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In silico analysis for miR-141 as a potential regulator in hepatocellular carcinoma

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Abstract
MicroRNAs are non-coding RNAs that play a pivotal role in gene expression. The regulatory role of miRNA for genes illustrates its involvement in cancer and many other infectious diseases. miRNAs regulate a single gene or multiple genes, which propose their regulatory mechanisms in diagnosing and treating many diseases. Therefore, miRNAs may act as tumor suppressors or oncogenes based on their targeted genes and the specific pathway for their regulation. The miRNA-141, as a member of the miRNA 200 family, plays a vital role in tumorigenesis. As in liver cancer cells, miRNA-141 can target the STAT4 gene expression, which inhibits its proliferation and migration. In this study, we try via *In Silico* analysis to identify the potential targeted genes for miRNA-141 using many *In Silico* tools and bioinformatics software like PicTar software to unleash the molecular role of miRNA-141 in human carcinoma tumorigenesis. Interestingly, the most identified targets with low required energy and high PicTar score include a variety of tumor and metastasis suppressor genes such as WTAP as a tumor suppressor gene. The deleted liver cancer -1 (DLC-1) that is regulated by miRNA141 and CHES1 which expresses the forkhead transcription factor checkpoint suppressor 1 CHES1 is reduced in many types of cancers. The deficient energy required for targeting these genes and completing the interfering reaction makes the data presented here a straightforward and spontaneous cellular event.

Keywords: MicroRNA, cancer progression, prediction, and bioinformatics tools

Introduction
MicroRNA (miRNA) is considered as a family of non-coding RNA. They consist of 20-25 nucleotides. Their discovery lies in 1993, in the nematode Caenorhabditis elegans [1]. The transcription of miRNAs may take many stages. First, miRNAs are transcribed from specific DNA sequences into primary miRNAs. This is followed by processing into precursor miRNAs before it is turned into mature miRNAs [2]. The composition of mature miRNA is completed after the cleavage of primary miRNA. The primary miRNA is usually involved in the effector complex RNA-induced silencing complex (RISC). The importance of the miRNA sequence is its role in the discovery of the targeted genes through base pairing with expected targets. The level of complementarity between the guide and mRNA target determines which silencing mechanism will be employed; cleavage of target messenger RNA (mRNA) with subsequent degradation or translation inhibition [1, 3]. The miRNAs are powerful gene regulators, and they not only help control mRNA stability and translation but are also involved in transcription. MiRNA are small, evolutionary conserved, single-stranded, non-coding RNA molecules that bind target mRNA to prevent protein production by one of two distinct mechanisms [4]. The role of miRNA is a post-transcriptional on the targeted genes. Consequently, they act via their binding to complementary sites on target mRNAs to induce cleavage or repression of productive translation [5]. This action may be called gene silencing which can be targeted by mRNA cleavage, translational repression, or DNA methylation [6]. The mechanism of action of miRNA relies basically on the regulation of other genes. It is well known that one miRNA can target one or many mRNA targets based on its targets. The miRNAs suppress gene expression due to their sequence which may be complementary with their target/s. This complementarity occurs at the 3′ UTR. In addition, such a mechanism prevents the translation of mRNA targets into protein via inhibition of the translation process of specific targeted genes [7].

Methods

PicTar (https://pictar.mdc-berlin.de/cgi-bin/PicTar_vertebrate.cgi) is an algorithm for the identification of microRNA targets. This searchable website provides details (3'UTR alignments with prognosticated spots, links to colorful public databases) regarding miRNA target prognostications in invertebrates, microRNA target prognostications in seven Drosophila species, microRNA targets in three nematode species, and mortal miRNA targets that aren't conserved but-expressed this means that the miRNA and mRNA are expressed in the same towel [8].

A string database: network (https://string-db.org/) was used to predict the protein-protein interactions. The availability of prediction of the targets on the protein level is also of great importance.

Results

Prediction of targeted genes in a single seeding region via miR-141

(-18.4), where the alternate point created In This study, the Pictar was used as a possible prediction tool for targets prediction of miRNAs. The results showed only a single seed region as shown in figure 1. The results summarized in the following two genes: CHES1 and WTAP. CHES1 demanded energy with response energy-16.6 The WTAP gene impacted liposarcoma in the suggested targeted end with the energy needed -18.6.

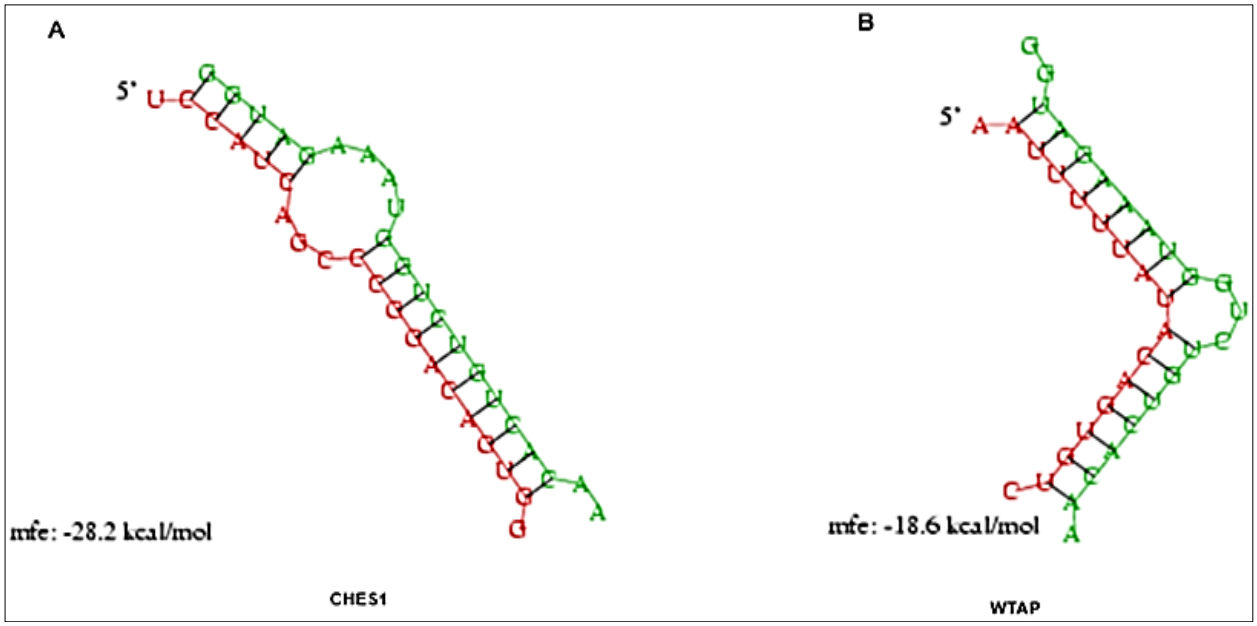

Fig 1: Predicted genes that potentially targeted by hsa-miR-141 in a single binding site

a) Seeding region for CHES1 sequence was detected using Pic-Tar software tool. The seeding region and binding affinity of hsa-miR-141 on targeted genes were shown. B) in WTAB, it showed the complementarity to a single binding site, and WTAB seeding region showed binding affinity to miR-141.

Table 1: Potential targeted genes and seeding regions in a single binding site for miR-141 indicated by PicTar software.

miR	Targeted genes	PicTar score	Related disease	Free energy
miR-141	CHES1	5.73	Decreases protein synthesis and cell proliferation in tumor cell lines	-28.2 -18.4 -16.6 -16.6 -18.2
miR-141	WTAP	5.75	A vital component of N6-methyltransferase complex involved in tumorigenesis. Contribute to Wilms tumor susceptibility.	-18.6 -19.3

Prediction of targeted genes in double seeding region via miR-141

In addition, the pictar was used as a possible prediction tool as well for targets prediction of miRNAs. Our results showed double seeding regions as shown in figure 2 and table 2. The results summarized in the following genes: P53 gene, DLEC1 gene and DLC1 gene. The P53 gene started with demanded energy (-17.4), the alternate point created with response energy-19.9. The DLEC1 gene impacted liposarcoma in the suggested with the energy needed -20.0. The DLC1 gene impacted liposarcoma in the suggested targeted end with the energy needed -20.7 while the alternate point with the energy needed 15.9.

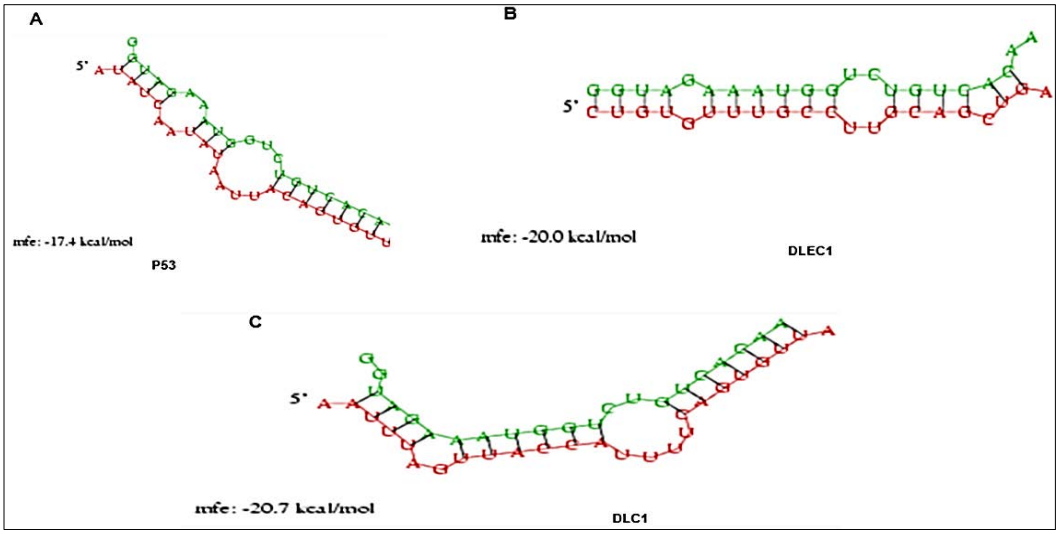

Fig 2: Predicted genes with double binding sites targeted by hsa-miR-141.

(A) Seeding region for P53 sequence was detected using PicTar software tool. The seeding region and binding affinity of hsa-miR-141 on targeted genes were shown. B) DLEC1 has two seeding regions that were detected. And C) Detected DLC1 gene sequences indicated also double binding sites of miR-141.

Table 2: Potential targeted genes and seeding regions in double binding sites for miR-141 indicated by PicTar software.

miR	Targeted genes	PicTar score	Related disease	Free energy
miR-141	P53	3.14	Tumor suppressor gene	-17.4 -19.9
miR-141	DLEC1	2.98	Tumor suppressor gene that plays an important role in the development and progression of hepatocellular carcinoma	-20.0
miR-141	DLC1	6.76	Deleted in liver cancer) is a Rho GTPase-activating protein actively involved in the regulation of cell proliferation, modulation of cytoskeletal dynamics and cell migration?	-20.7 -15.9

Prediction of targeted proteins in correlation with miR-141

The results showed the relationship between miRNA-141 and the predicted proteins. These proteins vary from targeting to oncogenes and interleukins that are incorporated in many biological processes.

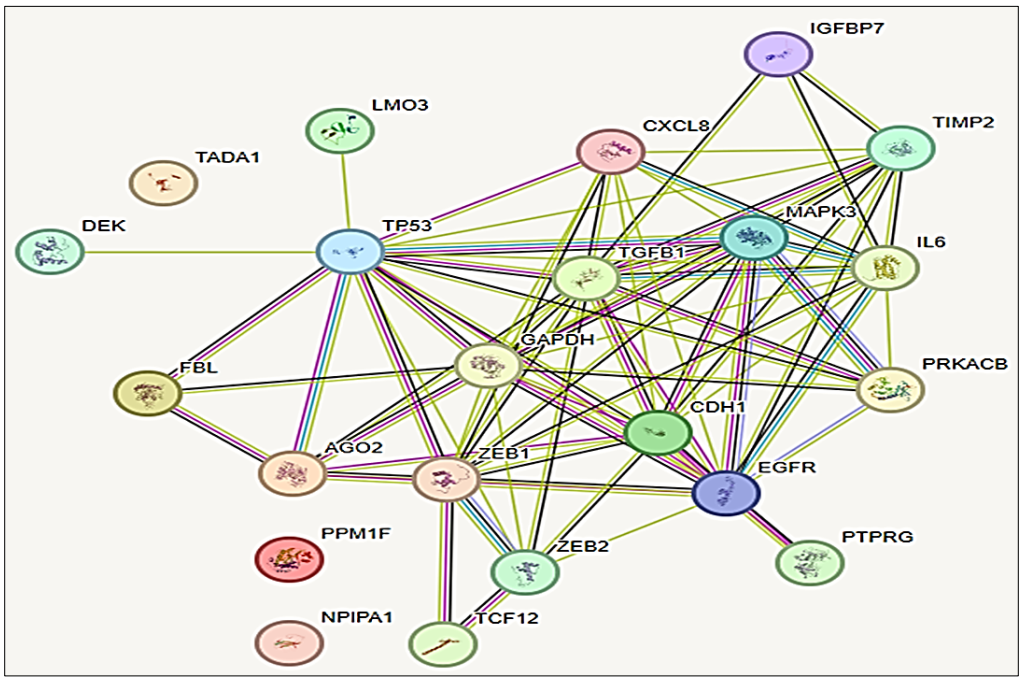

Fig 3: STRING database network showing significant protein–protein interactions. This figure illustrates the expected binding targets for miRNA-141 till the date for analysis. It presents a network for the published proteins that may be expected to bind with on the whole proteins in the body.

Discussion

The miRNAs are of pivotal importance in carcinogenesis. This effect may be due to the dysregulation of different miRNAs expression in carcinogenesis. Consequently, such dysregulation also may influence the targeted genes by miRNAs. Each miRNA can target one or more than one mRNA. Besides, single mRNA can be targeted by one or more miRNA. Therefore, the regulatory role of miRNAs depends also on the role of their targeted genes and their role in carcinogenesis as well. This effect occurs post-transcriptionally and on the transcription level as well [9]. For example, a single miRNA complex may bind to more than 200 target genes; this may have many functions like receptors, transcription factors and transporters. Hence, it is very challenging to identify the target transcripts and pathways which are regulated by different miRNAs [10]. The role of miRNAs may be of dual functions. It may function as tumor suppressor or as oncogene based on their role and on their targeted mRNAs. Also, miRNAs effect is very crucial in cancer via different pathways like effect on proliferation, resistance to cell death or even growth suppressors [11].

The role of miRNAs varies due to the type of cancer and the targets gens. For instance, miRNA18a elevated in prostate cancer. miR-18a is upregulated in clinical tumor specimens and cancer cell lines. The role of miR-18a act as oncomir in prostate cancer [12]. Besides, miR-200 family have an important role in liver cancer [13]. Moreover, Interestingly, miR-200 members are overexpressed in ovarian tissues, nasopharyngeal carcinoma, prostate cancer, classic papillary thyroid carcinoma, bladder cancer and colorectal cancers, while down-regulated in gastric cancer, pancreatic ductal adenocarcinoma, pancreatic cancer, osteosarcoma, prostate cancer hepatocellular, primary peritoneal carcinoma, choriocarcinoma, esophageal cancer, breast cancer and renal cell carcinoma, raising a controversial issue about the role of miR-141 in cancer progression. additionally, dysregulation of miR-141 depends on the type of cancer; in other words, miR-141 plays a dual role in tumorigenicity and can modulate cellular motility and control “stemness”. The miR-141 may be considered as an oncogene or as a tumor suppressor gene therefore can be used as cancer therapeutic agents [14]. On the other hand, the effect of miRNAs on metastasis is of great importance. Metastasis can involve the spread of cancer cells to surrounding tissues and to other organs. It can be considered as a basic reason of cancer mortality [15]. The predicted role of miRNA to the targeted genes was predicted *In Silico* which showed effects on different mRNAs.

Conclusion

The aim of the study was to predict the targets for miR-141 and the protein-protein interactions as well. In conclusion, we use tools to predict sites in different genes to uncover the correlation between miRNA 141 and its targeted genes. Besides, we tried to predict the protein-protein interactions via string databases network. The figures and tables summarize multiple examples of the miR-141, its targeted genes according to software prediction tools on specific websites. These different tools support our prediction for the role of miR-141 in carcinogenesis. Finally, we can conclude that miR-141 can play many pivotal roles in carcinogenesis, metastasis, and the development of many cancer types.

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Authors’ contributions

Ahmed Awad performed the analysis. Adel Guirgis helped in supervision. Hany Khalil designed the research plan, interpreted, and organized the results. Ahmed Awad wrote the manuscript.

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