up-expressed. In the CCDB database, the number of genes found in cervical cancer is 537, classified by molecular class.

Conclusion: Results of miRNAs involved in cervical cancer, retrieved from the dbDEMC database, can help identify molecular biomarkers, which can then serve as alternatives to invasive diagnostic methods such as biopsy.

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Introduction

Cervical cancer is one of the main and important causes of death and is the fourth most common malignancy in females worldwide. Identifying the type of cervical cancer may be helpful for prognosis and treatment approaches [1, 2]. Cervical cancer is classified into squamous cell carcinoma and adenocarcinoma according to microscope investigations. In the past several years, many studies have been conducted to find the molecular mechanisms and regulatory networks that play a role in tumorigenesis [3]. MicroRNAs play a critical role as regulators of cellular processes such as metastasis, invasion, apoptosis, and cell cycle progression [4, 5]. miRNAs, which are short non-coding RNAs, typically bind to the target in the 3' untranslated region, causing translational termination and mRNA degradation [6]. Even the slightest change in the expression of miRNAs can disrupt the regulation of multiple target genes and play an important role in many diseases, including cervical cancer [5, 7]. Aberrant expression of miRNAs in cervical cancer is associated with genetic alterations in miRNA loci, such as amplification, mutation, or gene deletion, as well as epigenetic silencing, which includes the deregulation of miRNA processors, DNA methylation, and transcription factors [8]. The expression levels of miRNAs are altered in all stages of cervical neoplasia and may be directly regulated by the primary viral proteins produced immediately after infection [9]. According to research, regardless of the clinical grade of the tumor, the miRNAs that are overexpressed in cervical neoplasia samples include miR-27a, miR-221, miR-196a, and miR-21, which indicate HPV positivity [10]. Moreover, miR-429 is downregulated in cervical cancer, leading to the activation of the IKKß/NF-κB pathway, which induces the production of IL6 and IFNß, thereby increasing inflammation and tumor progression [11]. In Hela cells, COX2 is considered an important functional target for miR-101. COX2 is involved in tumor development and inflammation, and miR-101 acts as a tumor suppressor by reducing COX2 expression, as well as decreasing invasion, cell proliferation, and inflammation [9]. By identifying miRNAs involved in different types and stages of cervical cancer, these miRNAs may be considered potential biomarkers for the early detection of cervical cancer or targeted therapy, leading to new therapeutic strategies. Therefore, we aimed to identify and summarize miRNAs expressed in various types and grades of cervical cancer using a database.

Materials and Methods

dbDEMC database

miRNAs are dysregulated and play important roles in most cancers. Most of the differentially expressed miRNAs in human cancers have been identified using high-throughput methods; therefore, having a unified collection of these miRNAs and their roles in tumor progression and oncogenesis can be helpful in cancer treatment. The dbDEMC database is a collection of differentially expressed miRNAs in human cancers, compiled from microarray and miRNA-seq data. In the third version of dbDEMC, it documents 403 datasets across 40 cancer types and 149 subtypes, along with a collection of 3,268 differentially expressed miRNAs. In dbDEMC database, users can easily and quickly find differentially expressed miRNAs in specific cancer types with a simple search [12]. In this database, we click on the "browse" icon in the top bar of the page, which opens a window. On the left side, in the cancer type section, we select the desired cancer, which in this case is cervical cancer, and then click submit. A page called "experiment list" will open, which contains 10 experiments related to cervical cancer. This page includes the characteristics of each experiment, such as the study method and the subgroup of cervical cancer, as well as the results of each experiment, which detail the miRNAs with increased or decreased expression. If we click on each experiment, its details are given, including the number of miRNAs with increased or decreased expression, which is listed in the last column of this table. In this study, we selected several experiments and compiled a list of the miRNAs with increased or decreased expression.

CCBD

The CCDB database is manually curated and imports genes that have been experimentally confirmed to be involved in cervical cancer at different stages. It has collected 537 genes related to processes such as gene amplification, mutation, methylation, changes in expression levels, and polymorphism associated with cervical cancer development. The CCDB database provides information on altered miRNAs in cervical cancer, offering easy access to the latest information on genes involved in cervical cancer. Given the importance of cervical cancer, access to information about the genes involved is essential [13]. In this database, by clicking on browse in the top bar of the page, a new window opens, and the genes are categorized. This categorization includes 69 genes related to methylation, 4 genes related to mutation, 5 genes related to proliferation, 110 genes related to

reduction, 257 genes related to overexpression, 23 genes related to polymorphism, and 141 genes that are not classified. Also, by clicking on "miRNA" on the main page, a list of miRNAs related to cervical cancer is displayed, along with their host genes and target genes in that table. On the main page of the database, by clicking on "database statistics," a window opens that presents important graphs of cervical cancer genes in terms of molecular class, molecular function, and biological processes of these genes.

Results

The dbDEMC database contains a set of miRNAs with differential expression in human cancers, derived from miRNA-seq and microarray data. By selecting cervical cancer, 10 experiments are displayed. Experiment EXP00166 was selected, in which the cervical cancer subtype is cervical adenocarcinoma. This study design is based on comparing normal tissue with cancer tissue, revealing that 42 miRNAs are overexpressed and 32 miRNAs are downregulated. Table 1 shows the list of miRNAs involved in the EXP00166 experiment.

By choosing the EXP00167 experiment, in which the cervical cancer subtype is cervical squamous cell carcinoma and the design is based on cancer versus normal tissue, it was found that 25 miRNAs were downregulated and 28 miRNAs were upregulated. Table 2 shows the list of these miRNAs.

By selecting the EXP00168 trial, which focuses on the cervical adenocarcinoma subtype and is designed to compare high-grade tumors with low-grade tumors, it was found that 15 miRNAs have decreased expression and 24 miRNAs have increased expression. Table 3 shows the list of these miRNAs.

By selecting the EXP00803 experiment, which is designed based on cancer versus normal tissues, it was found that 30 miRNAs were downregulated and 43 miRNAs were upregulated. Table 4 shows the list of these miRNAs.

In the CCDB database, the number of genes associated with cervical cancer is 537. In terms of molecular class, as shown in Figure 1, the genes involved in cervical cancer include a large number of transcription factors and transcription regulatory proteins, as well as adhesion molecules, cell cycle proteins, structural proteins, and growth factors. In terms of molecular function, the genes in this database are involved in transcription regulation, DNA binding, receptor activity, and more, as shown in Figure 2. In terms of biological processes, the genes in this database are involved in signal transduction, cell-cell adhesion, nucleic acid metabolism, protein metabolism, energy-related pathways, cellular metabolism, growth, the cell division cycle, and the immune response, as shown in Figure 3.

Discussion

mir-375 is one of the important miRNAs involved in cervical cancer. It was retrieved from databases, such as dbDEMC. According to the results retrieved from databases, such as dbDEMC, the expression level of mir-375 is reduced in cervical cancer. Ding et al. stated in 2020 that the expression pattern of mir-375 is reduced in cervical cancer; however, when mir-375 is upregulated, the proliferation, invasion, and migration of cervical cancer cells are reduced [14]. mir-375 has undergone epigenetic changes, which represent one of the fundamental mechanisms in carcinogenesis associated with the epigenetic regulation of miRNAs.

Liu et al. reported that DNMT1, an important enzyme that promotes DNA methylation, is regulated by the HPV-16 E6 protein, and that overexpression of HPV-16 E6 in SiHa and CaSKi cells increases DNMT1 expression [15]. mir-375 is also known to be a tumor suppressor whose expression level is reduced in cervical cancer. DNMT1-mediated reduction of mir-375 occurs due to promoter hypermethylation, which recent studies have shown to be a possible mechanism for the downregulation of mir-375 in cervical cancer cells through methylation-mediated transcriptional repression [16]. MiRNA-205 is another important miRNA in cervical cancer, which was retrieved from the dbDEMC and HMDD databases.

The HMDD database lists ASPP2 as a target of miR-205. Wang et al. reported in 2016 that ASPP2 was identified as a novel target of miR-205 in various cancers. ASPP2, which belongs to the P53 family, is a tumor suppressor. According to their research, miR-205 is increased and ASPP2 is decreased in cervical cancer, indicating an inverse relationship between miR-205 and ASPP2. As a result, ASPP2 is a direct target of miR-205 miR-205, which suppresses ASPP2 protein expression by inhibiting transcription. They also referred to miR-205 as a double-edged sword in cancer because it was initially considered a tumor suppressor, but its oncogenic functions have recently been discovered [17].

Liu et al. also reported in 2020 that miR-205 can act as a tumor suppressor by inhibiting proliferation, while

Table 1. miRNAs involved in the adenocarcinoma cervical cancer subtype according to the EXP00166 experiment, retrieved from the dbDEMC 3.0 database

Alteration	miRNA	Alteration	miRNA
Down-regulation	hsa-miR-575	Down-regulation	hsa-miR-205
Up-regulation	hsa-miR-223	Up-regulation	hsa-miR-192
Up-regulation	hsa-miR-425-5p	Up-regulation	hsa-miR-194
Up-regulation	hsa-miR-200a	Down-regulation	hsa-miR-222
Up-regulation	hsa-miR-429	Down-regulation	hsa-miR-221
Down-regulation	hsa-miR-23b	Down-regulation	hsa-miR-203
Down-regulation	hsa-miR-33	Up-regulation	hsa-miR-215
Down-regulation	hsa-miR-365	Down-regulation	hsa-miR-149
Down-regulation	hsa-miR-125b	Up-regulation	hsa-miR-92b
Down-regulation	hsa-let-7c	Down-regulation	hsa-miR-210
Down-regulation	hsa-miR-370	Down-regulation	hsa-miR-193b
Up-regulation	hsa-miR-34a	Up-regulation	hsa-miR-30a-5p
Down-regulation	hsa-miR-152	Up-regulation	hsa-miR-106b
Down-regulation	hsa-miR-560	Up-regulation	hsa-miR-21
Up-regulation	hsa-miR-19b	Down-regulation	hsa-miR-27a
Up-regulation	hsa-miR-25	Up-regulation	hsa-miR-200a
Up-regulation	hsa-miR-28	Up-regulation	hsa-miR-10a
Up-regulation	hsa-let-7g	Down-regulation	hsa-miR-27b
Up-regulation	hsa-miR-20b	Down-regulation	hsa-miR-200b
Up-regulation	hsa-miR-16	Down-regulation	hsa-miR-99a
Up-regulation	hsa-miR-363	Up-regulation	hsa-let-7i
Up-regulation	hsa-miR-125a	Up-regulation	hsa-miR-191
Up-regulation	hsa-miR-185	Down-regulation	hsa-miR-617
Down-regulation	hsa-miR-622	Down-regulation	hsa-miR-422b
Up-regulation	hsa-let-7d	Down-regulation	hsa-miR-23a
Up-regulation	hsa-let-7e	Up-regulation	hsa-miR-338
Up-regulation	hsa-miR-15b	Up-regulation	hsa-miR-107
Down-regulation	hsa-miR-493-3p	Down-regulation	hsa-miR-630
Up-regulation	hsa-miR-92	Down-regulation	hsa-miR-134
Up-regulation	hsa-miR-200c	Up-regulation	hsa-miR-93
Up-regulation	hsa-miR-650	Up-regulation	hsa-miR-146b
Up-regulation	hsa-miR-801	Down-regulation	hsa-miR-486

Alteration	miRNA	Alteration	miRNA
Down-regulation	hsa-miR-31	Up-regulation	hsa-miR-199a
Up-regulation	hsa-miR-18a	Up-regulation	hsa-miR-19a
Down-regulation	hsa-miR-451	Up-regulation	hsa-miR-199a
Down-regulation	hsa-miR-188	Down-regulation	hsa-miR-565
Up-regulation	hsa-miR-106a	Down-regulation	hsa-miR-572

Table 2. miRNAs involved in the squamous cell carcinoma subtype of cervical cancer according to the EX00167 experiments retrieved from the dbDEMC 3.0 database

Alteration	miRNA	Alteration	miRNA
Up-regulation	hsa-miR-301	Up-regulation	hsa-miR-106b
Up-regulation	hsa-miR-149	Up-regulation	hsa-miR-21
Up-regulation	hsa-miR-652	Up-regulation	hsa-miR-185
Up-regulation	hsa-miR-17-3p	Up-regulation	hsa-miR-25
Down-regulation	hsa-miR-199b	Up-regulation	hsa-miR-28
Down-regulation	hsa-miR-99a	Down-regulation	hsa-miR-560
Down-regulation	hsa-miR-193b	Down-regulation	hsa-miR-125b
Down-regulation	hsa-miR-494	Up-regulation	hsa-let-7i
Up-regulation	hsa-miR-15b	Down-regulation	hsa-miR-575
Up-regulation	hsa-miR-18a	Down-regulation	hsa-miR-203
Down-regulation	hsa-miR-638	Down-regulation	hsa-miR-370
Down-regulation	hsa-miR-572	Down-regulation	hsa-miR-375
Down-regulation	hsa-miR-148a	Down-regulation	hsa-miR-617
Up-regulation	hsa-miR-130b	Up-regulation	hsa-miR-93
Up-regulation	hsa-miR-92	Up-regulation	hsa-miR-16
Up-regulation	hsa-miR-19a	Down-regulation	hsa-miR-629
Down-regulation	hsa-miR-565	Up-regulation	hsa-miR-19b
Down-regulation	hsa-miR-451	Down-regulation	hsa-miR-622
Down-regulation	hsa-miR-422b	Up-regulation	hsa-miR-92b
Down-regulation	hsa-miR-376a	Up-regulation	hsa-miR-15a
Up-regulation	hsa-miR-181a	Up-regulation	hsa-miR-339
Up-regulation	hsa-miR-30c	Down-regulation	hsa-miR-365
Up-regulation	hsa-miR-363	Up-regulation	hsa-miR-34a
Down-regulation	hsa-miR-188	Up-regulation	hsa-miR-20b
Down-regulation	hsa-miR-486	Down-regulation	hsa-let-7c
Up-regulation	hsa-miR-146a	Up-regulation	hsa-miR-30e-3p
		Up-regulation	hsa-miR-151

Table 3. miRNAs involved in cervical adenocarcinoma comparing low-grade tumors with high-grade tumors according to EXP00168 experiments retrieved from the dbDEMC 3.0 database

Alteration	miRNA	Alteration	miRNA
Down-regulation	hsa-miR-565	Up-regulation	hsa-miR-192
Up-regulation	hsa-miR-30a-5p	Up-regulation	hsa-miR-194
Down-regulation	hsa-miR-221	Down-regulation	hsa-miR-205
Up-regulation	hsa-miR-429	Up-regulation	hsa-miR-215
Up-regulation	hsa-miR-338	Down-regulation	hsa-miR-222
Up-regulation	hsa-miR-200c	Up-regulation	hsa-miR-92b
Down-regulation	hsa-let-7c	Up-regulation	hsa-miR-200b
Up-regulation	hsa-miR-106b	Up-regulation	hsa-miR-193a
Up-regulation	hsa-miR-373	Up-regulation	hsa-miR-200a
Up-regulation	hsa-miR-200a	Down-regulation	hsa-miR-125b
Up-regulation	hsa-miR-107	Down-regulation	hsa-miR-99a
Up-regulation	hsa-miR-223	Down-regulation	hsa-miR-768-3p
Down-regulation	hsa-miR-210	Down-regulation	hsa-miR-224
Up-regulation	hsa-miR-10a	Up-regulation	hsa-miR-652
Down-regulation	hsa-miR-152	Down-regulation	hsa-miR-100
Up-regulation	hsa-miR-375	Up-regulation	hsa-miR-141
Up-regulation	hsa-miR-650	Up-regulation	hsa-miR-331
Down-regulation	hsa-miR-26b	Up-regulation	hsa-miR-425-5p
Up-regulation	hsa-miR-28	Down-regulation	hsa-miR-422b
		Down-regulation	hsa-miR-23a

other studies have shown that miR-205 can lead to tumor initiation [18]. MiR-205 has a dual function, which is consistent with the results from the data retrieved from the miRCancer database, where an increased expression pattern is observed, and from the dbDEMC database, where a decreased expression pattern is noted. Wang et al. also reported that, according to research conducted in other studies, when miR-205 is overexpressed, it suppresses two targets, CYR61 and CTGF, in cervical cancer, which are targets of miR-205 [17].

According to Xie et al., a key mechanism of miR-205 in cervical cancer is its suppression of the *CYR61* and *CTGF* genes. These genes, which are already reduced in cervical cancer, depend on miR-205 and acting as either tumor suppressors or promoters in processes like adhesion, angiogenesis, and tumorigenesis [19].

MiR-16 and its family are important miRNAs in cervical cancer. MiR-16 was retrieved from the dbDEMC databases, where an upregulated expression pattern was observed. Zubillaga-Guerrero et al. reported in 2020 that miR-16-1 is oncogenic in cervical cancer, being increased in cervical cancer cells and tissues. They found that the overexpression of miR-16-1 is associated with the activation of genes involved in the cell cycle, such as CDK27, CDK6, C10orf46, ARD10, and CCNE1, which promote cancer cell proliferation [20].

Zubillaga-Guerrero et al. reported in 2015 that *CCNE1*, a positive regulator of the cell cycle and a regulator of

Table 4. miRNAs involved in cervical cancer according to the EX00803 experiment retrieved from the dbDEMC 3.0 database

Alteration	miRNA	Alteration	miRNA
Down-regulation	hsa-miR-6068	Down-regulation	hsa-miR-3137
Up-regulation	hsa-miR-17-5p	Down-regulation	hsa-miR-1226-5p
Up-regulation	hsa-miR-92a-3p	Up-regulation	hsa-miR-7-5p
Down-regulation	hsa-miR-1185-2-3p	Up-regulation	hsa-miR-20b-5p
Down-regulation	hsa-miR-4695-5p	Down-regulation	hsa-miR-3188
Up-regulation	hsa-miR-363-3p	Up-regulation	hsa-miR-196a-5p
Up-regulation	hsa-miR-15b-5p	Up-regulation	hsa-miR-19b-3p
Up-regulation	hsa-miR-96-5p	Up-regulation	hsa-miR-93-5p
Down-regulation	hsa-miR-2861	Up-regulation	hsa-miR-3653
Up-regulation	hsa-miR-16-5p	Up-regulation	hsa-miR-15a-5p
Up-regulation	hsa-miR-205-3p	Up-regulation	hsa-miR-590-5p
Up-regulation	hsa-miR-19a-3p	Up-regulation	hsa-miR-21-5p
Up-regulation	hsa-miR-25-3p	Up-regulation	hsa-miR-20a-5p
Down-regulation	hsa-miR-638	Up-regulation	hsa-miR-106b-5p
Up-regulation	hsa-miR-141-3p	Up-regulation	hsa-miR-18a-5p
Up-regulation	hsa-miR-130b-3p	Down-regulation	hsa-miR-154-5p
Down-regulation	hsa-miR-299-5p	Up-regulation	hsa-miR-4284
Down-regulation	hsa-miR-3194-5p	Up-regulation	hsa-miR-301a-3p
Down-regulation	hsa-miR-100-5p	Up-regulation	hsa-miR-30e-5p
Down-regulation	hsa-miR-1224-5p	Up-regulation	hsa-miR-3651
Down-regulation	hsa-miR-1915-3p	Down-regulation	hsa-miR-4655-3p
Up-regulation	hsa-miR-146a-5p	Up-regulation	hsa-miR-361-3p
Down-regulation	hsa-miR-3911	Down-regulation	hsa-miR-195-5p
Down-regulation	hsa-miR-1183	Down-regulation	hsa-miR-654-3p
Up-regulation	hsa-miR-342-5p	Up-regulation	hsa-miR-183-5p
Up-regulation	hsa-miR-224-5p	Up-regulation	hsa-miR-625-5p
Down-regulation	hsa-miR-6724-5p	Down-regulation	hsa-miR-1229-5p
Up-regulation	hsa-miR-146b-5p	Down-regulation	hsa-miR-542-5p
Up-regulation	hsa-miR-4317	Down-regulation	hsa-miR-381-3p
Up-regulation	hsa-miR-135b-5p	Down-regulation	hsa-miR-762
Up-regulation	hsa-miR-664b-3p	Up-regulation	hsa-miR-200c-3p
Down-regulation	hsa-miR-4466	Up-regulation	hsa-miR-34a-5p
Down-regulation	hsa-miR-134	Up-regulation	hsa-miR-425-5p
Down-regulation	hsa-miR-4745-5p	Up-regulation	hsa-miR-24-3p
Up-regulation	hsa-miR-222-3p	Down-regulation	hsa-miR-497-5p
Up-regulation	hsa-miR-342-3p	Down-regulation	hsa-miR-2276
		Down-regulation	hsa-miR-5001-5p

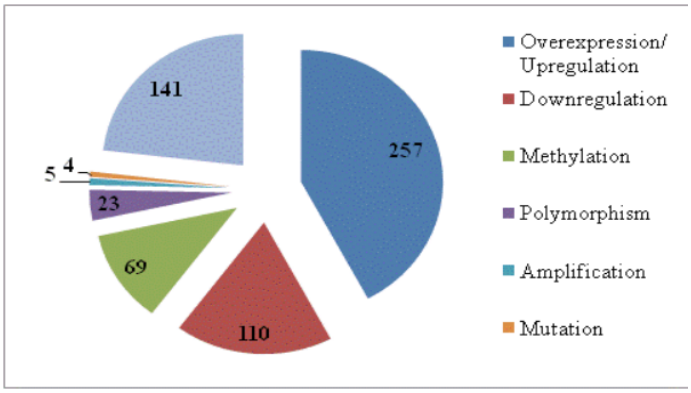

Figure 1. Gene ontology classification in cervical cancer

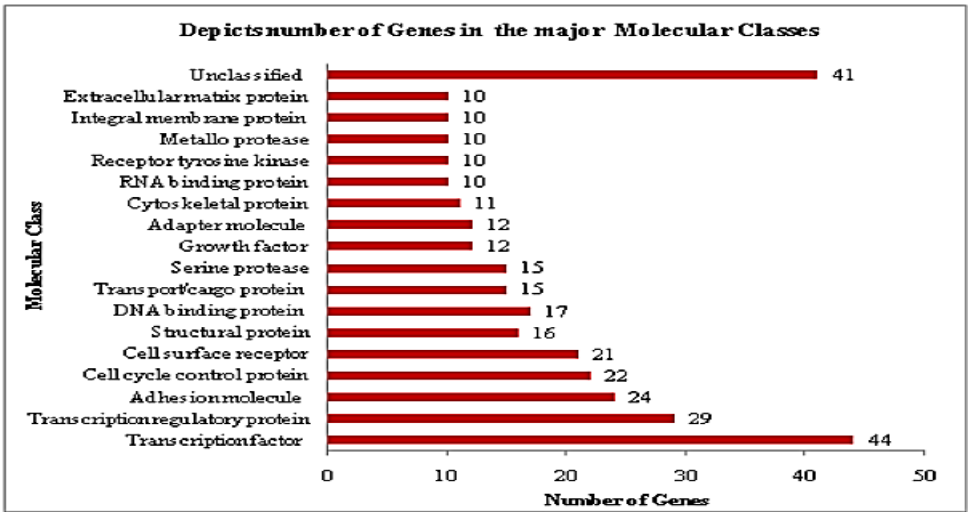

Figure 2. Number of genes involved in cervical cancer by molecular class retrieved from the CCDB database

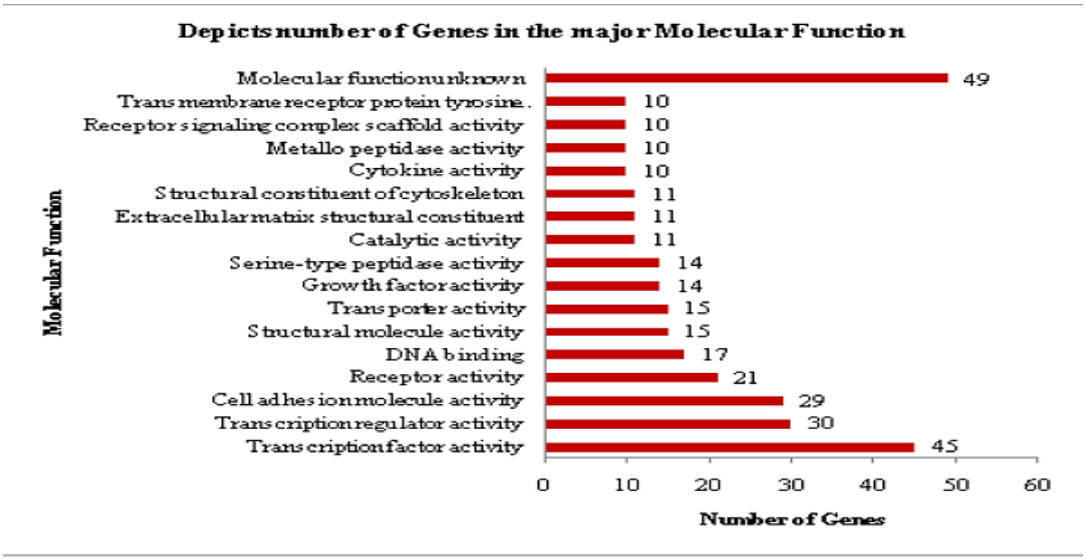

Figure 3. Number of genes involved in cervical cancer in terms of molecular function retrieved from the CCDB database

the G1-S transition, was down-regulated by miR-16-1 in cervical cancer [21]. Wu et al. reported in 2019 that miR-16-1 down-regulated *CCNE1* in human cervical cancer cells [22]. Ding et al. reported in 2020 that miR-16 has a tumor suppressor role, and that when overexpressed, miR-16 suppresses the proliferation of cervical cancer cells and facilitates their apoptosis by downregulating *KRAS* expression [23]. The results of these studies are consistent with the data retrieved from the databases.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

Authors declared no conflict of interest.

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