研究报告
**Research Report**

# 利用microRNA-mRNA相互作用研究卵巢癌中分子、细胞和生物活性的变化

Senol, Kurtovic

1 International Burch University, Genetics and Bioengineering Department, Francuske Revolucije bb, Ilidža, 71000 Sarajevo, Bosnia and Herzegovina

2 Department of Clinical Pathology, Clinical Center of the University of Sarajevo, Bolnicka 25, 71000 Sarajevo, Bosnia and Herzegovina

通讯作者, sdogan@ibu.edu.ba; 作者

计算分子生物学, 2015 年, 第 4 卷, 第 9 篇

收稿日期: 2015 年 10 月 07 日 接受日期: 2015 年 10 月 07 日 发表日期: 2015 年 10 月 07 日



**摘 要** microRNA 是非编码 RNA 序列，20-22 个核苷酸长，其在沉默基因表达中起作用。正常 microRNA 表达的变化可致癌。本研究阐明了卵巢癌中 microRNA 的表达与正常表达相比的变化，这样比较可以更好地理解卵巢癌发生。在肿瘤样品中，在 680 种 microRNA 类型中 230 种显示高表达，295 种显示低表达，155 种为非表达。当我们基于倍数增加>50 分类 microRNA 时，我们发现 microRNA 有 31 高表达和 89 低表达。异常表达的巨大差异显示 microRNA 活性的变化程度。使用 Cancerminer 工具我们发现了这些异常表达 microRNAs 的相应的 mRNA 目标。我们发现，由数据过程捕获的最多的靶基因与细胞增殖和癌发生有关。

**关键词** 卵巢癌；TCGA；REC 得分；Cancerminer

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

Senol DOGAN [1], Kurtovic-Kozaric A. [1,2]

1 International Burch University, Genetics and Bioengineering Department, Francuske Revolucije bb, Ilidža, 71000 Sarajevo, Bosnia and Herzegovina

2 Department of Clinical Pathology, Clinical Center of the University of Sarajevo, Bolnicka 25, 71000 Sarajevo, Bosnia and Herzegovina

Corresponding author, sdogan@ibu.edu.ba; Authors

**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

微小 RNA(miRNA)是由约 20-22 个核苷酸组成 的小的非编码 RNA，其通过结合互补基因转录物来

调节基因表达，从而引起 mRNA 的翻译抑制(Bartel 2009; Guo et al., 2010)，(Volinia et al., 2006)。由于 miRNA 对基因表达的负调控，超过 30％的微小 RNA 在几乎所有活生物体的基本过程中起关键作用，如分化、发育、细胞增殖和细胞凋亡(Bartel, 2004), (Esquela-Kerscher and Slack, 2006), (Calin and Croce, 2006), (Lagos- Quintana, 2001)。因为 miRNA 通常削弱和破坏其靶 mRNA，所以与 mRNA 的序列伙伴的反向表达关系是值得期待的(Baek et al., 2008), (Selbach et al., 2008)。

正常组织呈现与癌组织不同的 miRNA 表达谱(Lu et al., 2005), (Volinia et al., 2006)。miRNA 的调节异常能够促进肿瘤的形成和发展(Croce, 2009), (Lujambio and Lowe, 2012)。在对于相应对照的癌症中差异表达的 miRNA 之间的比较已经在先前的卵巢癌的研究中进行。表达水平被分为异常高和低，或没有 miRNA 的表达(Iorio et al., 2007), (Zhang et al., 2008), (Wyman et al., 2009)。例如，在卵巢癌中过表达的微小 RNA 是 mir-27a，mir-27b mir-23b，miR-503，miR-346 和 miR-424，其与转移的程度相关(Wang, Kim, and Kim, 2014), (Park et al., 2013)。相关研究已经表明 mir-199a 可以抑制 CD44 基因的表达，导致抑制卵巢癌起始细胞的致瘤性和多药耐药性(Cheng et al., 2012)。类似地，负责常见的 DNA 损伤反应途径的 hsa-miR-140-3p 靶向 RAD51AP1 基因显示卵巢癌中的表达显着降低(Miles et al., 2012)。

癌症基因组图谱(TCGA)是一个公共可用的癌基因组数据库，提供与个别人类癌症类型相关的基因组数据(“癌症基因组图谱-数据门户”2015)。在过去的十年中，癌症基因组图谱(TCGA)项目已经是一个大规模的合作项目和一个强大的数据库门户，让我们搜索和比较各种癌症的分子异常综合目录。数据使我们在卵巢癌中找到上调的和低调节的 miRNA。 我们使用无偏差的方法在癌症和正常对照中来选择最差异表达的 miRNA。我们使用一种新的策略来分类 microRNA 在卵巢癌的表达数据，因为 miRNA 和其目标 mRNA 有可能改变癌细胞中的分子和生物过程，导致发现新的治疗选择。

## 材料和方法

### 患者样品

卵巢癌 miRNA 和对照数据，级别 3，从 TCGA(02/05/2014)下载。数据分析如流程图所示(图 1)。 根据表达水平，使用 R 统计程序分选和提取 485 名癌症患者和 22 名对照的数据。 R 原始脚本已被写入以检测癌症中的异常 miRNA。

### 数据预处理

数据首先下载，然后分为两组，卵巢癌和对照组。然后分别收集相同的 ID 微 RNA 表达作为患者和对照。数据预处理已通过查找其倍数更改完成。

### 表达分析

提取的 miRNA 已经应用于 Cancerminer(www.cancerminer.org)，其是计算 miRNA-mRNA 之间可能的相互作用并产生作为 REC 分数的结果的基于网络的工具(“CancerMiner”2015)。高和低表达的 miRNA(图 3)通过生物信息学工具 HCE 3.5 软件程序(http://www.cs.umd.edu/hcil/hce/)(“HCE-Hierarchical Clustering Explorer”2015)分级聚类。软件程序具有不同的参数，但在本文中，欧几里德距离已被用于聚类并找到它们的相关性。靶基因的负面影响的分子和生物学功能使用 http://www.pantherdb.org/(“PANTHER-Gene List Analysis”2015)分类。

## 结果

### 数据的提取

R 代码将 680 种不同 miRNA 的表达分为 3 个主要组：高、低和未表达(图 1)。根据每百万绘图读数的表达值，数据显示了 230 个高表达的 miRNA 和 295 个低表达的 miRNA(图 2)。此外，其中 155 个几乎是被动的，并且在癌细胞和正常细胞中均不表达(图 2)。

一旦我们发现高和低表达的 miRNA，我们将它们与其在对照样品中的表达进行比较。我们发现一些 miRNA 在对照样品中根本不表达。因此，我们希望将候选 miRNA 分为两组：第 1 组是在对照中显示零表达的 miRNA，第 2 组是在对照样品中显示一些表达的 miRNA(图 3)。我们对高和低表达的 miRNA 进行了这种分析(图 3)(附表 1)。该分析发现 96 种不同的 miRNA 在癌症中高度表达，但在对照样品中没有表达。此外，在卵巢癌中高度表达的 134 种 miRNA 在对照样品中显示最小表达。

对于低表达 miRNA，我们发现 139 个 miRNA 在癌症样品中显示零表达并在对照中高表达。此

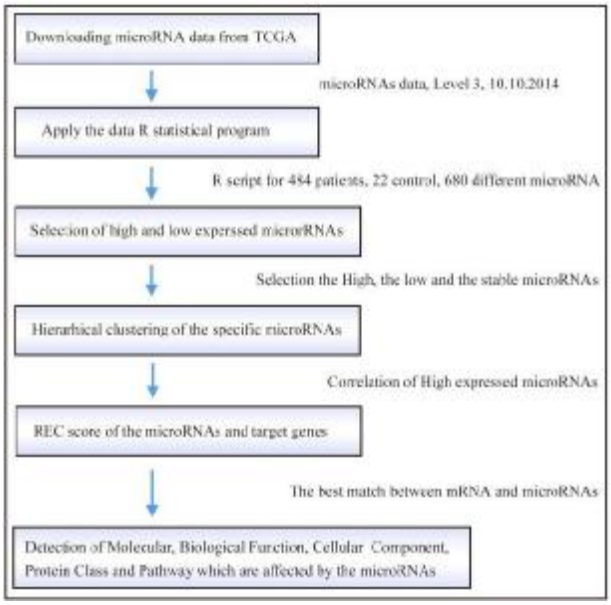


图 1 卵巢癌 miRNA 数据流程图. 该图呈现了数据挖掘工作的每一步; 从 TCGA 下载, R 统计过程, 选择 microRNA, REC 分数以及分子和生物学功能. 该流程图说明了整个数据挖掘过程

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

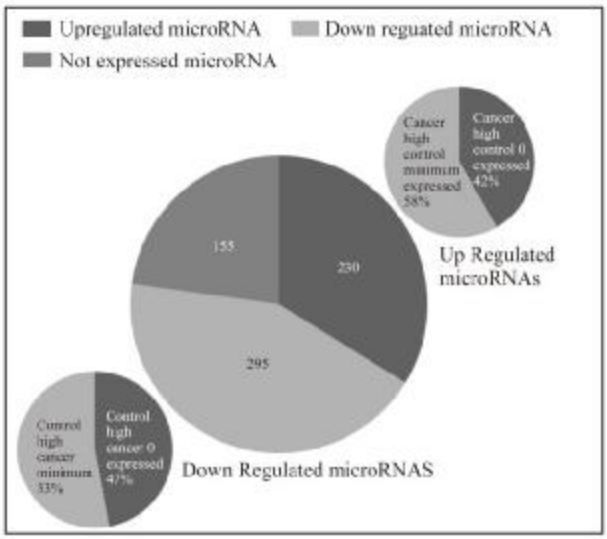


图 2 卵巢癌上调和下调 miRNA 数量. 图中的数字标记卵巢癌 miRNA 活性. miRNA 主要分为 3 组, 上调, 下调和不表达. 从数字可以容易地检测到作为癌症的结果有多少微小 RNA 表达已经改变

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

外，我们发现 156 个 miRNA 在癌细胞中具有最小表达，在对照中具有高表达(图 3)。 由于一些候选 miRNA 具有非常高或非常低的表达，我们决定仅选择表达改变>50 倍的候选物。该分析发现 31 个异常高和 89 个低表达的 miRNA(候选物的列表在附表 2 中给出)。非表达的 miRNA(n = 155)在附表 2 中给出。

**特定 miRNA 的分层聚类**

在癌症中通过 R 程序选择的高和低表达的 miRNA 被分层聚类以理解它们之间的可能的相关性。最相关的 17 个上调调节的癌症 miRNA 是分层聚类的。聚类图显示 miRNA 的活性和彼此之间的关系 (图 4)。 miRNA 家族如 mir-509-1,-2， -3、mir-129-1,-2、mir-663,-b 和 mir-200a,-b 是高度表达的，并且是最相关的。低表达的癌 miRNA 也彼此高度相关，并由除 mir-519a-2 和 mir-519a-1 之外的不同 miRNA 组成(图 4)。

**miRNA 和靶基因的 REC 评分**

为了找到 miRNA-靶相互作用之间的关系，已经开发了 Cancerminer 工具[22]。该工具将结果作为 REC 评分，基于秩的统计方法，已经被开发以理解具有阴性表达关联的 miRNA-mRNA 对具有与弱或正关联对相关的预测 miRNA-靶相互作用[22]。基因和 miRNA 的表达具有拮抗性。最高表达的 31 个 miRNA 已经应用于 Cancerminer 工具，但是其中只有 22 个具有确定的 REC 评分(表 1)。除了 REC 评分之外，在 22 种 miRNA 中已经确定卵巢癌中的相关性评分(表 1)。有趣的是，大多数靶 mRNA 参与肿瘤发生。清楚地发现 73％的微小 RNA 与肿瘤发生直接相关。

对低表达的 miRNA 进行类似的分析(表 2)。在 89 个具有>50 个更低表达的 miRNA 中，54 个 miRNA 定义了 REC 评分和相应的靶 mRNA。下调的 microRNA 与肿瘤发生的关系只有 22％。显然，上调的微小 RNA 与肿瘤发生更相关。

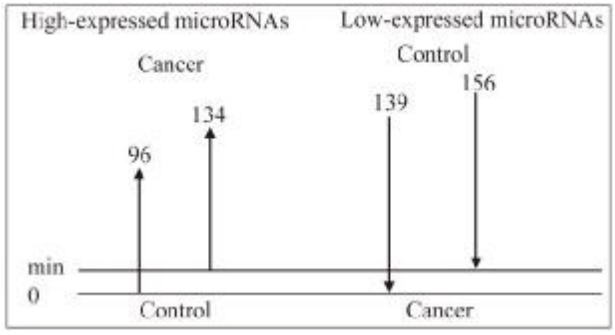


图 3 卵巢癌中高和低表达的 miRNA. miRNA 变化谱在卵巢癌中呈现高和低表达. 比较后，96 个未表达的 miRNA 和 134 个最小表达的 miRNA 被检测到高表达的 miRNA. 然而，在对照中 139 和 156 高表达的 miRNA 在卵巢癌中表达为 0 和最小

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

## 受 miRNA 影响的分子活性，生物功能，细胞组件和蛋白质类别

癌症的细胞活性显然受 miRNA 影响。根据 REC 评分，mRNA 被分类以便理解提取的 miRNA 如何在癌症类型中对分子活性、生物学功能、细胞组分(图 5)、蛋白质类别和途径(图 6)具有活性和负面影响。可以容易地观察到何种机制改变或可能改变，如通过癌症类型中的百分比检测。

## 结论

癌症和正常卵巢组织样品(高或低)之间的微小 RNA 表达的变化表明存在 miRNA 的动态表达。尽管 miRNA 的序列与许多基因互补，但它们显示了对特定基因的偏好。根据 miRNA 和 mRNA 之间的拮抗关系，细胞中的一些功能被抑制。本研究的主要目标是了解 miRNA 如何在卵巢癌中异常表达、破坏细胞平衡和致癌。我们发现在 680 种不同的 miRNA 中，230 显示高表达和 295 显示低表达。此外，与卵巢组织的对照样品相比，在癌症中，31 显示>50 倍更高的表达，和 89 显示在癌症中>50 倍更低的表达。这项工作将帮助分子遗传学家和临床医生制作针对不同基因的新药物。

## 缩写

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

## 利益冲突

作者声明本研究没有利益冲突。

## 作者贡献

SDogan 开展了生物信息学和数据挖掘研究，分析 microRNA 表达水平，进行统计分析，起草了稿件。AKozaric 实施了 microRNA 在癌症中的分子效应。本研究的设计由两位作者完成。两位作者阅读并同意了最终稿件。

## 致谢

首先，我们感谢 TCGA，癌症基因组 Atlas 数据门户，通过在线提供卵巢癌 microRNAs 基因表达数据。同时，我们感谢 Sead Banda 对图表的设计。

## 参考文献

Baek, Daehyun, Judit Villén, Chanseok Shin, Fernando D. Camargo, StevenP. Gygi, and David P. Bartel. 2008. “The Impact of microRNAs on Protein Output.” Nature, 455 (7209): 64-71. doi:10.1038/nature07242

http://dx.doi.org/10.1038/nature07242

Bartel, David P. 2004. “MicroRNAs: Genomics, Biogenesis, Mechanism, and Function.” Cell, 116 (2): 281-97

http://dx.doi.org/10.1016/S0092-8674(04)00045-5

Bartel, David P. 2009. “MicroRNAs: Target Recognition and Regulatory Functions.” Cell, 136 (2): 215-33. doi:10.1016/j.cell.2009.01.002

http://dx.doi.org/10.1016/j.cell.2009.01.002

Calin, George A., and Carlo M. Croce. 2006. “MicroRNA Signatures in Human Cancers.” Nature Reviews Cancer, 6 (11): 857-66. doi:10.1038/nrc1997

http://dx.doi.org/10.1038/nrc1997

“CancerMiner.” 2015. Accessed April 14. http://cancerminer.org/.

Cheng, Weiwei, Te Liu, Xiaoping Wan, Yongtao Gao, and Hui

表 1 基于 REC 评分选择的上调 miRNA 和其靶 mRNA。 基于它们在卵巢癌中的高表达，选择 miRNA 与对照相比。 使用 Cancerminer 数据库发现靶 mRNA, 并基于 REC 分数进行选择. 某些 miRNA 在 Cancerminer 数据库中没有发现, 排除了这些 miRNA. 73%的 microRNA 与肿瘤发生相关

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 | Assoc. | Function | Involved |
|---|---|---|---|---|---|---|
| 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 | 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 | 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 | 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 |

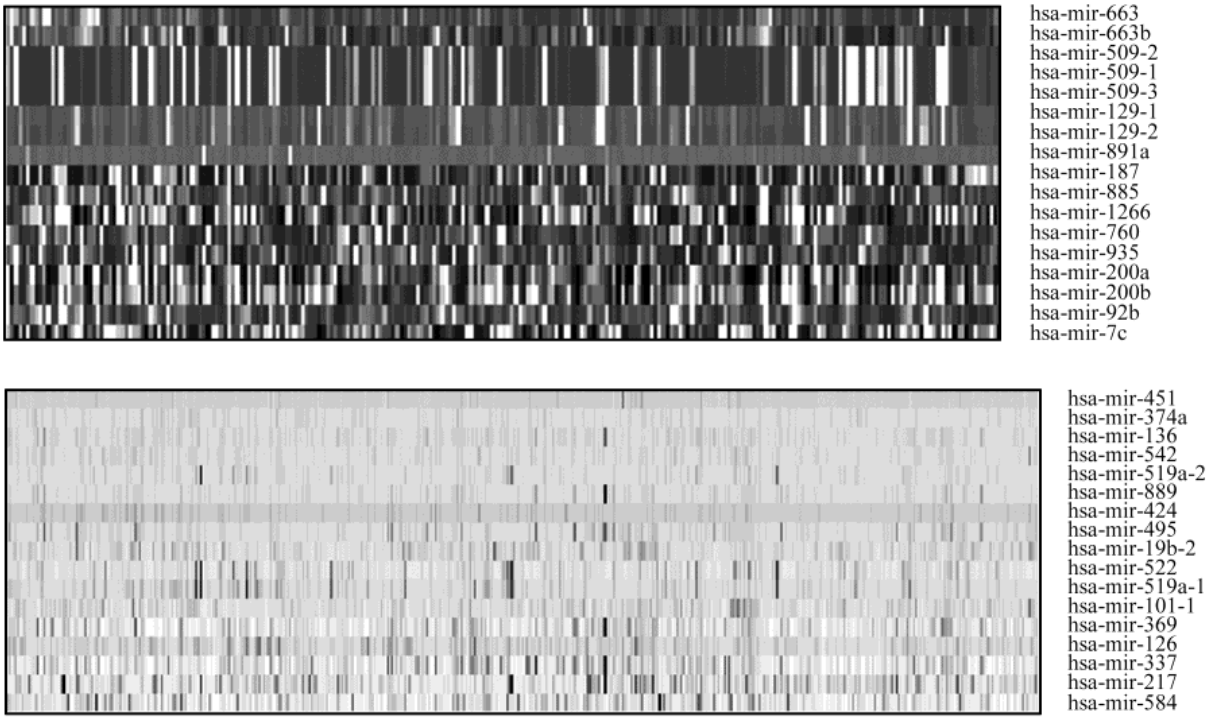


图4 高和低表达microRNA的分层聚类. 作为统计分析的结果，最高的17个和最低的17个相关的microRNA中的显示为热图. 第一个图显示上调的microRNA, 第二个图显示下调的microRNA

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

表2 基于REC评分选择的下调miRNA和其靶mRNA. 基于它们在卵巢癌中的低表达, 与对照相比选择miRNA. 使用Cancerminer数据库发现靶 mRNA, 并基于 REC 分数进行选择. 某些 miRNA 在 Cancerminer 数据库中没有发现, 这些从表中排除. 22%的microRNA 与肿瘤发生相关

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 | Assoc. | Function | Involved |
|---|---|---|---|---|---|---|
| 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 | 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 | 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 | 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 | No |
| hsa-mir-376b | 12p12.1 | BHLHE41 | -6 | -16.70 | Basic Helix-Loop-Helix Family, Member | 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 | No |
| hsa-mir-580 | 2q12.3 | SULT1C4 | -4.21 | | Sulfotransferase Family, Cytosolic, 1C, | 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) | 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 | No |
| hsa-mir-1277 | 6q25.2 | SYNE1 | -6.21 | | Spectrin Repeat Containing, Nuclear | 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 | 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 | 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 | 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 | 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 | No |
| hsa-mir-337 | 14q12 | PSME2 | -7.80 | -4.14 | Proteasome (Prosome) Activator Subunit | 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 |

Wang. 2012. "MicroRNA-199a Targets CD44 to Suppress the Tumorigenicity and Multidrug Resistance of Ovarian Cancer-Initiating Cells: MicroRNA-199a Inhibits Ovarian CIC Growth." FEBS Journal, 279 (11): 2047 -59.doi:10.1111/j.1742-4658.2012.08589.x
http://dx.doi.org/10.1111/j.1742-4658.2012.08589.x

Croce, Carlo M. 2009. "Causes and Consequences of microRNA Dysregulation in Cancer." Nature Reviews Genetics, 10 (10): 704-14. doi:10.1038/nrg2634
http://dx.doi.org/10.1038/nrg2634

Esquela-Kerscher, Aurora, and Frank J. Slack. 2006. "Oncomirs- microRNAs with a Role in Cancer." Nature Reviews Cancer, 6 (4): 259-69. doi:10.1038/nrc1840
http://dx.doi.org/10.1038/nrc1840

Guo, Huili, Nicholas T. Ingolia, Jonathan S. Weissman, and David P. Bartel. 2010. "Mammalian microRNAs Predominantly Act to Decrease Target mRNA Levels." Nature, 466 (7308): 835-40. doi:10.1038/nature09267
http://dx.doi.org/10.1038/nature09267

"HCE - Hierarchical Clustering Explorer." 2015. Accessed April 14. http://www.cs.umd.edu/hcil/hce/.

Iorio, Marilena V., Rosa Visone, Gianpiero Di Leva, Valentina Donati, Fabio Petrocca, Patrizia Casalini, Cristian Taccioli, et al. 2007. "MicroRNA Signatures in Human Ovarian Cancer." Cancer Research, 67 (18): 8699-8707
http://dx.doi.org/10.1158/0008-5472.CAN-07-1936

Jacobsen, Anders, Joachim Silber, Girish Harinath, Jason T Huse, Nikolaus Schultz, and Chris Sander. 2013. "Analysis of microRNA-Target Interactions across Diverse Cancer Types." Nature Structural & Molecular Biology, 20 (11): 1325–32. doi:10.1038/nsmb.2678
http://dx.doi.org/10.1038/nsmb.2678

Lujambio, Amaia, and Scott W. Lowe. 2012. "The Microcosmos of Cancer." Nature, 482 (7385): 347-55. doi:10.1038/nature10888
http://dx.doi.org/10.1038/nature10888

Lu, Jun, Gad Getz, Eric A. Miska, Ezequiel Alvarez-Saavedra, Justin Lamb, David Peck, Alejandro Sweet-Cordero, et al. 2005. "MicroRNA Expression Profiles Classify Human Cancers." Nature, 435 (7043): 834 -38. doi:10.1038/nature03702
http://dx.doi.org/10.1038/nature03702

Miles, Gregory D., Michael Seiler, Lorna Rodriguez, Gunaretnam Rajagopal, and Gyan Bhanot. 2012. "Identifying microRNA/mRNA Dysregulations in Ovarian Cancer." BMC Research Notes, 5 (1): 164
http://dx.doi.org/10.1186/1756-0500-5-164

"PANTHER - Gene List Analysis." 2015. Accessed April 14. http://pantherdb.org/.

Park, Young Tae, J. Y. Jeong, M. J. Lee, K. I. Kim, Tae-Heon Kim, Y. D. Kwon, Chan Lee, Ok Jun Kim, and Hee-Jung An. 2013. "MicroRNAs Overexpressed in Ovarian ALDH1-Positive Cells Are Associated with Chemoresistance." J Ovarian Res, 6 (1): 18 http://dx.doi.org/10.1186/1757-2215-6-18

Selbach, Matthias, Björn Schwanhäusser, Nadine Thierfelder, Zhuo Fang, Raya Khanin, and Nikolaus Rajewsky. 2008. "Widespread Changes in Protein Synthesis Induced by microRNAs." Nature, 455 (7209): 58-63. doi:10.1038/nature07228
http://dx.doi.org/10.1038/nature07228

"The Cancer Genome Atlas - Data Portal." 2015. Accessed April 14. https://tcga-data.nci.nih.gov/tcga/.

Volinia, Stefano, George A. Calin, Chang-Gong Liu, Stefan Ambs, Amelia Cimmino, Fabio Petrocca, Rosa Visone, et al. 2006. "A microRNA Expression Signature of Human Solid Tumors Defines Cancer Gene Targets." Proceedings of the National Academy of Sciences of the United States of America, 103 (7): 2257-61
http://dx.doi.org/10.1073/pnas.0510565103

Wang, Yongchao, Sangmi Kim, and Il-man Kim. 2014. "Regulation of Metastasis by microRNAs in Ovarian Cancer." Frontiers in Oncology 4 (June). doi:10.3389/fonc.2014.00143
http://dx.doi.org/10.3389/fonc.2014.00143

Wyman, Stacia K., Rachael K. Parkin, Patrick S. Mitchell, Brian R. Fritz, Kathy O'Briant, Andrew K. Godwin, Nicole Urban, Charles W. Drescher, Beatrice S. Knudsen, and Muneesh Tewari. 2009. "Repertoire of microRNAs in Epithelial Ovarian Cancer as Determined by Next Generation Sequencing of Small RNA cDNA Libraries." Edited by Sudhansu Kumar Dey. PLoS ONE, 4 (4): e5311. doi:10.1371/journal.pone.0005311
http://dx.doi.org/10.1371/journal.pone.0005311

Zhang, Lin, Stefano Volinia, Tomas Bonome, George Adrian Calin, Joel Greshock, Nuo Yang, Chang-Gong Liu, et al. 2008. "Genomic and Epigenetic Alterations Deregulate microRNA Expression in Human Epithelial Ovarian Cancer." Proceedings of the National Academy of Sciences, 105 (19): 7004-9
http://dx.doi.org/10.1073/pnas.0801615105

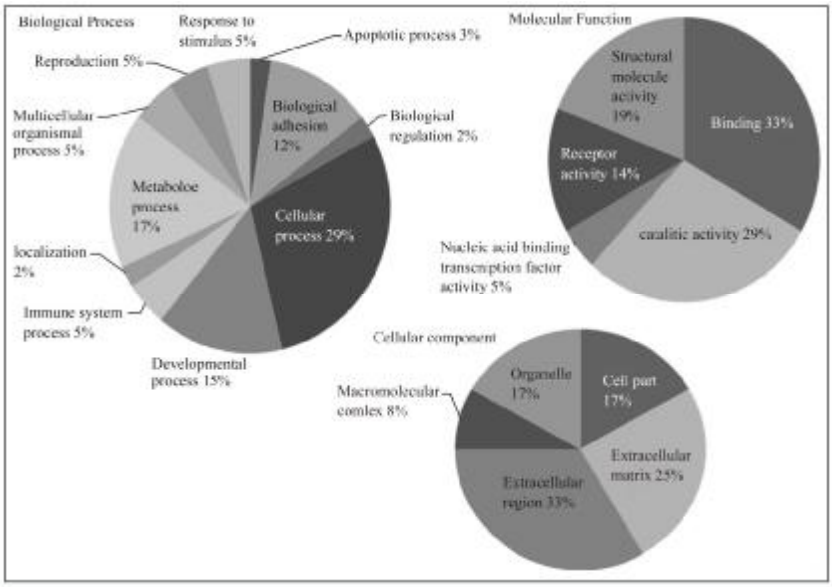


图 5 高表达的 miRNA 在卵巢癌中的生物过程, 分子功能和细胞组分的变化. 异常表达的 microRNA 抑制细胞中的一些重要过程. 根据 REC 评分, 列出 mRNA 并通过 REC 程序运行以发现其自身生物过程, 分子功能和细胞组分的变化. 所有的变化在图中以百分比给出以便清楚地检测变化.

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.

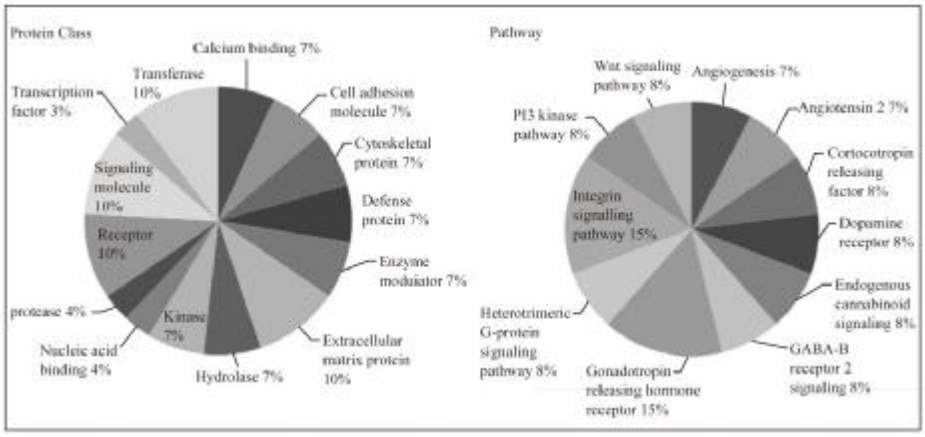


图 6 蛋白质类别和途径的变化

Figure 6 Changes of Protein Class and Pathway