



## Bioinformatic Evaluation of the MiR-5011 Effect on the Crucial Genes That Involved in Colorectal Cancer

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### ABSTRACT

*Introduction: The microarray technique has been established as the reference method for studying the genes that are in the control of miRNAs. However, the high cost of this method has hampered its use in most research centers. On the other hand, the improvement of the bioinformatical algorithms and computer modeling systems has led to the development of the bioinformatical softwares that can predict mRNA targets for miRNAs. Therefore, the aim of this theoretical study was bioinformatically evaluation of the effect of miR-5011 on genes that can be involved in colorectal cancer, by using various specific softwares.*

*Methods/Materials: By Using different algorithms in TargetScan, DIANA and miRWalk databases, the potential gene targets of miR-5011 were identified. Then, a score table from the candidate genes was prepared based on the affinity of the seed region of miR-5011 and the number of MRE in the 3'-UTR region of genes. Finally, genes with highest scores were chosen as the candidates for practical analysis.*

*Results: The results of bioinformatical analysis showed that SMAD6 and SMAD7 genes in TGFB signaling pathway and WNT3A and LRP6 genes in WNT signaling pathway are the most potential genes that might be affected by miR-5011 in colorectal cancer.*

*Discussion: It seems that WNT3A, LRP6, SMAD6 and SMAD7 suppressed by miR-5011 and this microRNA maybe act as a tumor suppressor and downregulated in colorectal cancer Therefore, this microRNA and its target genes can be considered as a suitable new candidate for experimental evaluation.*

**Keywords:** Bioinformatics, MicroRNA, Colorectal Cancer, MiR-5011

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### INTRODUCTION

In recent years, a new network of regulatory cycles at the level of mRNA has been considered. Among them can be a class of RNAs Non-coding agent called microRNAs. In 1993, the first microRNA, called 4-lin, was discovered [1]. The miRNA is referred to as small RNAs that they originated from the stem-loop structure and interfered with the regulation of the expression of the genes by targeting the mRNAs and degradation or by inhibiting the expression of their genes [2]. About seven nucleotides from the 5' end of the mature miRNA molecules is called seed region, and this region binds to the 3'-UTR from its complementary mRNA [3]. The miRNA sequence identifies the target mRNA molecule. If miRNA completely binds to the

target mRNA, it completely degrades mRNA, and if the binding to the target mRNA is incomplete, miRNA prevents the translation of the mRNA [4]. MiRNAs are involved in some biological processes including cell proliferation, differentiation, angiogenesis, apoptosis and tumorigenesis through targeting mRNAs [5].

Colorectal cancer (CRC) is one of the most common life-threatening malignancies that its symptoms shows up so late. recent study indicated that expression of various miRNAs are altered in CRC [6]. Almost all colorectal cancers (CRC) demonstrate hyperactivation of the WNT pathway and dysregulation of the transforming growth factor beta (TGF- $\beta$ ) signaling pathway, which in many cases is believed to be the initiating and driving events. MiRNAs are one of the key regulators of these pathways [7,8]

Today, with the help of techniques such as Northern blot, Microarray (hybridization in situ) and Real-time-PCR can be found the presence

of mi-RNA in the Specific tissues or the association of any mi-RNA with diseases. Multiple computer programs with Different algorithms to predict the mi-RNA targets exists [9].

Therefore, the aim of this theoretical study was bioinformatically evaluation of the effect of miR-5011 on genes that can be involved in colorectal cancer via WNT and TGF- $\beta$  signaling pathway, by using various specific softwares.

## 2. MATERIALS AND METHODS

### 2.1. Getting the miR-5011 sequence

The sequence of miR-5011 was captured from Entrez ( <http://www.ncbi.nlm.nih.gov/Entrez/>) and miRBase ([www.mirbase.org/](http://www.mirbase.org/)).

### 2.2. Bioinformatic analysis of miR-5011 target mRNAs

By Using different algorithms in TargetScan, DIANA and miRWalk databases, the potential gene targets of miR-5011 were identified. Then, an score table from the candidate genes was prepared based on the affinity of the seed region of miR-5011 and the number of MRE in the 3'-UTR region of genes. Finally, genes with highest scores were chosen as the candidates for practical analysis.

## 3. RESULTS

### 3.1. Analysis of miR-5011 at Targetscan database

Target Scan Software (<http://www.targetscan.org/>) is one of the case programs that use to predict mammalian mi-RNA targets. This software identifies seven or eight nucleotides of mRNA That is complementary to mi-RNA and it also examines thermodynamic stability (examination of secondary structures and intermolecular interactions of a nucleic acid). Pct Indicates that miRNA binding to the target area is Not based on chance, and the amount of this factor is between 0 to 1. The closer Pct to 1 indicated exclusively specific binding of miRNA to its target mRNA [10].

Based on the results of this study the genes listed in table 1 have the highest score as the target of miR-5011.

**Table 1.** The studied genes in Target scan software

Target gene	Conservity region	Poor conservity region	Aggregate Pct
SMAD6	3	1	0.97
SMAD7	2	0	0.99
LRP6	2	1	0.91
WNT3A	1	0	0.97

### 3.2. Analysis of miR-5011 at DIANA database

This algorithm identifies mRNA targets Based on several parameters calculated for each miRNA Separately. Then scores protected regions and unprotected combined and a general score of that Suggests changes in the expression of the target mRNA. Specifically, indicators for each program's forecast are the signal-to-background ratio and the accuracy score (this parameter is between 0 and 1, indicating the likelihood of being real mRNA is the target for any miRNA). Which serves as an indicator for detecting false positives is considered. Another parameters examined at this base Information, overall miTG score (this is in fact the final score Prophecy) and the Threshold score (Threshold). Higher values of the miTG suggests a near-expected reality [11].

Thus, the most highly rated genes in the algorithms of this software have been determined and specified which can play a role in the CRC are summarized in Table 2, respectively.

**Table 2.** The studied genes in DIANA software

Target gene	miTG score	Accuracy score	Threshold score	The signal-to-background ratio
SMAD6	10.9	0.7	4.65	7.2
SMAD7	29.7	0.86	6.6	7.2
WNT3A	23.7	0.79	6.76	7.2
LRP6	11.56	0.5	4.67	.2

### 3.3. Analysis of miR-5011 at miRwalk database

This database is based on the programming method Perl is written based on the complementary relationship between the region the core of miRNA with the target mRNA and according to complementarity the bases are based on Watson and Creek's law. In this software heptemer core sequence based on Watson's and Carrick's law. other databases are searched and when the region seven nucleotide were complemented by a target extends from both ends and this will go as long as one mis - mach goes on. After reaching mismatch extensions stops and eventually results analyzed, then the complementary seven nucleotide regions their ability to connect to the UTR-3 genes in the results list is shown. Also, the probability of distributing a pair of bundles Accidental sequences analyzed by Poisson distribution. The results are reported as p value [12].

Based on the results obtained from this software also genes are likely to be involved in CRC via TGFB and WNT signaling pthway that are

SMAD6 (p value= 0.022), SMAD7 (p value= 0.013), LRP6 (p value= 0.050) and (p value= 0.030).

#### 4. DISCUSSION

SMAD6 and SMAD7 genes as I-SMADS inhibit the formation and activation of R-SMAD-CO-SMAD complexes in TGF $\beta$  signaling pathway, therefore they will control and regulate TGF $\beta$  signaling pathway and involved in CRC [13,14,15]. LRP6 and WNT3A are the components of WNT signaling pathway and activate this pathway. These genes are mutated in many CRC cases and regulation of their expression is important [16,17].

According to the bioinformatics studies SMAD6, SMAD7, LRP6, WNT3A is most likely to be affected by miR-5011 in CRC. Although The proteins are all as high targets the points are scored among all three above-mentioned bases They agree, however, to arrange the results in between different databases are slightly different than this more because of different algorithms and minor modifications of scoring pattern is among these bases. It should be noted that threshold is in default on Diana software set to 7.2 Though this is the minimum threshold and has a capacity of up to 19, meaning that Software only targets that score above this threshold they are showing. Therefore, by increasing the threshold to the maximum could be more rigorous judgment thus only mRNAs with a threshold of 19 or Are higher, will be shown. Therefore, only targetss their overall miTG score is higher than the specified threshold the software filter will be displayed. So, considering the way it works SMAD6, SMAD7, LRP6 and WNT3A interference in CRC in previous studies by researchers Identified, based on data from analyzes bioinformatics seems to be SMAD6, SMAD7, LRP6 and WNT3A as the targets of miR-5011 controlled factors in CRC and can be a new good candidate for practical reviews.

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