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Changes of Molecular, Cellular and Biological Activities According to microRNA-mRNA Interactions in Ovarian Cancer

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Abstract microRNA is a noncoding RNA sequence, 20-22 nucleotides long, which functions in silencing gene expression. Changes in normal microRNA expression lead to cancer progression. The following study has been done to elucidate the changes in the expression of microRNAs in ovarian cancer compared to the normal expression because such comparison may lead to better understanding of ovarian carcinogenesis. In the tumor samples, out of 680 microRNA types, 230 show high expression, 295 show low expression and 155 are non-expressed. When we categorized microRNAs based on fold increase >50, we found 31 high and 89 low expressed microRNAs. The huge differences in aberrant expression show the extent of changes in microRNA activities. Using Cancerminer tool, we found the corresponding mRNA targets of these abberantly expressed microRNAs. We found that the most target genes which are captured by the data process are related to cellular proliferation and carcinogenesis.

Keywords Ovarian cancer microRNA; TCGA, REC Score; Cancerminer

Background

microRNAs (miRNAs) are small noncoding RNAs, consisting of around 20-22 nucleotides, that regulate gene expression by binding complementary gene transcripts, thus causing the translational suppression of mRNA (Bartel 2009; Guo et al., 2010), (Volinia et al., 2006). Because of miRNAs' negative regulation of gene expression, over 30% of microRNAs play critical roles in fundamental processes – such as differentiation, development, cell proliferation and apoptosis in almost all living organisms (Bartel, 2004), (Esquela-Kerscher and Slack, 2006), (Calin and Croce, 2006), (Lagos-Quintana, 2001). Because miRNAs commonly weaken and destroy their target mRNAs, reverse expression relationships with sequence partner of mRNAs is obviously expected (Baek et al., 2008), (Selbach et al., 2008).

Normal tissues present different miRNA expression profiles from cancer tissues (Lu et al., 2005), (Volinia et al., 2006). The dysregulation of miRNAs is able to facilitate tumor formation and development (Croce, 2009), (Lujambio and Lowe, 2012). Comparison between differentially expressed miRNA in cancer relative to the corresponding control has been already done in previous studies of ovarian cancer. The expression level is categorized as abnormally high and low, or no expression of miRNAs (Iorio et al., 2007), (Zhang et al., 2008), (Wyman et al., 2009). For example, microRNAs overexpressed in ovarian cancer are mir-27a, mir-27b mir-23b, miR-503, miR-346 and miR-424, which are correlated with the magnitude of metastasis (Wang, Kim, and Kim, 2014), (Park et al., 2013). It has been shown that mir-199a can repress the expression of *CD44* gene, resulting in the suppression of the tumorigenicity and multidrug resistance of ovarian cancer-initiating cells (Cheng et al., 2012). Similarly, hsa-miR-140-3p targets *RAD51AP1* gene, which is responsible for a common DNA damage response pathway, showed significantly decreased expression in ovarian cancer (Miles et al., 2012).

The Cancer Genome Atlas (TCGA) is a publicly available cancer genomic database that supplies the genomic data related with individual human cancer types ("The Cancer Genome Atlas - Data Portal"

2015). In the last decade, The Cancer Genome Atlas (TCGA) project has been a large-scale collaborative effort and a powerful database portal, which let us search and compare a comprehensive directory of molecular abnormalities in various cancers. The data led us to find up-regulated and low regulated miRNAs in ovarian cancer. We used an unbiased approach to select the most differentially expressed miRNAs in cancer and normal controls. We used a novel strategy to categorize the expression data of microRNAs in ovarian cancer because miRNAs and their target mRNAs have a potential to change molecular and biological processes in the cancer cells leading to the discovery of new therapeutic options.

Materials and Methods

Patient samples

Ovarian Cancer miRNAs and control data, Level 3, are downloaded from TCGA (02/05/2014). The data analysis is illustrated as a flow chart (Figure 1). According to the expression level, 485 cancer patients' and 22 controls' data are sorted and extracted by using the R statistical program. The R original script has been written to detect aberrant miRNAs in the cancer.

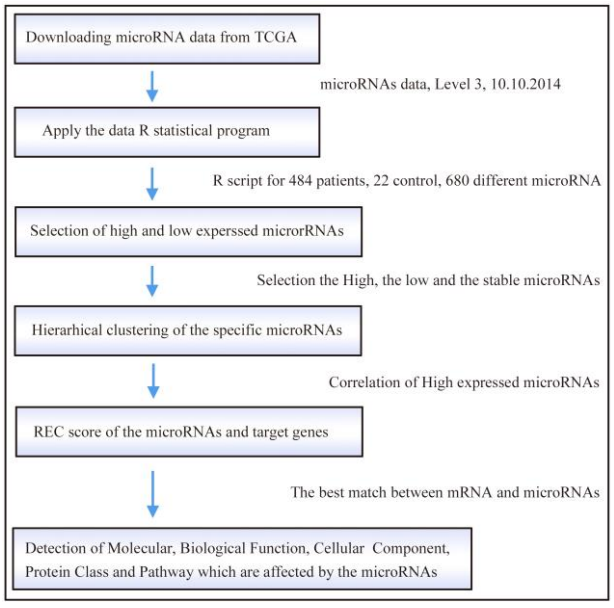

Figure 1 Flow chart of ovarian cancer miRNAs data process. The figure presents each step of the data mining work such as; downloading from TCGA, R statistical process, selection of the microRNA, REC score and molecular and biological functions. The flow chart explicates the whole data mining process

Data preprocessing

The data first downloaded and then separated into two groups, ovarian cancer and controls. Then the same ID microRNAs expression are collected as patients and controls separately. The data preprocessing has been completed by finding their fold changes.

Expression analysis

The extracted miRNAs have been applied to Cancerminer (www.cancerminer.org) which is a web-based tool that calculates the possible interaction between miRNAs-mRNAs and produces results as a REC score ("CancerMiner" 2015). The high and low expressed miRNAs (Figure 3) are hierarchically clustered by a bioinformatics tool, HCE 3.5 software program (http://www.cs.umd.edu/hcil/hce/) ("HCE - Hierarchical Clustering Explorer" 2015). The software program has different parameters, but in this paper Euclidean Distance has been used to cluster and find their correlation. Negatively affected molecular and biological functions of the target genes are categorized using http://www.pantherdb.org/ ("PANTHER - Gene List Analysis" 2015).

Results

The Extracted Data

The R code separates the expression of 680 different miRNAs into 3 main groups: high, low and not expressed (Figure 1). According to an expression value of reads per million mapped, the data shows 230 highly expressed miRNAs and 295 low expressed miRNAs (Figure 2). In addition, 155 of them are almost passive and are expressed in neither cancerous cells nor normal cells (Figure 2).

Once we found the high and low expressed miRNAs, we compared them to their expression in control samples. We found that some miRNAs are not expressed at all in control samples. Thus, we wanted to categorize the candidate miRNAs into two groups: group 1 is the miRNAs which show zero expression in controls and group 2 are the miRNA which show some expression in control samples (Figure 3). We have done this analysis for both high and low expressed miRNAs (Figure 3) (Supplementary Table 1). This analysis found 96 different miRNAs which are highly expressed in cancer, but showed no expression

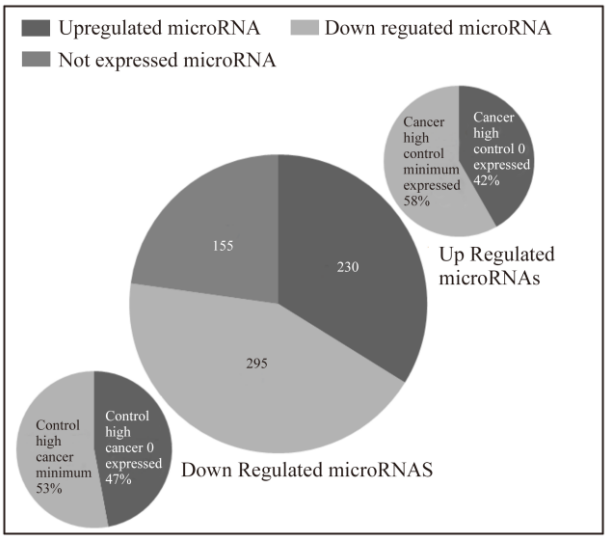

Figure 2 Ovarian Cancer Up and Down regulated miRNAs numbers. The numbers in the figure label ovarian cancer microRNA activities. The microRNAs are separated mainly into 3 groups, up regulated, down regulated and not expressed. From the numbers, it can be easily detected how many of the microRNAs expression have been changed or not as a result of the cancer

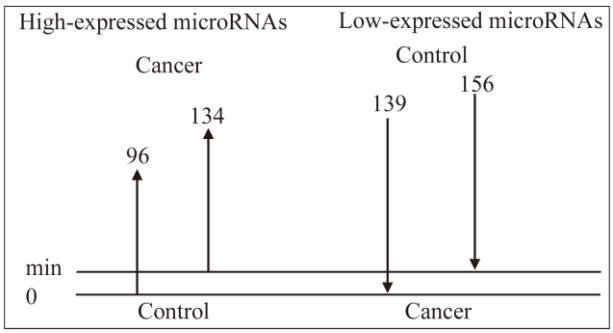

Figure 3 The high and the low expressed miRNAs in ovarian cancer. The miRNA changes profile is presented high and low expressed in ovarian cancer. After the comparison 96 non-expressed and 134 minimum expressed miRNAs are detected high expressed miRNAs. However, 139 and 156 high expressed miRNAs in control is expressed 0 and minimum in ovarian cancer

in control samples. Also, 134 miRNAs which are highly expressed in ovarian cancer show minimal expression in control samples.

For the low expression miRNAs, we found 139 miRNAs that showed zero expression in cancer samples and high expression in controls. Furthermore, we found 156 miRNAs that had a minimal expression in the cancer cells and high expression in controls (Figure 3).

Since some candidate miRNAs have very high or very low expression, we decided to select only the candidates with >50 fold change in expression. This analysis found 31 aberrantly high and 89 low expressed miRNAs (the list of candidates is given in Supplementary Table 2). The non-expressed miRNAs (n=155) are given in Supplementary Table 2.

Hierarchical clustering of the specific miRNAs

The high and low expressed miRNAs which are selected by the R program in the cancer are clustered hierarchically to understand the possible correlation among them. The most correlated 17 up-down regulated cancer miRNAs are clustered hierarchically. The clustering heat map shows us the miRNAs activity and relation between each other (Figure 4). The families of miRNAs such as, mir-509-1,-2,-3, mir-129-1,-2, mir-663, -b and mir-200a, -b are highly expressed and are the most correlated. The low expressed cancer miRNAs are also highly correlated with each other and consist of different miRNAs except mir-519a-2 and mir-519a-1 (Figure 4).

REC score of the miRNAs and target genes

To find the relation between miRNA-target interactions, the Cancerminer tool has been developed [22]. The tool gives the result as a REC score which is a rank-based statistical approach that has been developed to understand that miRNA-mRNA pairs with negative expression association has significantly better predicted miRNA-target interactions related with weakly or positively associated pairs [22]. The expression of genes and miRNAs come out antagonistically. The highest expressed 31 miRNAs have been applied to the Cancerminer tool but just 22 of them have a determined REC score (Table 1). In addition to the REC score, the association score in ovarian cancer has been determined in 22 miRNAs (Table 1). Interestingly, most of the target mRNAs were involved in tumorigenesis. It is clearly found that 73% microRNAs are directly related to tumorigenesis.

Similar analysis has been done for the low expressed miRNAs (Table 2). Out of 89 miRNAs which had >50

Table 1 The up regulated miRNAs and their target mRNAs selected based on the REC score. miRNAs are selected based on their high expression in ovarian cancer as compared to controls. The target mRNAs were found using Cancerminer database and selected based on REC score. Some miRNAs were not found in the Cancerminer database and those were excluded.%73 of the microRNAs are related to tumorigenesis

miRNA	Location	Cancerminer	REC Score	Assoc. Score	Function	Involved tumorigenesis
hsa-mir-885	3p25.3	SEPT 2	-4.22	-11.59	cyclin-dependent kinase 2	Yes
hsa-mir-663b	2q21.2	LTBP3	-4.26	-10.04	HRAS-like suppressor family	Yes
hsa-mir-449b	5q11.2	C1S	-2.69	-13.72	sirtuin 1	Yes
hsa-mir-1266	15q21.2	SNAI2	-9.92	N/A	snail family zinc finger 2	Yes
hsa-mir-383	8p22	PODNL1	-4.82	-1.41	vascular endothelial growth factor A	No
hsa-mir-1911	Xq23	NEXN	-5.55	N/A	nexilin (F actin binding protein)	No
hsa-mir-663	20p11.1	BBS1	-5.01	-7.20	jun B proto-oncogene	Yes
hsa-mir-760	1p22.1	IGFBP7	-8.10	-1.15	casein kinase 2, alpha 1 polypeptide	No
hsa-mir-449a	5q11.2	FN1	-8.45	-12.03	cell division cycle 25 homolog A	Yes
hsa-mir-1234	8q24.3	FAM168A	-4.22	-9.99	family with sequence similarity 168	Yes
hsa-mir-513c	Xq27.3	POSTN	N/A	-22.92	met proto-oncogene	Yes
hsa-mir-206	6p12.2	EVA1C	-4.07	-7.83	frataxin	No
hsa-mir-506	Xq27.3	TNFAIP6	-4.03	-23.47	tumor necrosis factor	Yes
hsa-mir-510	Xq27.3	TNFAIP6	-2.84	-23.89	tumor necrosis factor	Yes
hsa-mir-135a-2	12q23.1	GNB4	-5.44	-19.51	protein tyrosine phosphatase	Yes
hsa-mir-200b	1p36.33	TGFB1I1	-10.52	-11.48	protein tyrosine phosphatase	Yes
hsa-mir-200a	1p36.33	ZEB1	-10.88	-16.43	distal-less homeobox 5	Yes
hsa-mir-509-3	Xq27.3	POSTN	-4.09	-35.80	neurotrophic tyrosine kinase	Yes
hsa-mir-891a	Xq27.3	UFC1	-3.50	-6.81	ubiquitin-fold modifier conjugating enzyme	No
hsa-mir-187	18q12.2	CSGALNACT2	-2.355	-6.45	tubulin, gamma 1	No
hsa-mir-92b	1q22	NBL1	-5.75	-9.04	coronin, actin binding protein	Yes
hsa-let-7c	21q21.1	PCTP	-4.88	-8.45	cyclin-dependent kinase 6	Yes

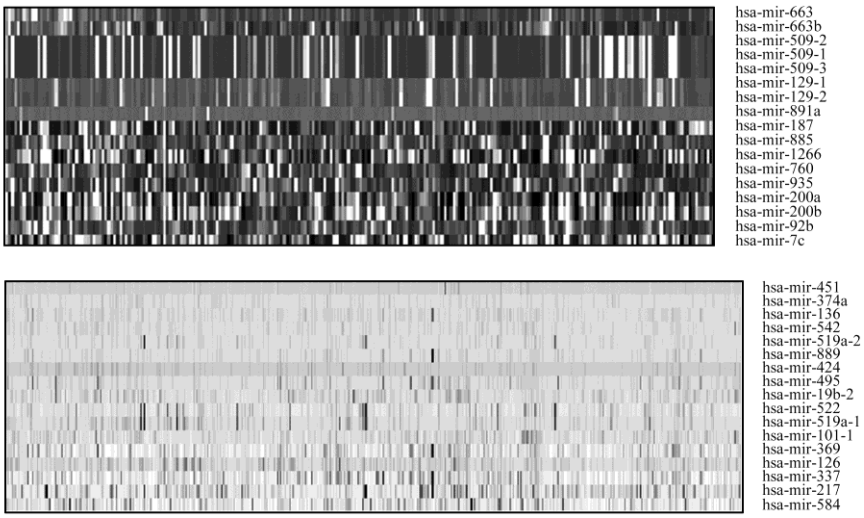

Figure 4 Hierarchical clustering of high and low express microRNA. As a result of the statistical analyses, 17 of the highest and 17 of the lowest correlated microRNAs are shown as a heat map. The first figure shows up regulated microRNAs, and the second figure shows down regulated microRNAs

Table 2 The down regulated miRNAs and their target mRNAs selected based on the REC score. miRNAs are selected based on their low expression in ovarian cancer as compared to controls. The target mRNAs were found using Cancerminer database and selected based on REC score. Some miRNAs were not found in the Cancerminer database and those were excluded from the Table. 22% of the microRNAs are related to tumorigenesis

miRNA	Location	Cancerminer	REC Score	Assoc. Score	Function	Involved in tumorigenesis
miR-515-3p	8q24.3	ARHGAP39	-3.52	-5.51	Rho GTPase Activating Protein	No
hsa-mir-519c	20p13	MAVS	-3.19	-4.77	Mitochondrial Antiviral Signaling Protein	No
hsa-mir-524	11p11.2	OR4B1	-3.20	-6.42	Olfactory Receptor, Family 4,	No
hsa-miR-498	19p12	TMEM59L	-4.34	-1.02	Transmembrane Protein 59-Like	No
hsa-mir-519e	17q22	DGKE	-3.24	0.93	Diacylglycerol Kinase	No
hsa-mir-519b	8q24.13	FAM83A	-3.65	-1.52	Family With Sequence Similarity 83	No
hsa-mir-519d	18q21.1	DYM	-3.29	1.10	Dyggve-Melchior-Clausen Syndrome Protein	No
hsa-mir-527	1q21	S100A2	-3.83		S100 Calcium Binding Protein A2	Yes
hsa-mir-520f	2q21.1	TSN	-3.50	1.69	Recombination Hotspot-Binding Protein	Yes
hsa-mir-520d	11p14.2	FIBIN	-3.35	0.57	Fin Bud Initiation Factor Homolog	No
hsa-mir-516b-1	8q24.3	ZNF7	-4	-5.81	Zinc Finger Protein	No
hsa-mir-520e	8p21.3	PHYHIP	-4.17	-2.00	Phytanoyl-CoA 2-Hydroxylase Interacting Protein	No
hsa-mir-520h	4p15.2	CCDC149	-3.52	-4.77	Coiled-Coil Domain Containing	No
hsa-mir-520g	6q16.2	FAXC	-3.26	0.63	Failed Axon Connections Homolog	No
hsa-mir-520c	2q24	SLC25A12	-3.40	1.30	Solute Carrier Family 25	No
hsa-mir-1323	18q21.33	SERPINB5	-4.18		Serpin Peptidase Inhibitor, Clade B (Ovalbumin)	Yes
hsa-mir-523	16p13.2	ABAT	-4.20		4-Aminobutyrate Aminotransferase	No
hsa-mir-520b	8p21.3	PHYHIP	-3.74	-1.92	Phytanoyl-CoA 2-Hydroxylase Interacting Protein	No
hsa-mir-376b	12p12.1	BHLHE41	-6	-16.70	Basic Helix-Loop-Helix Family, Member E41	No
hsa-mir-376c	15q14-q15	CCNDBP1	-7.72	-0.84	Cyclin D-Type Binding-Protein 1	No
hsa-mir-372	18q11.2	KCTD1	-4.50	-0.55	Potassium Channel Tetramerization Domain	No
hsa-mir-580	2q12.3	SULT1C4	-4.21		Sulfotransferase Family, Cytosolic, 1C, Member 4	No
hsa-mir-944	8q23-q24	SNTB1	-5.21		Syntrophin, Beta 1 (Dystrophin-Associated	No
hsa-mir-656	17q25.3	TMC6	-5.05	-0.41	Transmembrane Channel-Like	No
hsa-mir-655	3p21.31	PRKCD	-7.10		Protein Kinase C	Yes
hsa-mir-137	11p15.3	SCUBE2	-5.65	-0.41	hsa-mir-137	No
hsa-mir-653	10q11.22	ANXA8	-5.16		Annexin A8	Yes
hsa-mir-373	8q24.3	ADCK5	-3.57	-4.96	AarF Domain Containing Kinase	No
hsa-mir-551b	12q13.11	VDR	-7.03	-3.42	Vitamin D (1,25- Dihydroxyvitamin D3) Receptor	Yes
hsa-mir-570	7q33	CALD1	-5.85	-2.53	Caldesmon 1	No
hsa-mir-19a	3p21.31	FYCO1	-11.12	-13.78	FYVE And Coiled-Coil Domain Containing 1	No
hsa-mir-1277	6q25.2	SYNE1	-6.21		Spectrin Repeat Containing, Nuclear Envelope 11	No
hsa-mir-215	14q22.1	FRMD6	-8.87	-11.44	FERM Domain Containing 61	No
hsa-mir-607	2q12.3	SULT1C4	-4.01		Sulfotransferase Family, Cytosolic, 1C	No
hsa-mir-371	15q26.3	LRRK1	-4.21	-4.85	Leucine-Rich Repeat Kinase 1	No
hsa-mir-144	7p14.1	SFRP4	-8.18	1.45	Secreted Frizzled-Related Protein	No
hsa-mir-518c	21q22.13	CLDN14	-3.72	-1.16	Claudin 14	No
hsa-mir-526b	19p13.3	NFIX	-4.36	-1.25	Nuclear Factor I/X (CCAAT-Binding	No
hsa-mir-517a	4p15.2	CCDC149	-3.26	-3.33	Coiled-Coil Domain Containing 149	No
hsa-mir-517b	19p13.3	NFIC	-3.23	-0.69	Nuclear Factor I/C (CCAAT-Binding	No
hsa-mir-520a	11p11.2	OR4B1	-4.12	-4.82	Olfactory Receptor, Family 4, Subfamily B	No
hsa-mir-518b	16q12.2	IRX5	-3.83	1.43	Iroquois Homeobox 51	Yes
hsa-mir-451	6q22.1	COL10A1	-7.25	0.36	Collagen, Type X, Alpha	No
hsa-mir-374a	2q31.1	HOXD8	-7.03	-1.34	Homeobox D8	Yes
hsa-mir-136	6q14.1	PHIP	-6.13	0.76	Pleckstrin Homology Domain Interacting Protein	Yes
hsa-mir-542	19q13.32	BBC3	-5.41	-7.19	BCL2 Binding Component 3	Yes
hsa-mir-889	16q22.1	TRADD	-7.26	-4.19	TNFRSF1A-Associated Via Death Domain	Yes
hsa-mir-424	22q13.1	CBX7	-6.83	-2.99	Chromobox Homolog 7	Yes
hsa-mir-495	18q23	HSBP1L1	-7.02		Heat Shock Factor Binding Protein 1-Like 11	No
hsa-mir-522	9q31.1	TMEM246	-3.95	-3.36	Transmembrane Protein 246	No
hsa-mir-369	2q13	PSD4	-6.68	1.18	Pleckstrin And Sec7 Domain Containing 4	No
hsa-mir-337	14q12	PSME2	-7.80	-4.14	Proteasome (Prosome) Activator Subunit 2	No
hsa-mir-217	2p23.3	RAB10	-4.90		RAB10, Member RAS Oncogene Family	No
hsa-mir-584	18q12.2	ZNF396	-5.40	-2.55	Zinc Finger Protein 396	No

lower expression, 54 miRNAs had defined REC score and the corresponding target mRNA. The down regulated microRNAs relation to tumorigenesis is only 22%. It is obviously shown that up regulated microRNAs are more related to tumorigenesis.

Molecular Activities, Biological Function, Cellular Component and Protein Class affected by the miRNAs

The cancer's cellular activities are obviously affected by miRNAs. According to the REC score, the mRNAs are categorized in order to understand how the extracted miRNAs are active and negatively affecting molecular activities, biological function, cellular component (Figure 5), protein class and pathway (Figure 6) in the cancer type. It is easily observable what kinds of mechanisms change or could potentially change as detected by a percentage in the cancer type.

Conclusion

The changes in microRNA expression between cancer and normal ovarian tissue samples, either high and low, show that there is a dynamic expression of the miRNAs. Although the sequence of miRNAs is complementary to many genes, they show a preference for specific genes. Depending on the antagonistic relationship between miRNAs and mRNAs, some of the functions in cells are suppressed. The main target of this study was to understand how miRNAs are aberrantly expressed in ovarian cancer, destroying the cellular balance and progressing to cancer. We found that out of 680 different miRNAs, 230 show high and 295 show low expression. Furthermore, 31 show >50 fold higher expression in cancer, and 89 show >50 fold lower expression in cancer as compared to control

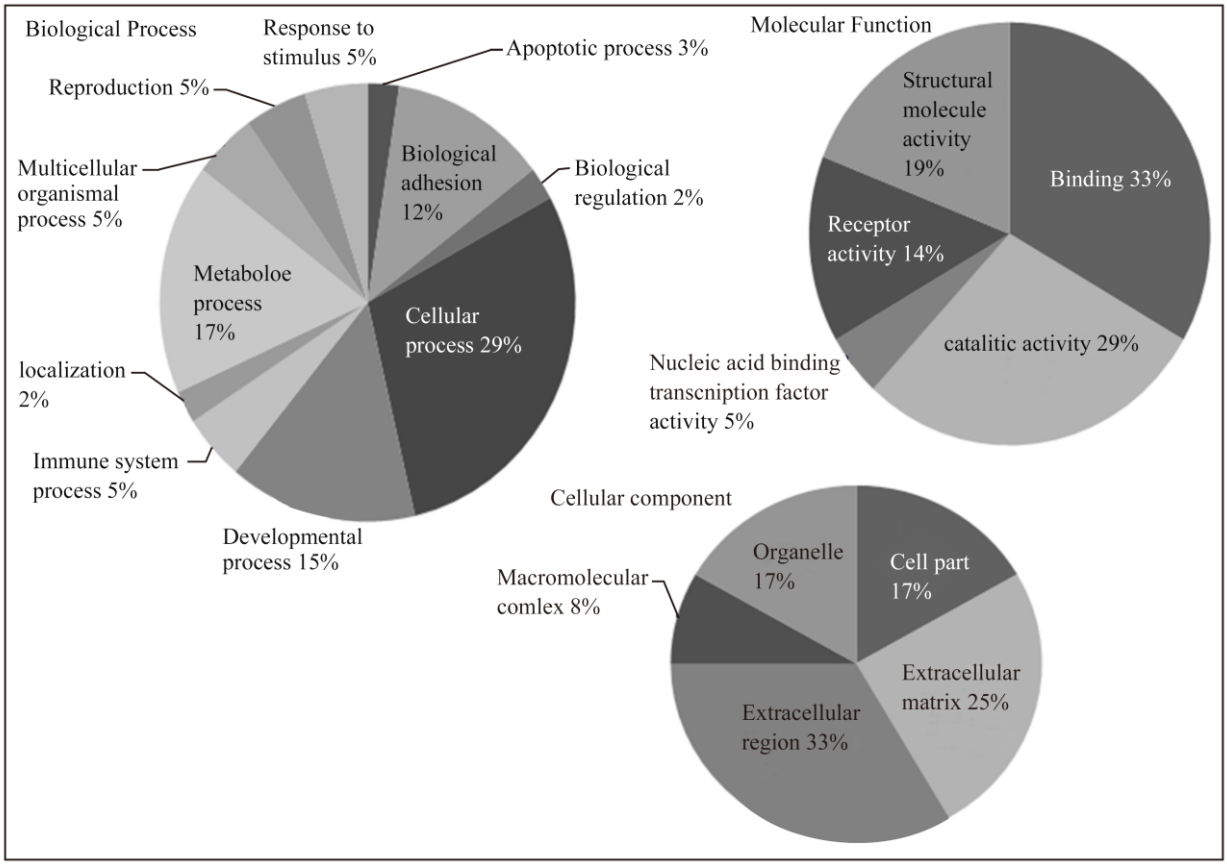

Figure 5 Changes in biological process, molecular function, and cellular component in ovarian cancer by high expressed miRNAs. Aberrantly expressed microRNAs repress some vital processes in the cell. According to REC score, mRNAs are listed and run through the REC program to find changes in their own biological process, molecular function and cellular component. All of the changes are given as a percentage in the figure to clearly detect the changes.

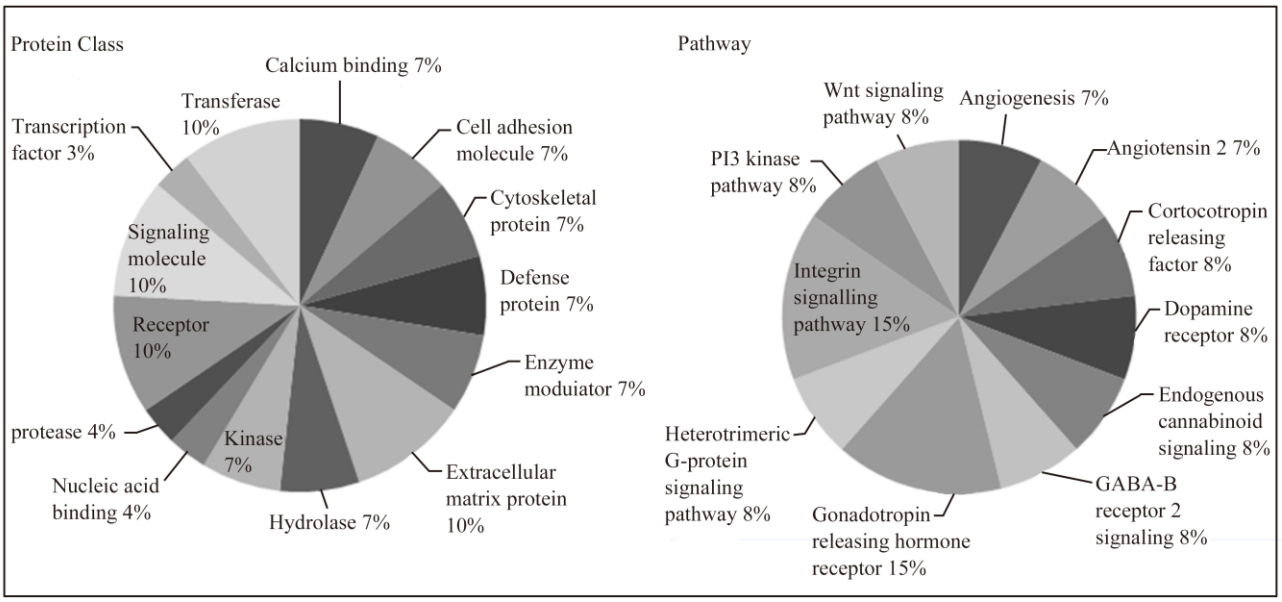

Figure 6 Changes of Protein Class and Pathway

samples of ovarian tissue. The work will help the molecular geneticist and clinicians to make a new drug which targets the different genes.

Abbreviations

TCGA, The Cancer Genome Atlas Data Portal REC Score, association recurrence (REC) score Cancerminer, microRNA finder tool

Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

SDogan carried out the Bioinformatics and data mining studies, analyzing microRNA expression level, performed the statistical analysis, and drafted the manuscript. AKozaric carried out the molecular effects of microRNA in the cancer. The design of the study has been done by the two authors. All authors read and approved the final manuscript

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