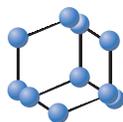
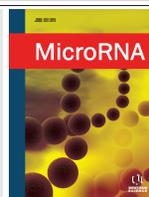


SYSTEMATIC REVIEW ARTICLE

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SCIENCE

A Systematic Review and Bioinformatics Study on Genes and micro-RNAs Involving the Transformation of Endometriosis into Ovarian Cancer



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Abstract: Background: Along with the description of tumorigenesis processes in endometriosis-related ovarian cancer, identifying dysregulated miRNAs, the target genes of these miRNAs, and the processes abnormally affected by dysregulated miRNAs is essential, which was our goal.

Methods: Two reviewers individually evaluated the articles which collected relevant information including genes and miRNAs involved in the transformation of endometriosis into ovarian cancer. To assess the mature sequence of miRNAs and also their chromosomal positions, miRPathDB software was employed. To determine the main target gene predicted for each considered miRNAs, the TargetScanS Web server was applied. The interaction of each gene with other genes associated with endometrial-related ovarian cancer was determined by GeneMANIA software. Finally, to design integrated model of miRNAs-targeted genes interaction network, the Cytoscape software was used.

Results: The final number of studies available for analysis was 6 manuscripts including 22 miRNAs described as involved in the transformation of endometriosis into different subtypes of ovarian cancers (14 miRNAs up-regulated and 8 miRNAs down-regulated). Three miRNAs of miR-141 (up-regulated), miR-205 (down-regulated), and miR-125b (down-regulated) were revealed as the originator for genetic interactions leading to carcinogenesis. We could show some common loops and pathways including uncontrolled cell proliferation and abnormal apoptosis (mediated by PTEN gene induced by miR-21 and miR-214), and disaggregation and epithelialization (mediated by ZEB1 and ZEB2 genes induced by miR-200).

Conclusion: According to our analysis, up-regulation of miR-141 and down-regulation of miR-205 and miR-125b have a central role in transforming endometriosis to ovarian cancer.

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1. INTRODUCTION

Endometriosis is a frequent benign gynecological disorder characterized by the presence of endometrial-like glandular epithelium outside the uterus. According to the global literature, about 10 to 15 percent of women in reproductive ages suffer from this phenomenon [1], but its prevalence is expected to be higher in infertile women and in those with chronic pelvic pain [2, 3]. Although, endometriosis has been known as a benign disease, the risk of endometriosis malignant transformation remains controversial [4]. Some large studies evidenced ovarian carcinoma in 5% to 10% of cases suffering endometriosis, while in some others, malignant

transformation through endometriosis has been shown clinically in 0.7% to 1.6% of patients in long-term follow-up [5]. The pathological malignant transformation can be found in different histologic subtypes of ovarian cancer with more dominance for clear cell carcinoma and endometrioid. The primary evidence on the transformation of endometriosis into ovarian cancer was presented by Sampson and colleagues in 1925 [6]. Since then, the likelihood of ovarian cancer in women with history of endometriosis has been exclusively studied. Especially since common predisposing factors of both conditions such as early age at menarche, late age of menopause, or nulliparity as well as common inhibitory factors such as using contraceptives, hysterectomy, tubal ligation, and pregnancy were identified [7]. Overall, according to systematically assessment of both cohorts and case-control clinical studies and considering different confounding factors, the risk of developing ovarian cancer following the oc-

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currence of endometriosis is 1.34 to 8.95 times higher than the normal population [8]. The estimated risk has been relatively higher in some subtypes of ovarian cancer including clear cell carcinoma, low-grade serous and endometrioid tumor [9]. However, in some studies, a weak association was indicated between endometriosis and ovarian cancer [10, 11] and even some studies have indicated the lack of association between endometriosis and cancer [12]. In other words, the association between endometriosis and some types of ovarian cancer such as mucinous, borderline tumors, and high-grade serous invasive subtypes remains obscure [13]. Therefore, it seems that the pathogenesis of endometriosis, as well as its high affinity to transforming ovarian cancer, is basically multifactorial which is dependent on genetic, endocrinological and immunological factors [14, 15]. In this regard, the role of genetic variants has been strongly emphasized. In this regard, several genes have been shown as possible candidates responsible to neoplastic tendency of endometriosis and the critical role of some genes such as PTEN, KRAS, and TP53 has been demonstrated [16, 17]. In subsequent efforts, the signaling pathways resulting in the activation or suppression of these genes which lead to the development of cancer were described. For instance, it has been shown that specific mutations in PTEN gene located on chromosome 10 can activate PI3K signaling pathway leading to develop clear cell subtype of ovarian cancer [18, 19]. Therefore, the key role of genetic variants and mutations, as well as their related pathways became obvious.

By discovering MicroRNAs (miRNAs) as the major regulatory elements, a new perspective emerged about the role of genetic abnormalities in cancer development. MiRNAs are a family of small non-coding RNAs with a broad role in the regulation of gene expression and protein synthesis. MiRNAs bind to target mRNA to stimulate or inhibit the production of regulatory proteins in different cellular pathways [20]. A wide range of biological processes and cellular pathways are regulated by up-regulation or down-regulation of miRNAs and in this regard, deregulation of these particles has been exclusively shown in different types of cancer cells. Until now, more than 1800 annotated human miRNA precursor genes have been identified that processed to about 2600 miRNA sequences [21]. The activation of miRNAs is based on different pathways. Firstly, miRNAs can act as a ligand activating signaling pathways such as pro-inflammatory processes in cancer cells leading tumor progression and metastasis [22]. In fact, abnormal up-regulation or down-regulation of miRNAs due to abnormal changing transcriptional control, chromosomal defects, epigenetic changes, or any defects in machinery of miRNA biogenesis. In other words, any changes in both chromosomes and the genes as amplification defects, translocation or deletion can result in abnormal changes in genomic miRNA copy numbers leading to the changes in normal regulatory functions of miRNAs [23]. Genome-wide association studies could discover many genes encoding miRNAs in cancer-related genomic regions that might be oncogene or have tumor-suppressing role [24, 25]. As initially described by Teague in 2010, miR-125a and miR-125b are tumor suppressor miRNAs that are up-regulated in the endometriotic lesions and involve in control-

ing cell migration and invasion. They could show that inactivation of these miRNAs may involve in creating ovarian endometrioid adenocarcinomas arising from endometriosis by elevating ERBB2 as an oncogenic component of the Epidermal Growth Factor (EGF) receptor family. They also showed that up-regulation of three miRNAs of miR-21, miR-26a and miR-214 might be related to endometrioid cancer progression sourced by endometriosis. Suryawanshi *et al.* in 2013 introduced some miRNAs including miR-21, miR-362-5p, and miR1274a that differentiate between endometriosis and ovarian cancer. In 2014, Wu *et al.* showed different expression of some tumor suppressor miRNAs (miR-1, miR-133a, and miR-451) and also the oncogenic miRNAs (miR-141, miR-200a, miR-200c, and miR-3613) in women suffering from ovarian cancer as compared to those with endometriosis and finally hypothesized that the pointed miRNAs may involve in tumorigenesis from endometriosis transformation. Dong *et al.* in 2015 described overexpression of miR-191 in endometriosis-associated ovarian cancer than in those with endometriosis alone. They also demonstrated that overexpression of miR-191 could regulate TIMP3 expression that affects malignant cell proliferation and induces ability to invasion. As shown by Chang *et al.* in 2016, genetic variants in miR-100 and miR-196A2 involve in endometriosis transformation into ovarian cancer. Suppressing these variants could suppress cell growth by flaring cell arrest at G2/M stage. Finally, Braicu *et al.* [31] showed that up-regulation of some miRNAs is involved in inflammatory processes (miR-325) and those which activate epithelial-mesenchymal transition process (miR-200a, miR-200b, miR-200c, miR-141, miR-429, miR-30a, miR-145 and miR-205) can contribute to malignant transformation from endometriosis.

The expression of own miRNAs is mediated by different transcription factors such as different proteins and enzymes that any change in the expression of such factors provides the basis for tumorigenesis. Overall, any abnormality in biogenesis of miRNAs may induce tumor development mainly by disturbance in the signaling pathway, resistance of cell death, inducing processes of metastasis and inducing angiogenesis. Therefore, along with description of tumorigenesis processes, identifying dysregulated miRNAs, the target genes of these miRNAs, and the processes abnormally affected by dysregulated miRNAs is essential.

2. MATERIALS AND METHODS

The present study had two phases including a systematical review of the literature and an informatics-based study. In the first step, we performed a massive search in several search databases including PubMed (Medline), Google Scholar, Web of Science, and Scopus databases. We also browsed the Cochrane Central Register of Controlled Trials (CENTRAL) and the Connecting Research in Security to Practice/Research Portfolio Online Reporting Tool (CRISP/RePORT) National Institutes of Health (NIH) databases for unpublished trials. The search keywords included: “endometriosis”, “ovarian cancer”, “gene”, and “miRNA”. After this massive search, titles and abstracts of retrieved documents were screened and all irrelevant articles were excluded. The

Table 1. The details of the studies evaluated for our systematic review.

Author, Year	Study Type	No. of Patients	Study Method	Genes Studied	miRNAs Associated with Transformation
Teague, 2010	Systematic Review	---	Reviewing the literature	ZEB1, ZEB2, PTEN, KRAS,	miR-200a, miR-200b, miR-200c and miR-429, miR-125a, miR-125b, miR-26a, miR-21, miR-221, miR-145,
Suryawanshi, 2013	Prospective Cohort	20	RT-qPCR technique	----	miR-21, 362-5p, and 1274a, 628-3p
Wu, 2014	Prospective Cohort	19	RT-qPCR technique	----	miR-1, miR133a, miR-451, miR-141, miR-200a, miR-200c, and miR-3613
Dong, 2015	Prospective Cohort	36	RT-qPCR technique	TIMP3	miR-191
Chang, 2016	-	218	RT-qPCR technique	HOXA5, MAP3K1	miR-100, miR-196A2, miR-26A1, miR-499, miR-423
Braicu, 2017	Prospective Cohort	78	RT-qPCR technique	PTEN, KRAS, HRAS, HMGA-2	miR-93, miR-141, miR-155, miR-429, miR-200c, miR-205, miR-492

study categories included case reports, case series, clinical trials, experimental studies and review studies. The exclusion criteria were: non-English language studies and studies with incomplete data or full-text unavailability. Two reviewers extracted data separately regarding study details (study design, publication year and patient number), patient characteristics, and details of the molecular assessments (Tables 1 and 2). The un-blinded reviewers individually evaluated the articles without divergences in data collection to collect relevant information including genes and miRNAs involved in the transformation of endometriosis into ovarian cancer. Any discrepancies between the two reviewers about the inclusion or exclusion of studies were discussed with the third researcher to reach the consensus. The kappa coefficient test was applied in order to assess the level of agreement between the reviewers. To assess the mature sequence of miRNAs and also their chromosomal positions, miRPathDB software (version 1.1) was employed (<https://mpd.bioinf.uni-sb.de>). Also, to determine the main target gene predicted for each considered miRNAs, the TargetScanS Web server (version 3.1) (<http://www.targetscan.org>) was applied which included miRNA target prediction for ~17,000 genes against 163 conserved miRNA families (corresponding to 238 miRNAs). The interaction of each gene with other genes associated with endometrial-related ovarian cancer was determined by GeneMANIA software (<https://genemania.org/>) indexing 2277 association networks containing more than 500 million interactions mapped to 163.599 genes in human. The interactions were calculated on the basis of FDR (False Discovery Rate) and coverage classified under four categories a) Shared protein domains, b) Co-expression, c) Co-localization and d) Genetic interactions. To assess interactions between each miRNAs with a cluster of the targeted genes, the Freiburg metaMIR software was used (<http://rna.informatik.uni-freiburg.de>). In this tool, the pointed interactions were weighted by considering a score such that a higher score indicates more powerful interaction. Finally, to design integrated model of miRNAs-targeted genes interaction network, the Cytoscape software (version 3.6.1.0) was applied.

3. RESULTS

3.1. Study Selection

In total, 15 citations were found in the initial literature search out of which 9 citations were excluded as they did not meet the inclusion criteria (Fig. 1). The final number of studies available for analysis was 6 manuscripts including 22 miRNAs described as involving in transformation of endometriosis to different subtypes of ovarian cancers (14 miRNAs up-regulated and 8 miRNAs down-regulated) [26-31].

3.2. MiRNAs and Targeted Genes are Involved in the Transformation of Endometriosis into Ovarian Cancer

Using the miRPathDB software, in total 22 miRNAs were identified as the main candidates for the transformation of endometriosis into different subtypes of ovarian cancers (Table 2). The positions of the pointed genes include the chromosomes 1,3,5,6,11,12,13,17,18,19, and X. The main target genes for these 22 miRNAs are shown in Table 2. Some miRNAs target a single gene and some others target a cluster of the genes, however the conditions of target genes such as PTEN (targeted by 6 miRNAs), ZEB1 (targeted by 6 miRNAs), and ZEB2 (targeted by 5 miRNAs) are more highlighted. As shown in Fig. (2), many pathways and gene to gene interactions seem to be involved in the transformation of endometriosis into ovarian cancer. In this regard, many genes can interact with multiple pathway genes, but the prominent genes interaction included co-expression of the genes in about 56% of the cluster (Table 3). In this regard, the main pathways which are activated in the background of this cluster based on FDR values are transforming growth factor beta receptor signaling pathway, response to transforming growth factor beta, cellular response to transforming growth factor beta stimulus, negative regulation of intracellular signal transduction, sequence-specific DNA binding, growth factor binding, negative regulation of cell-substrate adhesion, and core promoter proximal region DNA binding. Table 4 shows enriched pathways in transforming endometriosis to ovarian cancer ($FDR < 0.05$), with FDR ascending

Table 2. The microRNAs and the target genes involved in transformation of endometriosis to ovarian cancer.

miRNA	Sequence	Chromosomal Position	Main Target	Role	Type of Ovarian Cancer
miR-200a	UAACACUGUCUGGUAAC-GAUGU	chr1:1167916-1167937	ZEB1, ZEB2, SIP1, FOXA2, KRAS, PTEN	Up-regulated	Serous, Endometrioid, clear cell
miR-200b	UAAUACUGCCUGGUAUU-GAUGA	chr1:1167160-1167181	ZEB1, ZEB2, SIP1	Up-regulated	Serous, Endometrioid
miR-200c	UAAUACUGCCGGGUAUU-GAUGGA	chr12:6963742-6963764	ZEB1, ZEB2, SIP1	Up-regulated	Serous, Endometrioid, clear cell
miR-141	UAACACUGUCUGGUAUU-GAUGG	chr12:6964155-6964176	ZEB1, ZEB2, KLF12, ZFR	Up-regulated	Mucinous, serous, Endometrioid
miR-429	UAAUACUGUCUGGU-AAAACCGU	chr1:1169055-1169076	ZEB1, ZEB2, KIAA0101	Up-regulated	Mucinous, serous, Endometrioid
miR-30a	UGUAAAACAUCUCGACUGAAACAUCUCGACUG-GAAG	chr6:71403595-71403616	CELSR3, FLJ35954, LYRIC, BCL2A1, IER3	Up-regulated	Clear cell
miR-191	CAACGGAAUCCAAAA-GCAGCUG	chr3:49020672-49020694	IGF1R, FANCC, FANCF, FANCD2, MLH3, DAPK1	Up-regulated	Endometrioid
miR-196a	UAGGUAGUUUCAU-GUUGUUGGG	chr12:53991762-53991783	HOXA10	Up-regulated	Endometrioid
miR-100	AACCCGUAUAUCCGAAC-UUGUG	chr11:122152275-122152296	THAP2, KBTBD8, C4orf16	Up-regulated	Clear cell
miR-21	UAGCUUAUCAGACUGAU-GUUGA	chr17:59841273-59841294	PTEN	Up-regulated	Serous, Endometrioid, Clear cell
miR-26a	UUCAAGUAAUCCAG-GAUAGGCU	chr12:57824658-57824679	MYC	Up-regulated	Serous
miR-214	ACAGCAGGCACAGA-CAGGCAGU	chr1:172138798-172138907	PTEN	Up-regulated	Serous
miR-362	AAUCCUUGGAAC-CUAGGUGUGAGU	chrX:50008968-50008991	PTEN	Up-regulated	Clear cell, Serous
miR-3613	ACAAAAAAAAAAAA-GCCCAACCCUUC	chr13:49996415-49996501	PTEN	Up-regulated	Serous
miR-125a	UCCUGAGACCCUUU-AACUGUGA	chr19:51693254-51693339	ERBB2	Down-regulated	Serous, Endometrioid, Clear cell
miR-125b	UCCUGAGACCCUAACU-UGUGA	chr11:122099809-122099830	ERBB2	Down-regulated	Serous, Endometrioid, Clear cell
miR-1	UGGAAUGUAAAGAA-GUAUGUAU	chr18:21829015-21829036	THBS1, TIMP3	Down-regulated	Endometrioid, clear cell
miR-133a	UUUGGUCCCUUCAAC-CAGCUG	chr18:21825712-21825733	CTGF, IGF1-R	Down-regulated	Serous, Endometrioid, clear cell
miR-451	AAACCGUUACCAU-UACUGAGUU	chr17:28861403-28861424	PTEN	Down-regulated	Serous, Endometrioid, clear cell
miR-205	UCCUUAUCCACCG-GAGUCUG	chr1:209432166-209432187	PTEN, SMAD4, ZEB1	Down-regulated	Endometrioid, Serous
miR-325	CCUAGUAGGUGUCCAGU-AAGUGU	chrX:77005464-77005486	HMGB1	Down-regulated	Endometrioid
miR-145	GUCCAGUUUCCAG-GAAUCCU	chr5:149430661-149430683	MYC, MUC1, p70S6K1, TRIM2	Down-regulated	Serous, clear-cell

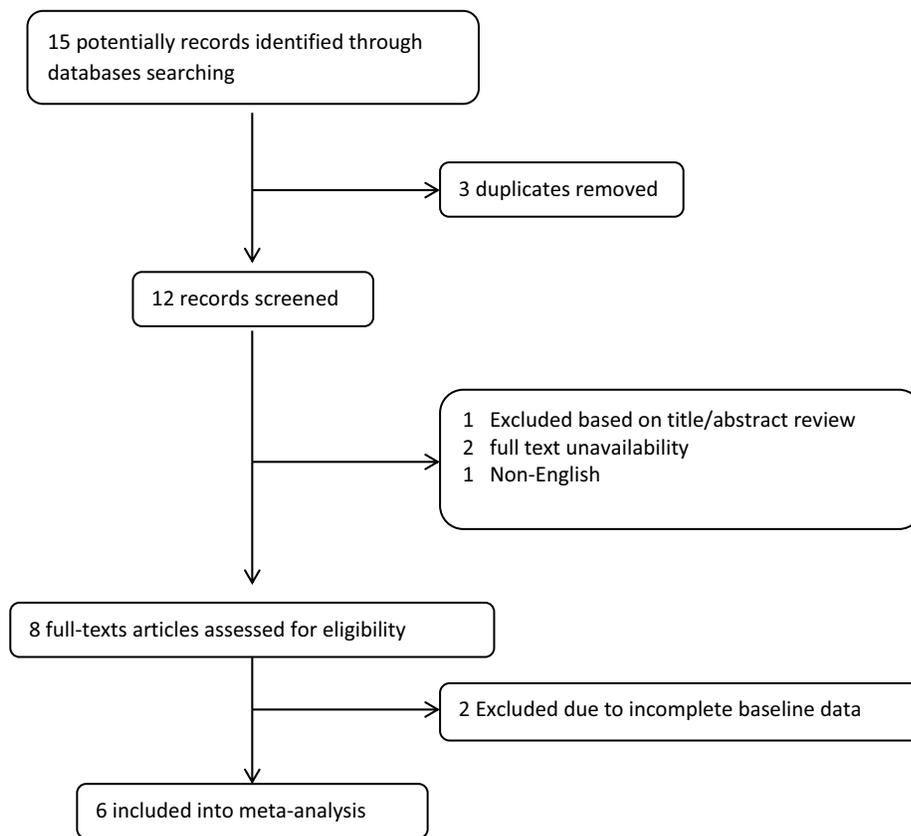


Fig. (1). The flowchart of screening the eligible studies.

order. The second and third columns are the number and names of the Top genes in a given enriched pathway. Bold face indicates that the gene is newly predicted. Regarding association between miRNAs and different subtypes of ovarian cancer, up-regulation or down-regulation of some miRNAs is involved in processing a single subtype of ovarian cancer, but some miRNAs can mediate suppressing or flaring-up of processes involved in transforming endometriosis into a cluster of ovarian carcinomas. By applying metaMIR, the interactions of each miRNA with a cluster of genes related to transforming endometriosis into ovarian cancer were identified and summarized in Table 5. Considering the power of such interactions based on the final power score presented by the Freiburg metaMIR group, we found the strongest interactions for three miRNAs of miR-141 (up-regulated), miR-205 (down-regulated), and miR-125b (down-regulated). For instance, up-regulation of miR-141 can induce progression of endometriosis-related ovarian cancer especially subtypes of Endometrioid carcinoma, Mucinous carcinoma, and serous ovarian cancer by establishing the strongest multilateral interactions between the genes of DAPK1, FANCF, FOXA2, HMGB1, KIAA0101, KLF12, KRAS, PTEN, THBS1, ZEB1, ZEB2, and ZFR. Thus, 22 miRNAs described in the present study can induce different endometriosis-related ovarian cancer subtypes by inducing a huge genes interaction network. Some interactions are strong and some are weak. Based on the DIANA tool for assessing pathways related to miRNAs-gene interaction pathways and comparing the revealed miRNAs and gene targets in the present analysis

and overall discovered pathways for ovarian cancer (Fig. 3), we could show some common loops and pathways including uncontrolled cell proliferation and abnormal apoptosis (mediated by PTEN gene induced by miR-21 and miR-214), and disaggregation and epithelialization (mediated by ZEB1 and ZEB2 genes induced by miR-200).

Table 3. Categories of gene-gene interactions based on FDR.

Type of Interaction	Percentage of Overall Interaction
Co-expression	53.66%
Physical interactions	23.60%
Pathway	11.87%
Genetic interactions	4.25%
Shared protein domains	3.59%
Co-localization	2.77%
Predicted	0.26%

4. DISCUSSION

A large amount of information suggests that microRNAs are deregulated in individuals suffering from different kinds of malignancies. It has been suggested that some of microRNAs may have an oncogenic function and some others

Table 4. The main pathways which activated in the background of gene cluster based on FDR values.

Pathway	Genes	FDR	Coverage	Significance
Transforming growth factor beta receptor signaling pathway	MYC, 8MAD4, THBB1, TGFB3, BMAD1, CDK8	2.71e-2	6/150	Significant
Response to transforming growth factor beta	MYC, 8MAD4, THBB1, TGFB3, BMAD1, CDK8	2.71e-2	6/169	Significant
Cellular response to transforming growth factor beta stimulus	MYC, 8MAD4, THBB1, TGFB3, BMAD1, CDK8	2.71e-2	6/169	Significant
Transmembrane receptor protein serine/threonine kinase Signaling pathway	MYC, 8MAD4, THBB1, TGFB3, BMAD1, CDK8	9.25e-2	6/218	Non-significant
Negative regulation of intracellular signal transduction	PTEN, NYC, MUC1, IGF1R, THBB1, BCL2A1	1.17e-1	6/235	Non-significant
Sequence-specific DNA binding	FOXA2, FOXF1, POU2F2, MLH3, MUC1, 8MAD4	1.40e-1	6/255	Non-significant
Growth factor binding	ERBB2, THBB1, IGF1R, TGFB3	1.40e-1	4/79	Non-significant
Negative regulation of cell-substrate adhesion	PTEN, THBB1, AP1AR	1.48e-1	3/30	Non-significant
Core promoter proximal region DNA binding	FOXA2, MUC1, 8MAD4	1.68e-1	3/34	Non-significant

Table 5. The micro-RNAs which made networks between the different genes.

MicroRNA http://rna.informatik.uni-freiburg.de/metaMIR/Result.jsp?t_output_row=0&t_output_rows=749&t_output_srt=miRNA&toolName=metaMIR&jobID=1881844	Final Score	Positive Combo
hsa-miR-141-3p	2.69	DAPK1, FANCF, FOXA2, HMGB1, KIAA0101, KLF12, KRAS, PTEN, THBS1, ZEB1, ZEB2, ZFR
hsa-miR-205-5p	2.43	DAPK1, FANCD2, FANCF, KBTBD8, KLF12, KRAS, PTEN, SMAD4, THBS1, ZEB1, ZEB2, ZFR
hsa-miR-125b-2-3p	2.06	FANCC, FANCD2, FANCF, HOXA10, KBTBD8, SMAD4, THAP2, THBS1, ZEB2, ZFR
hsa-miR-214-3p	1.93	DAPK1, ERBB2, MYC, PTEN, TIMP3
hsa-miR-191-5p	1.89	CELSR3, DAPK1, FANCC, KLF12, TIMP3
hsa-miR-200a-3p	1.89	DAPK1, FOXA2, HMGB1, KIAA0101, KLF12, PTEN, TIMP3, ZEB1, ZEB2, ZFR
hsa-miR-21-3p	1.78	FANCC, FANCD2, FOXA2, KBTBD8, KIAA0101, KLF12, SMAD4, THAP2, THBS1
hsa-miR-26a-1-3p	1.75	FANCD2, KBTBD8, KLF12, KRAS, PTEN, THAP2, THBS1
hsa-miR-200b-3p	1.63	FANCC, KIAA0101, KLF12, KRAS, MYC, PTEN, ZEB1, ZEB2, ZFR
hsa-miR-30a-3p	1.59	ERBB2, HMGB1, HOXA10, KLF12, KRAS, MYC, THAP2, ZEB1, ZEB2, ZFR
hsa-miR-200c-3p	1.56	HMGB1, KBTBD8, KIAA0101, KLF12, KRAS, PTEN, ZEB1, ZEB2, ZFR
hsa-miR-3163	1.39	CELSR3, DAPK1, HMGB1, TIMP3, ZEB2
hsa-miR-362-3p	1.38	CELSR3, CTGF, DAPK1, FANCC, KBTBD8, KLF12, MUC1, SMAD4, TIMP3
hsa-miR-325	1.33	FANCD2, HMGB1, KIAA0101, KRAS, PTEN
hsa-miR-30a-5p	1.21	CELSR3, DAPK1, FANCF, KIAA0101, KLF12, PTEN, TIMP3
hsa-miR-429	1.14	HMGB1, KBTBD8, KIAA0101, KLF12, MYC, PTEN, ZEB2

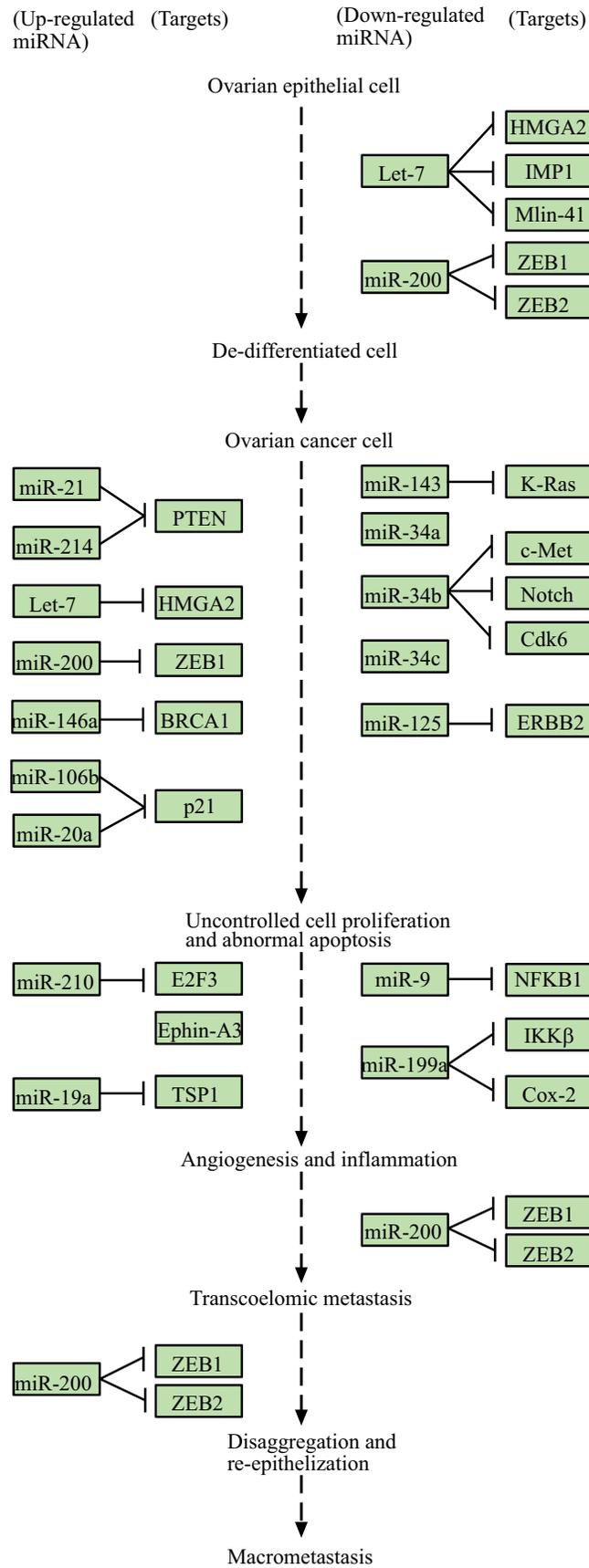


Fig. (3). The pathways including different genes and microRNAs involving ovarian cancer.

the effect of miRNAs on the mRNA translation suppression is exacerbated. In the first step, what should be considered in evaluating changes in the expression of proteins, enzymes or genes is the identification of specific miRNAs associated and predicting their behavior in the development and progression of cancerous tissue. In the present study, using bioinformatics fundamentals, we could effectively reveal some important genes and miRNAs involved in the transformation of endometriosis (a common benign phenomenon in women whole of the world) into ovarian cancer (a life-threatening malignancy among women). We could well show that overall 22 miRNAs have been detected which target a collection of genes involving malignant behavior of endometrioma and its transformation into different types of ovarian cancer. Of these miRNAs, up-regulation of 14 and adverse down-regulation of 8 were responsible for such behavioral changes. More importantly, a huge interactive genetic network interferes with such processes with the different mechanisms including gene to gene interactions, co-expression of the genes, regulation of intracellular signal transduction, or change in protein expression which all can be flared or suppressed with the identified miRNAs. Of course, the contribution of different miRNAs in such pathways is very different and the role of some genes and miRNAs seems to be more highlighted so the critical role of the expression of some genes in creating ovarian cancer has been clearly determined. For instance, it has been revealed that methylation of the PTEN gene might play a subordinate role in appearance and progression ovarian cancer [32]. As clearly shown in our survey, PTEN can be targeted by some miRNAs such as miR-200, miR-21, miR-214, miR-362, miR-3613, miR-451, and miR-205 that mediate over-expression or inhibition of PTEN gene involved in the transformation of endometrioma tissue into ovarian cancer. Another gene candidate, ZEB1, is known as a member of the Zinc-Finger E-box binding Homeobox (ZFH) family that suppresses the expression of some microRNAs, such as miR-183, miR-203, and miR-200 family members, which function as inhibitors of stem-like hallmarks as well as positive inducers of epithelial differentiation [33]. However, ZEB1 can be self-targeted by some microRNAs such as miR-200, miR-141, miR-429, and miR-203 which mediate the pathways involved in the pointed malignant tissue transformation.

We could finally show that up-regulation of miR-141 and down-regulation of miR-205 and miR-125b have a central role in transforming endometriosis into ovarian cancer. The role of these three miRNAs in such transformation has also been indicated in some previous studies based on molecular assessments. As shown by Wu *et al.* [28], the expression of miR-141 was different in women suffering from ovarian cancer with and without previous history of endometriosis and thus they concluded that the up-regulation of miR-141 may involve in the transformation of endometriosis into ovarian cancer. Braicu *et al.* [31] also showed that over-expression of miR-141 and miR-205 might contribute to the transformation of endometriosis into ovarian cancer. Regard-

ing the role of miR-125b in such transformation, Teague *et al.* [26] could describe up-regulation of these miRNAs, the endometriotic lesions and its tendency to transforming such lesions into cancer. They also described some related pathways such as the elevation of ERBB2 as an oncogenic component of the Epidermal Growth Factor (EGF) receptor family leading to the activation of cell migration and invasion.

Due to the potential of microRNA targeting a large number of mRNAs, this group of oligonucleotides is involved in almost all biological phenomena including cell cycle regulation, cell growth, apoptosis, cell differentiation, and stress response. Increasing evidence suggests that microRNAs play an important role in cancer biology, and recent studies have confirmed the role of oncogenic and inhibitory tumorigenic microRNAs in cancer cells and have also shown that expression of these microRNAs can be self-regulated by oncogenes and tumoral inhibitors. The expression of microRNAs both *in vitro* and *in vivo* can be regulated by the synthesis of pre-microRNA molecules or antisense oligonucleotides, which is a promising prospect for cancer treatment.

CONCLUSION

Identifying specific microRNAs targeting the genes involved in transforming endometrioma into ovarian cancer as well as discovering related molecular pathway can open the new ways to prevent premeditation of benign tissues to malignancy. However, it should be noted that the current study led to only some bioinformatics-based findings on the candidate microRNAs and their interaction with the target genes involving transformation of endometriosis into ovarian cancer that should be tested in molecular setting to confirm the critical role of such microRNAs in the progression of endometriosis to ovarian carcinoma.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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