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Finding the Therapeutic Role of miRNAs in Hepatocellular Carcinoma (HCC)

Afifah Zamir[1], Kashif Abrar[2], Mehwish Jabeen[3]
[1]WMO at THQ level hospital Chowk Azam Layyah
[2]THQ hospital Fort Abbas Bahawalnagar
[3]WMO at MCHC RHC Sardarpur Kabirwala, Khanewal

ABSTRACT: Hepatocellular carcinoma (HCC) has become the second most common cause of cancer-related death worldwide, with approximately 782,500 new cases and 745,500 deaths occurring in the global during 2012. The main objective of the study is to find the therapeutic role of miRNAs in Hepatocellular Carcinoma (HCC). This study was conducted using a systematic search on Google scholar, Pubmed and Web of science published until 20th June 2020. The cited references of retrieved articles and previous reviews were also manually checked to identify any additional eligible studies. MiRNAs perform their tumor suppressor functions through downregulating oncogene expression. Increasing evidence suggests that miRNAs are essential for the regulation of liver development, regeneration, and metabolic functions. It is concluded that deregulation of miRNAs significantly contributes to the development of HCC. miRNAs mainly functions to down regulate the expression of targeted genes. However, they may have other yet unknown functions including the activation of gene transcription.

KEY WORDS: Carcinoma, Cellular, Liver, MiRNA.

INTRODUCTION

Hepatocellular carcinoma (HCC) has become the second most common cause of cancer-related death worldwide, with approximately 782,500 new cases and 745,500 deaths occurring in the global during 2012. In the beginning phase of HCC, careful resection, liver transfer, nearby removal and other corrective treatments can improve patient's endurance [1]. Nonetheless, the 5-year repeat rate is extremely high, it might reach as high as 80%-90% even the HCC patients have gotten conceivably therapeudic treatments. It has been now cutting-edge stage for a great many people when HCC was analyzed 5. For the high level stage, the little atom focused on therapeutics drugs sorafenib and regorafenib are the standard medicines that have been supported by the US Food and Drug Administration (FDA) [2]. Sorafenib is the lone standard first-line foundational treatment accessible for cutting edge HCC, however the middle endurance was accounted for just 3 months. Regorafenib is a second-line drug when HCC patients were advancing on sorafenib treatment, though, the middle endurance was still just 10.6 months as indicated by a stage 3 clinical preliminary report [3]. Despite the fact that sorafenib and regorafenib can improve generally speaking endurance of HCC patients, it isn't excessively long. Besides, the concerns for drug obstruction and unfriendly activity of these medications are ascending also. Thusly, it is earnest to investigate new treatments, particularly look for more precise markers for early conclusion, treatment and visualization in HCC. Nucleic corrosive based medications like microRNAs (miRNAs) may have the promising helpful potential for HCC treatment. MiRNAs are critical members and controllers in the turn of events and movement of HCC. What's more, exosomal miRNAs additionally assume significant parts in the turn of events and movement in HCC [4].

The essential tumor of the liver and the sixth most continuous reason for cancer all through world is the hepatocellular carcinoma. Its analysis is basically accomplished by biomarkers and correlated diagnostics test including ultrasound, Liver capacity tests and fibroscan on clinical grounds [5]. Cirrhosis of liver is the principle factor prompting HCC on the grounds that more the 70% of cirrhotic liver patients at some stage by one way or another advancement to HCC. Cirrhosis of liver have itself numerous causes yet in our nation like Pakistan where there is poor financial status individuals gets tainted with Hepatitis B and C infection and goes undiscovered causing liver harm and cirrhosis [6]. Hepatits C have 5 % hazard of creating cirrhosis when contrasted with Hepatitis B which has just 1 % of hazard. Other danger components of cirrhosis incorporates high liquor utilization, hemochromatosis, non-alcoholic steatohepatitis and α1-antitrypsin inadequacy [7].

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Hepatocellular carcinoma emerges dominatingly in a cirrhotic liver because of rehashed irritation and continuous fibrogenesis. The dysplasia happens due to the both interaction going one next to the other irritation and fibrogenesis.The hereditary and epigentic factors additionally assume a part during the time spent hepatocellular carcinoma because of heterogeneity and modifications in the flagging pahways. HCC have a sublime heterogeneity, p53, PIK3CA, and β-catenin seem, by all accounts, to be every now and again changed in patients [8].

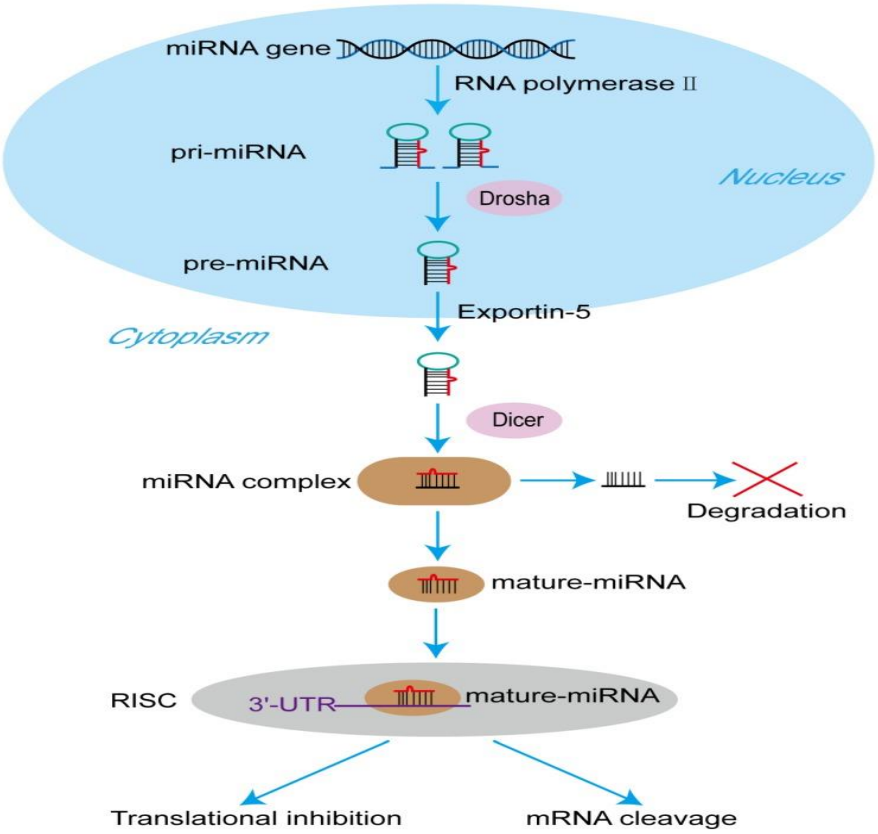

Figure 01: The process of miRNA formation. At first, miRNA genes are transcribed to primary pri-miRNAs by RNA polymerase II in the nucleus.

OBJECTIVES

The main objective of the study is to find the therapeutic role of miRNAs in Hepatocellular Carcinoma (HCC).

METHODOLOGY OF THE STUDY

This study was conducted using a systematic search on Google scholar, Pubmed and Web of science published until 20th June 2020. The cited references of retrieved articles and previous reviews were also manually checked to identify any additional eligible studies.

DATA COLLECTION

All citations were imported into a bibliographic database and duplicates were removed. Title, abstract and then full-text of all articles were screened for eligibility. All the studies which was directly included the role of dietary supplements were included in this study. The following information was extracted from each study: a) details of the study (study setting, year of publication and study design), b) study population, sample size (male/female) and age of the subjects in years is explained in the study.

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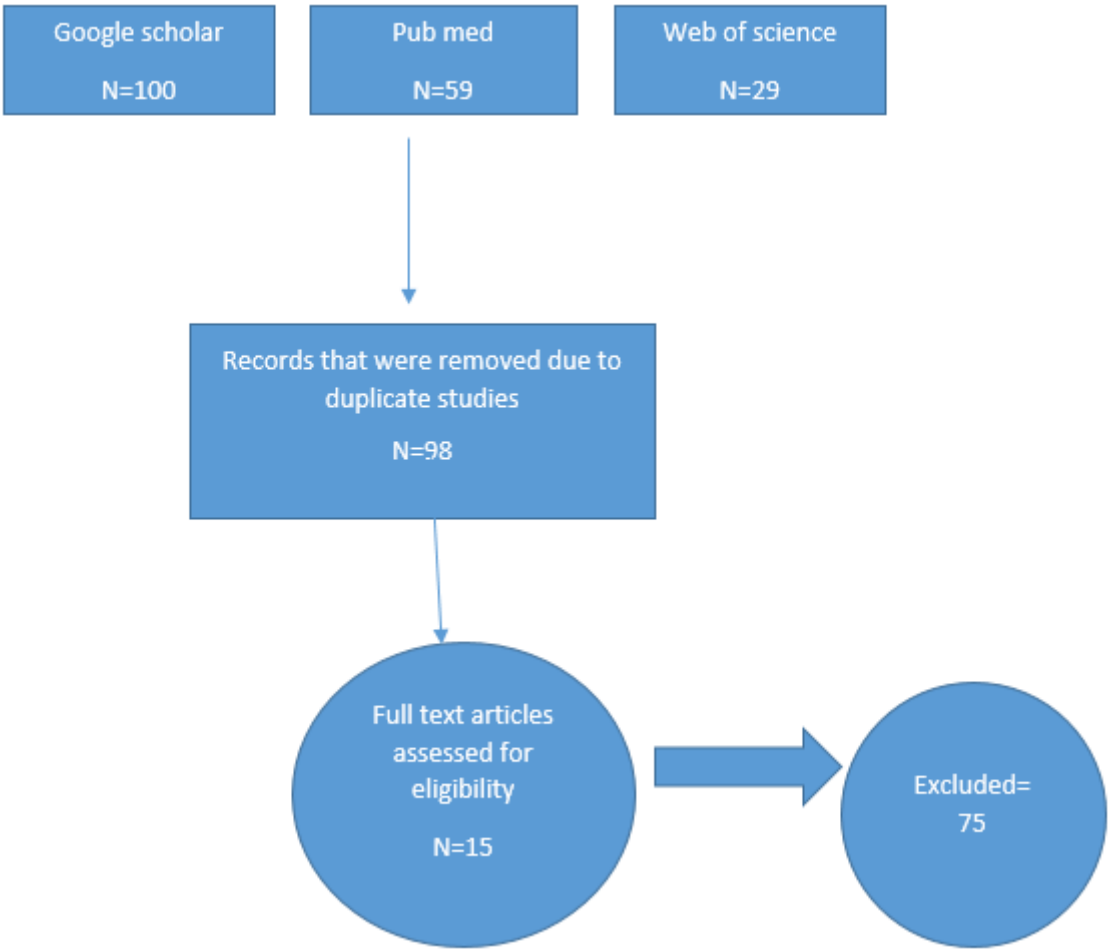

Figure 02: Flow of information through the different phases of a systematic review.

Serum Biomarkers Related to Hepatocellular Carcionoma

The data dependent on evidance for HCC, remembering just two randomized preliminaries for patients with persistent hepatitis B disease (HBV) with a critical danger and a few observational examinations in cirrhosis, reconnaissance for HCC is extensively suggested by global rules. The populace in danger incorporating patients with constant (HBV) or (HCV) contaminated, and patients with other persistent reason for liver sickness with serious fibrosis or cirrhosis. There are an alternate serum biomarkers for HCC conclusion found uptill now, among which the Alpha-Fetoprotein is the most usually recommended by the specialists [9].

Alpha-Fetoprotein (AFP)

Serum AFP can be raised in other kindhearted or threatening conditions rather than HCC. The particularity of this AFP is low a result of its rise in some other ailments too which incorporates intense and constant hepatitis, intrahepatic cholangiocarcinoma, and embryogenic tumors. Especially, raised AFP levels in patients with constant HCV renders this biomarker conflictive for HCC screening purposes in this populace (related with necro-fiery movement) [10].

Des-γ-Carboxy Prothrombin (DCP)

It is otherwise called prothrombin prompted by nutrient K nonattendance II (PIVKA-II), this unusual protein without coagulant work is probably brought about by a gained deformity in the posttranslational carboxylation of the prothrombin antecedent in threatening cells [11].

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Glypican-3

Glypican-3 is glycosylphosphatidylinositol-moored cell-surface heparin-sulfate proteoglycans which has a place with glypican family . Glypican-3 has significant tasks to carry out during the phone multiplication and tumor concealment. An investigation led by Sung et al discovered GPC3 was upregulated in HCC tissues acquired from patients and accordingly affirmed its emission by HCC-determined cell lines [12].

miRNAs

The recent researches in regulation of miRNAs and its role in HCC formation. Some miRNAs have been found to be upregulated in HCC, which can be seen in the Table 1, and some downregulated can be seen in the Table 2 [13]. The administrative components of miRNAs in various resarches incorporates the accompanying multiplication, apoptosis, attack, metastasis, angiogenesis, drug obstruction and autophagy for the movement and advancement of hepatocellular carcinoma. What's more, some miRNAs can likewise be as potential symptomatic and forecast markers in HCC [14].

Characteristic of miRNAs

miRNAs are little (21-23 nucleotides), noncoding RNA particles that down-direct quality articulation by base blending with 3′ untranslated areas (3′ UTRs) of target courier RNAs (mRNAs). Lee et al. discovered the lin-4 family in 1993, Since numerous tantamount miRNAs have been perceived in plants, animals and diseases through nuclear cloning and bioinformatic approaches [15]. These revelations suggest that miRNAs are a gigantic gathering of post-transcriptional regulators and control various developmental and cell measures in eukaryotic animals [16].

Studies have shown that miRNAs accept a critical part in the physiological pattern of animals and plants, similar to advancement, improvement, detachment and engendering, and that odd enunciation is solidly related to human disorder [17]. miRNAs have emerged as critical parts in tumorigenesis, which has provoked an alter in context in oncology. miRNA microarrays have been used to show that different miRNAs fill in as likely biomarkers for malignancy. miRNA profiles reflect the developmental family and partition periods of tumors. Various miRNAs have been perceived to go about as oncogenes, tumor silencers, or modulators of malignancy lacking cells and metastasis. The quick disclosure of various miRNA targets and their significant pathways has added to the progression of miRNA-based therapeutics [18].

Table 1: Upregulated miRNAs in HCC

MiRNA	Targets	Mechanisms
miR-10b	CSMD1	Migration, invasion
miR-21	CAMSAP1, DDX1, MARCKSL1	No mentioned
miR-25	RhoGDI1, TRAIL	EMT, apoptosis
miR-32	No mentioned	Prognostic marker
miR-92a	FBXW7	Cell growth, prognostic marker
miR-96-5p	Caspase-9	Apoptosis
miR-107	Axin2, HMGA2, HMGCS2	Proliferation, prognostic marker
miR-135a	FOXO1	Migration, invasion
miR-155-5p	PTEN	Proliferation, apoptosis, invasion, migration
miR-181a	Atg5	Autophagy
miR-182	TP53INP1	Drug resistance

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Table 2: Downregulated miRNAs in HCC

MiRNA	Targets	Mechanisms
miR-7	mTOR, TYRO3	Autophagy, drug resistance
miR-7/21/107	Maspin	Drug resistance, prognostic marker
miR-26	ULK1	Autophagy
miR-29a	CLDN1	Proliferation, migration
miR-30a-5p	AEG-1	Cell growth, apoptosis
miR-30e	MTA1	EMT
miR-31	NDRG3	Drug resistance
miR-31-5p	SP1	Proliferation, migration, invasion
miR-33a	No mentioned	Prognostic marker
miR-33a-5p	No mentioned	Drug resistance
miR-33b	SALL4	Proliferation, metastasis
miR-98	EZH2	Proliferation
miR-101	Mcl-1, RAB5A, STMN1, ATG4D	Apoptosis, autophagy, diagnostic marker
miR-105-1	NCOA1	Diagnostic and prognostic marker

MicroRNAs and Metabolism in HCC

Metabolic reprogramming is a survival strategy of cancer cells to adapt to harsh environments where glucose and oxygen supplies are limited. Glucose uptake is increased in cancer cells which shift their metabolism to "aerobic glycolysis" leading to energy production independent from oxygen availability, which can be insufficient especially in fast-growing tumors. Metabolic reprogramming, also known as Warburg effect, is considered a hallmark of cancer and is associated with poor prognosis [19]. Cancer cells adopt this metabolic change to face increased energetic and anabolic requirements needed for rapid proliferation and clonal expansion. The Warburg effect favors the employment of glucose as a carbon source to obtain energy and metabolic intermediates from non-oxidative phosphorylation giving advantages to highly proliferating malignant cells. In addition to the Warburg effect, the stabilization of hypoxia-inducible factor 1 (HIF-1α) enables the reduction of mitochondria-associated reactive oxygen species (ROS) that have deleterious effects on highly proliferating cells [20].

Tumor suppressor miRNAs in liver cancer

MiRNAs perform their tumor suppressor functions through downregulating oncogene expression. Increasing evidence suggests that miRNAs are essential for the regulation of liver development, regeneration, and metabolic functions [21-23]. Hence, alterations in intrahepatic miRNA networks have been associated with risk factors for liver cancer development, including hepatitis, steatosis, and cirrhosis. In this section, we describe the crosstalk between several tumor miRNAs and signaling pathways in various types of liver cancer [24-25].

CONCLUSION

It is concluded that deregulation of miRNAs significantly contributes to the development of HCC. miRNAs mainly functions to down regulate the expression of targeted genes. However, they may have other yet unknown functions including the activation of gene transcription. The discovery of new types or novel functions of miRNAs provides us with more and deeper insights into the molecular mechanism underlying the pathogenesis of HCC.

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