miRNAs and the Hippo pathway in cancer: Exploring the therapeutic potential (Review)

TARUNA ARORA[1], MOHD. ADNAN KAUSAR[2], SHIMAA MOHAMMED ABOELNAGA[3], SADAF ANWAR[2], MALIK ASIF HUSSAIN[4], SADAF SADAF[5], SIMRAN KAUR[6], ALAA ABDULAZIZ EISA[7], VYAS MURTI MADHAVRAO SHINGATGERI[6], MOHAMMAD ZEESHAN NAJM[6] and ABDULAZIZ A. ALOLIQI[8]

[1]Division of Reproductive Biology, Maternal & Child Health, Department of Health Research, ICMR, MOHFW, Government of India, Ansari Nagar, New Delhi 110029, India; [2]Department of Biochemistry, College of Medicine, University of Hail, Hail, KSA-2240; [3]Deanship of Preparatory Year, University of Hail, Hail, KSA-2240; [4]Department of Pathology, University of Hail, Hail, KSA-2240, Saudi Arabia; [5]Department of Biotechnology, Jamia Millia Islamia, New Delhi 110025; [6]School of Biosciences, Apeejay Stya University, Sohna, Haryana 122103, India; [7]Department of Medical Laboratories Technology, College of Applied Medical Sciences, Taibah University, Medina, KSA-344; [8]Department of Medical Biotechnology, College of Applied Medical Sciences, Qassim University, Buraydah 51542, Saudi Arabia

Received April 13, 2022; Accepted May 17, 2022

DOI: 10.3892/or.2022.8346

Abstract. Cancer is recognized as the leading cause of death worldwide. The hippo signaling pathway regulates organ size by balancing cell proliferation and cell death; hence dysregulation of the hippo pathway promotes cancer-like conditions. miRNAs are a type of non-coding RNA that have been shown to regulate gene expression. miRNA levels are altered in various classes of cancer. Researchers have also uncovered a crosslinking between miRNAs and the hippo pathway, which has been linked to cancer. The components of the hippo pathway regulate miRNA synthesis, and various miRNAs regulate the components of the hippo pathway both positively and negatively, which can lead to cancer-like conditions. In the present review article, the mechanism behind the hippo signaling pathway and miRNAs biogenesis and crosslinks between miRNAs and the hippo pathway, which result in cancer, shall be discussed. Furthermore, the article will cover miRNA-related therapeutics and provide an overview of the development of resistance to anticancer drugs. Understanding the underlying processes would improve the chances of developing effective cancer treatment therapies.

Correspondence to: Dr Mohammad Zeeshan Najm, School of Biosciences, Apeejay Stya University, Palwal Road, Sohna, Haryana 122103, India
E-mail: biotechzeeshan@gmail.com

Dr Abdulaziz A. Aloliqi, Department of Medical Biotechnology, College of Applied Medical Sciences, Qassim University, 1 King Abdulaziz Road, Almulida, Buraydah 51542, Saudi Arabia
E-mail: aaalieky@qu.edu.sa

Key words: Hippo pathway, microRNAs, YAP, TAZ, tumorigenesis, drug-resistant

Contents

1. Introduction

Cancer is defined as uncontrolled cell growth in any part of the body. It accounts for ~10 million deaths in 2020 (1). However, researchers are striving to establish effective cancer treatments, and microRNAs (miRNAs or miRs) and the hippo signaling pathway have just been discovered in this regard. The Hippo signaling pathway is a mechanism that regulates the organ's size in mammals and humans. The size of the organ is regulated by mediating cell growth, division and death (2). Any dysregulation in the hippo pathway disrupts mediation, leading to the activation of the transcriptional co-activators, that is, YAP and TAZ. Their elevated levels result in escalated cell proliferation and reduced cell death, leading to tumorigenesis (3).

miRNAs play a regulatory role and work by targeting and regulating a certain mRNA. miRNAs have oncogenic and tumor-suppressive characteristics, and their altered levels are detected in cancer. A previous study has revealed that miRNAs can function as a positive or negative regulator to modulate the core components of the hippo pathway (4). Furthermore, YAP and TAZ interact with the components involved in the miRNA biogenesis, and the inactivation of the Hippo pathway or constitutively expression of YAP can result in reduced miRNA biogenesis (5). Understanding the interlinkage between the hippo pathway and miRNAs is crucial for figuring out the root cause of cancer. The dysregulated miRNAs and hippo pathway contribute to uncontrolled growth by regulating each other and even conferring resistance to anticancer treatments. Previous studies have highlighted the mechanism through which miRNAs and hippo regulate each other (2,4). This provides a ray of hope for advancing treatment strategies for patients with cancer. At present, the miRNAs therapeutics are in pre-clinical and clinical trials. These therapeutics would pave the way for cancer treatment. Furthermore, it would even break the resistance developed against the anticancer drugs, thereby boosting the efficiency of the existing treatments (4).

2. Recapitulation of the Hippo pathway

In mammals, the Hippo signaling pathway is a mechanism that maintains the size of the organ by controlling cell proliferation and cell death (6). Previous studies revealed that the hippo pathway is linked to several cancer-like traits, including increased cell proliferation and the development of drug resistance (7,8). The mammalian hippo signaling pathway is described as a cascade mechanism, including the four key tumor suppressors, which are the Mammalian sterile 20-like kinase 1/2 (MST1/2), Salvador Homolog 1 (SAV1), Large tumor suppressor1/2 (LATS1/2), and MOB kinase activator 1A/B (MOB 1A/B). The cascade is initiated when the activated MST1/2-SAV1 complex phosphorylates the LATS1/2-MOB1A/B complex, resulting in its activation (9). When the LATS1/2-MOB1A/B complex is activated, it causes the transcriptional co-activators YAP and TAZ to be downregulated, thus inactivating them (10). The LATS1/2-MOB1A/B complex is activated and works by phosphorylating YAP/TAZ at various locations. When the LATS1/2-MOB1A/B complex is activated, it phosphorylates YAP/TAZ at numerous sites. The phosphorylation causes YAP/TAZ to have a higher binding affinity for 14-3-3 protein. This interaction aids the cytoplasmic localization of the YAP/TAZ. When Ser127 and Ser397 on YAP and Ser89 and Ser311 on TAZ are phosphorylated, the activity of both proteins is significantly reduced (11-13). Phosphorylated Ser397 on YAP and Ser311 on TAZ cause ubiquitination and proteasomal degradation of YAP/TAZ (12) (Fig. 1).

The absence of phosphorylation due to the dysregulated hippo pathway leads to the YAP/TAZ upregulation. The activated YAP/TAZ then moves toward the nucleus, where it interacts with Transcriptional Enhanced Associate Domain (TEAD), a transcriptional factor. YAP/TAZ and TEAD interact and bind to activate the expression of subsequent genes. Increased cell proliferation and decreased apoptosis are two cancer-like properties induced by the activated genes (10,14).

In conclusion, as the hippo pathway modulates the activation of YAP/TAZ, any disruption would elevate the levels of YAP/TAZ, thereby promoting tumorigenesis.

3. Hippo pathway: regulation and cancer development

The hippo signaling system regulates organ size in mammals by controlling cell growth, division, survival and apoptosis (15). As a result, the dysregulation in the hippo pathway can cause YAP/TAZ levels to rise. Additionally, these altered levels stimulate the activation and overexpression of associated genes such as *CYR61, CTGF, MYC, and AREG*, increasing cell proliferation and tumorigenesis (16,17). The functioning and activity of the hippo pathway involve regulation by various molecules and at different levels of the kinetic cascade (18). Upstream regulators include molecules like KIBRA, RASSFs, Merlin, and hEx. They are responsible for promoting and modulating the MST1/2 activity. The Ajuba molecule, on the other hand, is classified as a negative regulator since it inhibits the phosphorylation of YAP/TAZ by downregulating the LATS1/2 by interfering with its function (4). α-catenin, ZO-2, 14-3-3, and AMOT are molecules that promote the retention of YAP/TAZ in the cytoplasm (18). Their action aids in the regulation of YAP/TAZ levels.

Apart from the molecular regulation, the hippo signaling pathway can be crosslinked with other signaling pathways, resulting in hippo pathway modulation and hence malignant situations. The Wnt and AMPK pathways are responsible for YAP protein downregulation. In the case of the Wnt pathway, the scaffold protein DVL acts as a link between the hippo and the Wnt signaling pathway. DVL protein comprises the nuclear export signals, which promote YAP cytoplasmic translocation (19). Since it increases the phosphorylation of YAP at numerous locations, the AMPK pathway can affect the hippo pathway. AMPK also phosphorylates AMOTL1, and phosphorylated AMOTL1 stimulates the upregulation of the LATS1/2, according to a previous study (20). Increased LATS1/2 activity causes YAP inactivation, which is accomplished by phosphorylation. In addition, TAZ interacts with the heteromeric Smad2/3-Smad4 complexes in the TGF-pathway, proving it to be a positive regulator. The binding results in the sustainability of Smad2/3-Smad4 complexes accumulating in the nucleus (21). TAZ phosphorylation and inactivation reduce the ability of the Smad2/3-Smad4 complexes to accumulate in the nucleus, thereby altering the transcription process. TGF signaling is inhibited in the absence of TAZ, which impacts neural epithelial development (22). In KRAS signaling, the protein sends signals to the cells directing the cell to grow and divide, but the *KRAS* gene is identified as the oncogene, meaning that upon mutation, it results in the uncontrolled growth of the cells (23). Studies have shown that the YAP can be understood as the rescuer of the *K-Ras4B*-inhibited cells (24,25). The YAP, along with β-catenin, can induce resistance by managing the advancement of the cells to the S phase in the cell cycle (16). In MAPK/ERK signaling, the YAP protein can promote the development of resistance against the MAPK/ERK kinase (MEK)-targeted inhibitor therapy (26). The increased effect

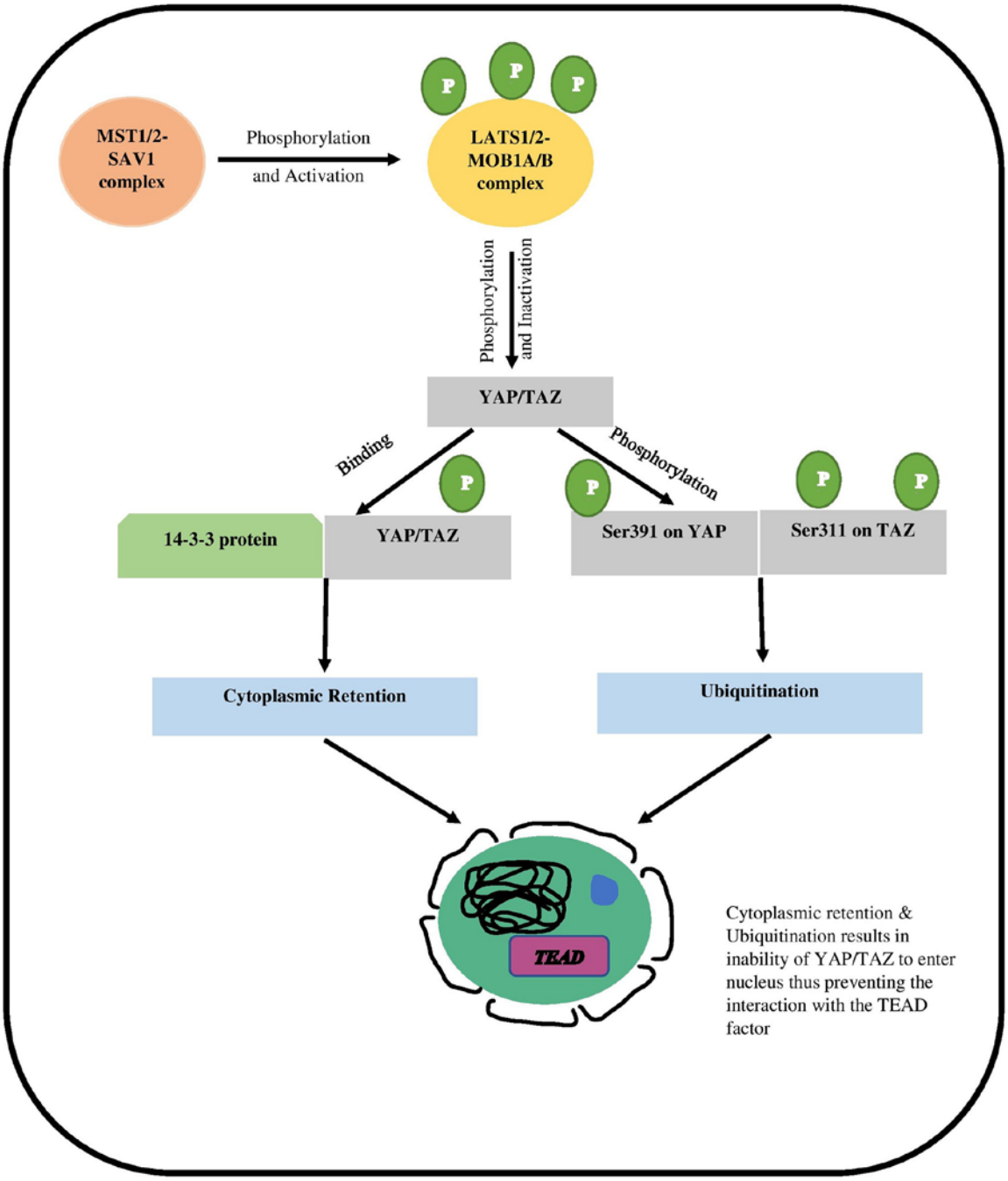

Figure 1. Hippo signaling pathway mechanism in mammals. In mammals the core components of the hippo pathway regulate the expression of the transcriptional co-activators YAP and TAZ thereby maintaining the balance between cell proliferation and apoptosis.

of the active YAP directly affects the MEK inhibitors, thereby predicting the therapeutic effect.

The process of hippo pathway regulation is modulated by various molecules and signaling pathways, either directly or indirectly. Therefore, any sought of disruption responsible for the altered YAP/TAZ levels would result in uncontrolled cell growth and reduced apoptosis due to activation of subsequent genes, thereby developing cancer-like properties (27).

4. Understanding the miRNAs

miRNAs belong to the class of non-coding endogenous RNA, also characterized as small single-stranded nucleotides which play a key regulatory role in various biological processes in plants and animals (28,29). miRNAs range from 21 to 25 nucleotides in length and work by targeting the specific mRNA by translational inhibition, degradation, or mRNA destabilization to regulate the target (29,30). The concept of miRNAs emerged back in 1993 when the miRNAs were first discovered in *Caenorhabditis elegans (C. elegans)* by Ambros and Ruvkun groups (31,32). Previous studies showed that in protein LIN-14, the expression was regulated by a non-coding RNA, and this modulation resulted in the defected development *in Caenorhabditis elegans*. The protein LIN-14 is coded by the heterochronic gene *lin-14*, which controls the developmental timing in *C. elegans* (33). The discovery

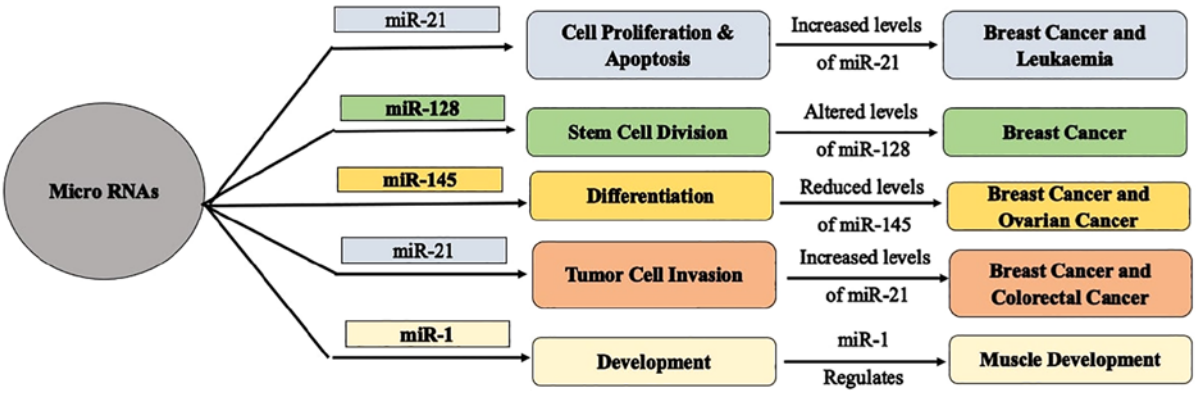

Figure 2. Regulatory role of miRNA. MiRNAs are known to play a regulatory role and works by regulating various components which helps in mediating the cell proliferation and apoptosis. miRNA or miR, microRNA.

of miRNAs was advantageous for researchers working in the molecular biology domain. The miRNAs detected are known to be highly conserved and mainly play the regulatory role across the species (34,35). Researchers are still exploring the miRNAs and their role in gene regulation.

The majority of the miRNAs interact with the target mRNA through the 3' untranslated region (UTR), referred to as 3'(UTR), which promotes the suppression of expression, and the targeted mRNA is degraded (36). A previous study has shown that apart from 3'UTR, miRNAs also interact with the other regions of mRNA, such as coding sequence, gene promoters, and 5'UTR (29). MicroRNAs hold significance in mediating cell proliferation and apoptosis due to their regulatory functioning (37), play a vital role in stem cell division (38), and regulate differentiation, development, and tumor cell invasion (28) (Fig. 2). Since miRNAs mediate cell growth and cell death, any dysregulation in miRNAs pattern would result in uncontrolled growth of the affected cells, thereby depicting cancer-like properties (tumorigenesis).

5. Biogenesis of miRNAs

The biogenesis of miRNAs is a convoluted process. The synthesis of the miRNAs involves a two-step process wherein the first step occurs in the nucleus and the second one takes place in the cytoplasm (36). The process initiates with the formation of primary miRNA (pri-miRNA), which is achieved through gene transcription. The transcription is performed by RNA polymerase II but occasionally can also be performed by RNA polymerase III (39,40). The primary miRNA transcript structures are 5' capped and 3' polyadenylation (41). The cleavage of pri-miRNA is conducted through a microprocessor complex. The microprocessor complex incorporates Drosha, an RNase III enzyme that is responsible for cleaving the pri-miRNA in the nucleus, and DGCR8, a RNA binding protein (3,42). The microprocessor complex is responsible for cleaving the pri-miRNA as the DGCR8 recognizes the ssRNA-dsRNA junction found on pri-mi RNA. This dictates Drosha to give rise to a 60-nucleotide hairpin-like precursor miRNA (pre-miRNA) (41,43). The transfer of pre-miRNA from the nucleus to the cytoplasm is aided by Exportin-5-Ran-GTP. Dicer ribonuclease, which is another RNase III enzyme, cleaves the pre-miRNA in the cytoplasm. When pre-miRNA is cleaved, a miRNA duplex of 21-23 nucleotides is formed, which includes the complementary strand and mature miRNA strand (4,25). The mature miRNA is then integrated into the RNA-induced silencing complex (RISC), a protein complex that also includes the Argonaute (44). The integration targets the 3'UTR of mRNAs, lowering their post-transcriptional or translational levels through mRNA degradation or translational suppression (45,46). (Fig. 3).

6. miRNAs: Regulation and cancer development

MicroRNAs are known to regulate gene expression in both plants and animals. According to a previous study, the number of miRNAs in cancer varies depending on the processes and microenvironment (47). The synthesis of miRNAs is controlled at several levels, including transcription and transportation. It has been identified that SMAD proteins and DEAD-box RNA helicases play a role in miRNA maturation mediated by Drosha (48,49). Methyltransferase-like 3 methylates pri-miRNAs, allowing DGCR8 to recognize and process them, making them the biogenesis regulator (50). KSRP also controls miRNA biogenesis by functioning as a complement to Drosha and Dicer (51). Any disruption in these regulators may cause fluctuations in miRNA levels, resulting in changes in miRNA expression.

The altered levels of miRNAs are one cause leading to cells developing cancer-like properties as numerous miRNAs act as either tumor suppressors or tumor promoters. Thus, the altered levels of these miRNAs result in tumorigenesis. For instance, miRNA-21 and miRNA-155 are identified as miRNAs whose increased expression is observed in malignant tumors. On the other hand, the downregulation of these miRNAs has been revealed to cause controlled cell proliferation, thereby resulting in reduced tumor growth (52,53). Let-7 is another miRNA that acts as a tumor suppressor, and its levels are highly downregulated in case of cancer (54).

7. Deciphering the interlinkage of miRNAs and the Hippo pathway

The hippo signaling pathway is primarily responsible for regulating the size of the organ, which is achieved by mediating cell

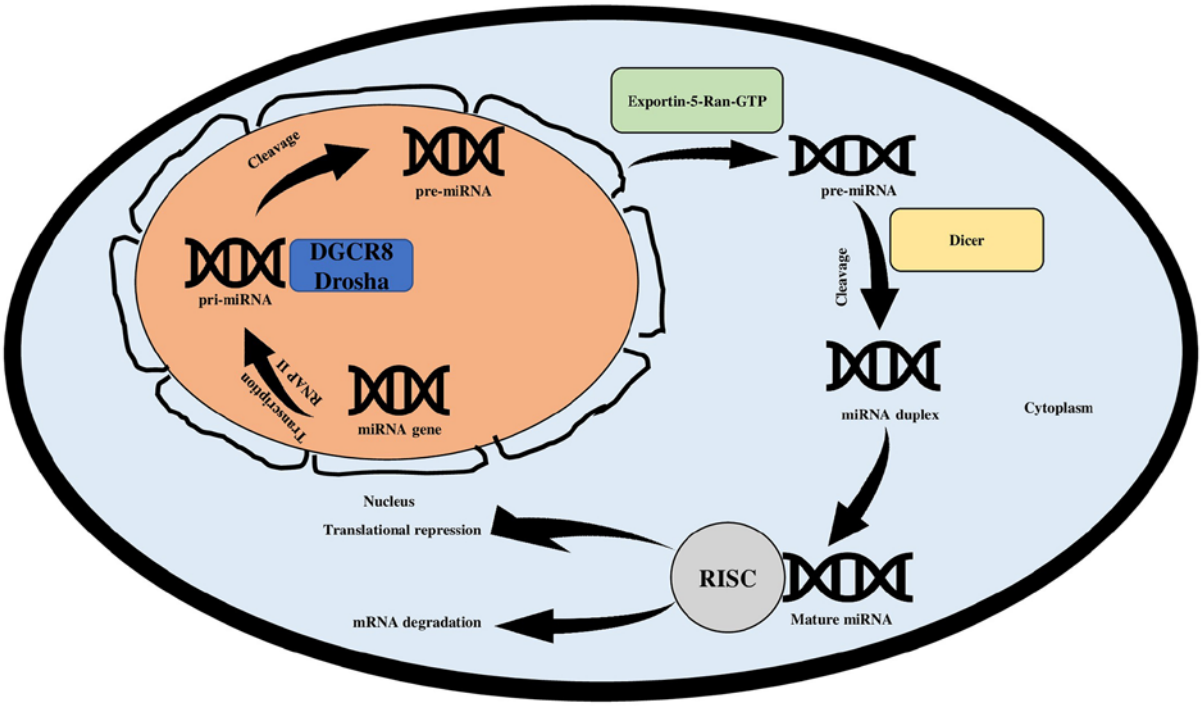

Figure 3. Biogenesis of miRNA. The biogenesis of miRNA is followed to a set of events starting from the formation of the pri-miRNA to the cleavage of the pre-miRNA so as to get mature miRNA which would bind to the targeted mRNA. miRNA or miR, microRNA.

proliferation, apoptosis and regeneration (55). Downregulation of the hippo pathway causes YAP/TAZ to be activated, resulting in escalated cell proliferation and reduced cell-cell adhesion leading to tumorigenesis. The miRNAs are small non-coding RNA and play a regulatory role in gene expression by targeting the specific miRNAs. In cancer, altered miRNAs level are observed due to dysregulated miRNA expression. The dysregulation of expression of miRNAs occurs due to the defective miRNAs biogenesis or the fluctuating levels of the miRNAs genes (30).

The interlinkage between miRNAs and the hippo signaling pathway, which leads to cancer, has been proven through advances in research. The YAP and TAZ, two critical components of the hippo pathway, have been demonstrated to influence miRNA biogenesis directly, implying that they play an important role in cancer progression. On the other hand, various miRNAs can regulate key elements of the hippo pathway, resulting in cancer (5). As a result, it is critical to figure out how the hippo pathway and miRNAs are linked and how they interact to figure out how to treat cancer with therapeutic approaches.

8. The Hippo pathway as a regulator of miRNAs

The research conducted to understand the crosslinks between the hippo and miRNAs suggested that the hippo pathway functions as a regulator for miRNA synthesis in a cell density-dependent manner, implying that the regulation of the hippo pathway contributes to carcinogenesis. It operates by interfering with the microprocessor complex that forms pre-miRNA from pri-miRNA. Furthermore, because it is sensitive to cell density and disruption of the hippo pathway is a prominent hallmark of tumors, studies have revealed that it is a regulator of cell density-dependent miRNA synthesis (5,55,56).

In case of lower cell density, the suppression of the hippo pathway, leads to activation of YAP, and the activated YAP moves towards the nucleus. This set of events causes the activation of subsequent genes accountable for elevated cell growth, thereby suppressing the biogenesis of miRNAs (8). The cell density increases with the increase in proliferation, and this promotes the phosphorylation and cytoplasmic retention of YAP by adherens such as E-cadherin (55) and α-catenin (57). p72 (DDX17) is an accessory protein that forms part of the DROSHA-containing complex and plays a role in the pri-miRNA processing by interacting with DROSHA and DGCR8 (50,58). Since p72 detects the VCAUCH sequence, which is present in the 3' flanking region of pri-miRNA, its interaction with the microprocessor enhances biogenesis (5). In low density, p72 interacts with YAP rather than DROSHA and DGCR8, resulting in YAP's retention of p72 in the nucleus and reduced miRNA biosynthesis (59). (Fig. 4).

9. miRNAs as a regulator of the the Hippo signaling pathway

Depending on their environment, miRNAs are known to act as either oncogenic or tumor suppressors in certain malignancies (60). According to previous findings, miRNAs positively and negatively affect the hippo pathway, implying that some oncogenic miRNAs adversely regulate the hippo pathway, resulting in cancer. By contrast, certain miRNAs regulate the hippo pathway positively, thereby maintaining the hippo pathway.

miR-31 and miR-135b are identified as oncogenic miRNAs, and elevated expression is observed in the case of

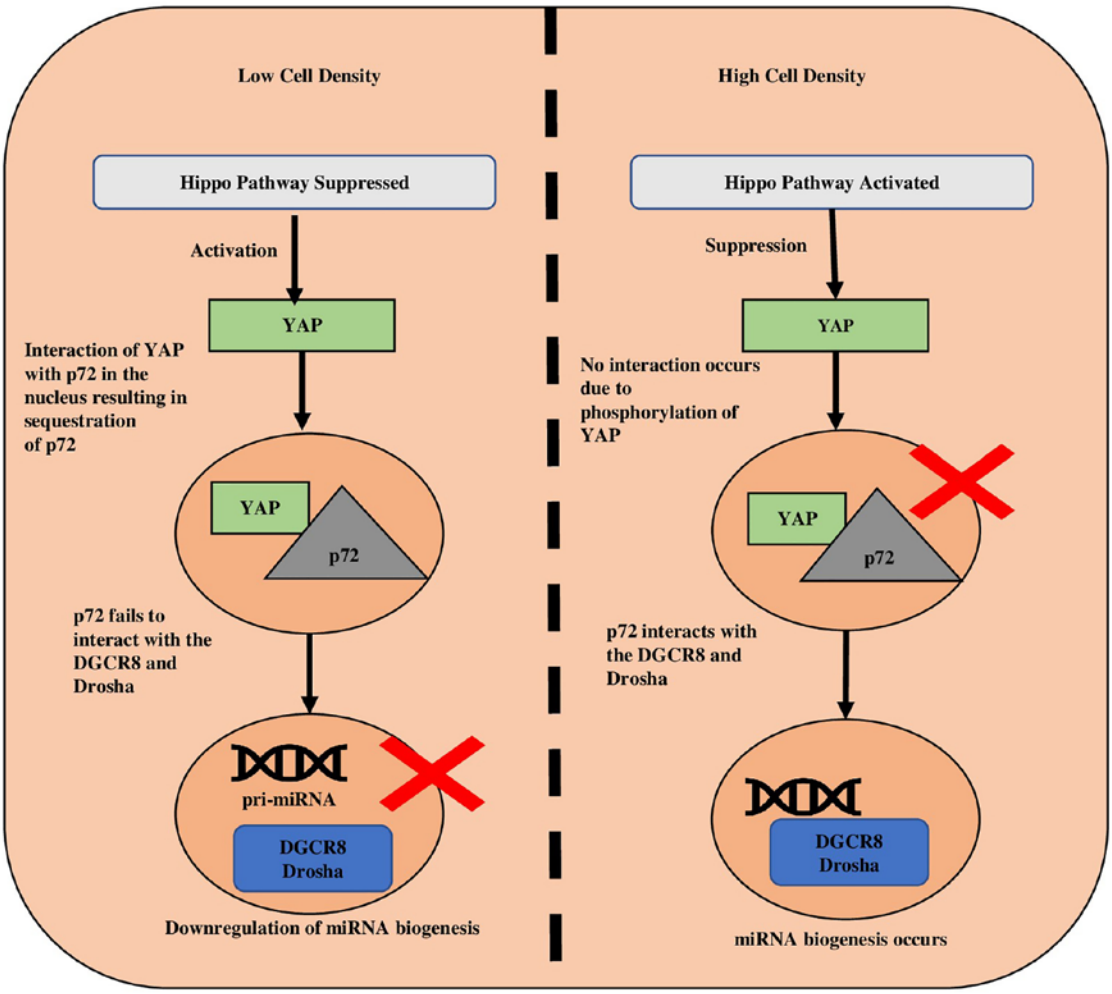

Figure 4. Hippo Pathway as regulator of miRNA biogenesis. miRNA biogenesis is regulated by the Hippo pathway through various set of events and abnormality of Hippo pathway can affect the miRNA biogenesis which results in tumorigenesis. miRNA or miR, microRNA.

cancer (61). Overexpression of these miRNAs is one cause that results in the reduced levels of LATS1/2, which is a core component of the hippo pathway. Downregulation of LATS1/2 promotes the activation of YAP, which travels towards the nucleus and, upon reaching, interacts with the TEAD. The interaction between YAP and TEAD is the activation of the subsequent genes, thereby increasing cell proliferation and apoptosis (62). miR-130 works in a feedback loop with YAP, and its increased levels are found in various types of cancer including oesophageal squamous cell carcinoma, gastric and bladder cancer (63,64). miR-130 is known to play a regulatory role in *PTEN* expression and Akt phosphorylation in cancerous cells, and the increased levels of miRNA-130 is induced by the YAP (4). The miR-130 negatively regulates the *VGLL4*, which is responsible for the downregulation of the YAP-TEAD complex in the nucleus. The consequence of the downregulation of *VGLL4* has increased YAP activity, thereby promoting carcinogenesis (4,65). miR-3910 is another miRNA exhibiting oncogenic properties. It promotes cell proliferation and cell migration, and in mice, its overexpression has resulted in the formation of hepatocellular carcinoma (HCC) (66). The miR-3910 negatively regulates the MST1, and its increased levels lead to the downregulation of MST1. As MST1 negatively regulates YAP, its reduced levels increase YAP levels. The absence of phosphorylation of YAP promotes the expression of the genes such as *CTGF*, *MYC* and *BMI1*, thereby inhibiting apoptosis and promoting tumor formation (66).

The tumor suppressor miRNAs work as a regulator for cell proliferation and apoptosis, thereby regulating the hippo pathway by targeting either YAP or TAZ (4). For example, miRNA-375 is known as a tumor suppressor, and its levels are found to be reduced in HCC. In addition, 3' UTR of *YAP1* is targeted by miRNA-375, which suppresses the *YAP1* levels, thereby regulating the hippo pathway (67). miR-186 also acts as the regulator of YAP expression by acting on the *YAP1* gene, which suppresses YAP (68).

miR-137 and miR-9 are known to regulate the YAP by promoting the activity of LATS1 negatively. The increased activity of *LATS1* results in the phosphorylation of YAP, thereby downregulating the expression of *ARE*, *CYR61* and *CTGF*, which are responsible for causing gastric cancer (69). miR-9-3p, which is formed by processing the 3' arm of miR-9, has been shown to downregulate TAZ, thus regulating the pathway (70). The tumor suppressor miR-129-5p has shown a direct relationship with the hippo pathway as its downregulation causes the activation of YAP/TAZ, followed by the interaction with the TEAD (71). A previous study has shown the relation between the elevated miR-195 levels and YAP

Table I. miRNA therapeutics under pre-clinical and clinical trials.

Drug Name	Targeted miRNA	Category of therapeutics	Target cancer	Stage of trials	Clinical trial number	(Refs.)
-	miR-10b	Anti-miRNA	Glioblastoma, breast cancer	Trails in pre-clinical models	-	(75)
-	miR-200 family	Mimic-miRNA	Lung cancer, Breast cancer, Ovarian cancer	Trails in pre-clinical models	-	(75)
MRX34	miR-34	Mimic-miRNA	Various solid tumors such as liver cancer, lymphoma	Phase-I: Terminated Phase I: Withdrawn	NCT01829971 NCT02862145	(75,80)
MesomiR-1	miR-16	Mimic-miRNA	Lung cancer	Phase I: Completed	NCT02369198	(75,80)
Miravirsen	miR-122	Anti-miRNA	Lung cancer	Phase I: Status: Complete Phase II: Status: Complete Phase II: Status: Complete Phase II: Status: Complete Phase II: Unknown Phase II: Unknown	NCT01646489 NCT02508090 NCT02452814 NCT01200420 NCT01872936 NCT01727934	(75,80)

miR, microRNA.

activity. The reduced levels of miR-195 in cancer cells show high levels of YAP, indicating the direct regulation of YAP by miR-195 (72). The regulation of YAP by miR-195 demonstrates that the miRNAs regulate the hippo pathway, and the regulation of the biogenesis of miRNAs by the hippo pathway is interlinked. Together this contributes to the development of cancer-like properties and tumorigenesis.

10. miRNAs therapeutics for the treatment of cancer

Apart from all the treatment methods available, such as chemotherapy, the use of therapeutics to eliminate cancer cells proves to be advantageous for the treatment of cancer (3). Since miRNAs play a regulatory role in gene expression and their altered levels are found in various cancers, studies are at present diverted towards the therapeutics miRNAs in order to destroy the cancerous cells, as the miRNAs play a vital role in tumor formation and expansion (37,73). The miRNAs can target various proteins by interacting with the various target mRNA, therefore, demonstrating to be a suitable candidate for the treatment of cancer (74). Because miRNAs have both oncogenic and tumor-suppressive roles in organisms, scientists are working on therapies that consist of miRNA mimics and anti-miRNAs (75). Mimic miRNAs mimic tumor-suppressive miRNAs and raise their levels in situations where tumor-suppressive miRNAs are low. They are non-naturally occurring oligonucleotide duplexes that mimic the function of tumor-suppressive miRNAs (75). Anti-miRNAs are miRNAs that serve as antagonists against oncogenic miRNAs. They have complementary sequences to the targeted miRNAs, blocking oncogenic miRNAs and lowering their overexpressed levels in malignancies (76). miRNAs therapeutics are introduced in the pre-clinical models so as to improve the efficacy of therapeutics via viral vectors (77), nanoparticles (78) and liposome delivery (79).

Researchers have been working on miRNA therapies for years, but only a few have progressed to the stage of clinical trials. Due to the variability of miRNA expression, the most significant challenge is to identify the miRNA targets and creat a delivery mechanism that is not hazardous (75). miRNA therapies are now being examined and could be beneficial to patients with cancer in the future. In addition, because miRNAs have been proven to regulate the hippo pathway, researchers can employ treatments to break the resistance to anticancer therapies induced by the dysregulated hippo pathway, demonstrating application in carcinogenesis. A few miRNAs therapeutics under pre-clinal and clinical trials are listed in Table I (75,80).

11. miRNAs, Hippo and resistance to anticancer drugs

miRNAs are accountable for regulating gene expression, and the altered levels of miRNAs are detected in patients who have cancer. Since miRNAs also regulate the genes that directly influence the response of cells when anticancer drugs are administered, the dysregulated levels result in the development of resistance against the anticancer drugs, thereby affecting the therapeutic effect of the drug (81). The component of the Hippo pathway, that is, the YAP and TAZ, are involved in imparting resistance against the anticancer drugs. The elevated levels of YAP/TAZ result in the altered levels of the various proteins and pathways, thereby affecting the normal cascade. This alteration results in the development of resistance to anticancer drugs. For example, the elevated levels of

Table II. miRNA and Hippo Pathway components affecting therapeutics in different cancers.

miRNA	Expression in tumour	Affected component of the Hippo pathway	Dysregulation of the Component	Resistance to Drug	Cancer	(Refs.)
miR-21	Increased	YAP	Upregulation	Doxorubicin, Trastuzumab	Breast cancer	(83,84)
miR-135a/b	Increased	LATS1/2 YAP	Downregulation Upregulation	CDDP	Lung cancer	(85)
miR-9	Decreased	LATS1/2 YAP	Upregulation Downregulation	Doxorubicin, CDDP	Ovarian cancer	(86)
miR-338-3p	Decreased	TAZ	Downregulation	Sorafenib	Hepatocellular cancer	(87)

miR, microRNA.

TAZ result in increased multidrug resistance protein, which results in the development of resistance against Paclitaxel (an anticancer drug) (3).

Previous studies have also highlighted the role of the Hippo pathway in the therapeutic effect, as the dysregulated pathway results in resistance against the drugs (3,8). As the miRNAs mediate the hippo pathway, it is crucial to deeply analyze the crosslinking between the hippo pathway and miRNAs and how this can affect the resistance against the anticancer drugs to develop effective treatment strategies. The miRNAs, its target hippo component, and which drug's therapeutic action is affected in specific cancer (82) are listed in Table II (83-87).

12. miR-21

miR-21 is an oncogenic miRNA, and its increased levels are observed in different types of cancer, including breast, cervical and colon cancer (88). Doxorubicin is a therapeutic drug administered to treat various types of cancer. It promotes cell apoptosis by binding with topoisomerase II thereby inhibiting its enzymatic activity (89). Studies have shown that in the case of breast cancer, the increased levels of miR-21 promote resistance against the anticancer drug as the miR-21 downregulates the PTEN expression (83,84). Furthermore, increased miR-21 levels result in the downregulation of *RUNX1*. As *RUNX1* inhibits the YAP expression, its downregulation results in the YAP activation. The upregulation of YAP promotes the partial actuation of the MAPK pathway, which results in tumorigenesis (3). This, along with altered levels of YAP, results in the development of resistance against doxorubicin. By administering anti-miRNAs, the levels of miR-21 would be regulated, breaking the doxorubicin resistance. Studies have indicated that trastuzumab resistance has a similar sequence of events, apart from doxorubicin resistance. Trastuzumab is a chemotherapeutic medication that inhibits cancer cell growth by binding to the HER2 protein (90). Resistance to the anticancer medicine trastuzumab develops due to overexpression of miRNA and decreased expression of *PTEN*. Overexpression of YAP and TEAD enhances treatment resistance in breast cancer, and increased miRNA levels boost YAP activation (91). Trastuzumab resistance can be minimized by using antisense miRNA-21 oligonucleotides to maintain the levels of miR-21, which regulates the levels of YAP and so reduces resistance against trastuzumab to some extent (84).

13. miR-135a/b

miRNAs fall into the category of both oncogenic miRNAs and tumor suppressor miRNAs. The research has highlighted that increased levels of miR-135a/b are detected in the case of lung cancer (92). Cisplatin is identified as a therapeutic drug utilized to treat various types of cancer. It works by binding to the DNA upon entry into the cell and causing damage to the DNA leading to apoptosis (93). The increased levels of miR-135a/b result in the progression of resistance against cisplatin as the miR-135b targets *Mcl1*, which leads to the hampering of the apoptosis process (94). miR-135 is also known to regulate the hippo pathway negatively by downregulating the LATS1/2, which results in increased levels of the YAP, leading to cancer-like properties. The upregulation of YAP also aids in the development of resistance and its progression against cancer drugs. Regulation of miR-135a/b through therapeutics, that is, by anti-miRNAs, would help maintain the miR-135a/b levels, which would, in turn, maintain the YAP levels leading to a reduction in the chemoresistance.

14. miR-9

MiR-9 has been identified as a tumor suppressor, with lower levels reported in ovarian and breast cancer. The medications doxorubicin and cisplatin, which function by destroying DNA, are routinely used to treat ovarian cancer. Certain DNA damage repair enzymes, on the other hand, fix the damage, allowing the cell to survive (81). The downregulation of miR-9 is one of the ways malignant cells develop resistance. In ovarian cancer, miR-9 targets DNA damage repair-related enzyme genes such as BRCA1, preventing BRCA1 action (86). In addition, the miR-9 stimulates the phosphorylation of YAP by upregulating the LATS1/2, acting as a positive regulator of the hippo pathway. As a result, miR-9 levels are lowered in patients with cancer. The reduced miR-9 levels can decrease LATS1/2, which ultimately leads to the increased expression of cancer-promoting factors, that is, YAP and TAZ, and can result in tumorigenesis (69). The hyperactivation of YAP/TAZ is also one cause resulting in resistance to anticancer drugs. The regulation of miR-9 levels via therapeutics would result in the dephosphorylation of YAP, leading to increased efficacy of the anticancer drugs.

15. miR-338-3p

miR-338-3p works as a tumor suppressor and its levels are detected to be reduced in case of HCC. Sorafenib is identified as a kinase inhibitor and works by targeting and blocking the enzymes and proteins found in and on the surface of cancerous cells to inhibit their growth (95). The miR-338-3p inhibits the Hypoxia-inducible factor-1 (*HIF-1*), which is the mediator of the hypoxia signaling pathway, which results in increased cell apoptosis (88). The lower levels of miR-338-3p result in the upregulation of HIF-1α, which results in tumor growth and the development of sorafenib resistance (96-98). miR-338-3p also directly acts on the TAZ and inhibits it, reducing its levels. The increased levels of YAP and TAZ promote resistance to anti-cancer drugs. The maintained levels of miR-338-3p would help to break the resistance against sorafenib, thereby increasing the efficiency.

16. Conclusion

Researchers have been able to broaden horizons in the field of cancer thanks to their understanding of miRNAs. The role of microRNAs in cancer progression and carcinogenesis has been identified. The Hippo pathway and miRNA have been identified to be interconnected, and their dysregulation may contribute to carcinogenesis.

It was attempted to establish the interlinkage of miRNAs and the hippo pathway using potential information in the present review and relate it to treatment resistance in cancer. Researchers may be able to manage difficult-to-treat drug resistance linked with cancer with an improved understanding of the crosslink. The studies and clinical trials involving miRNA and the hippo pathway remain in their early phases, and there is markedly more to learn. The relationship between miRNAs and the hippo pathway is complicated and requires further research. Researchers will be able to unravel the origin of cancer and design successful treatment techniques in the near future with a thorough understanding of the underlying molecular process and study of crosstalks.

Acknowledgements

Not applicable.

Funding

The researcher(s) would like to thank the Deanship of Scientific Research, Qassim University for funding the publication of this project.

Availability of data and materials

Not applicable.

Authors' contributions

MZN, TA, MAK, SMA and SK collaboratively helped in curating the recent studies. AAA, MZN and SS guided in analyzing the curated data. SA, VMS and AAE prepared the figures and tables.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A and Bray F: Cancer statistics for the year 2020: An overview. Int J Cancer: Apr 5, 2021 (Epub ahead of print).
2. Zygulska AL, Krzemieniecki K and Pierzchalski P: Hippo pathway-brief overview of its relevance in cancer. J Physiol Pharmacol 68: 311-335, 2017.
3. Zeng R and Dong J: The Hippo signaling pathway in drug resistance in cancer. Cancers (Basel) 13: 318, 2021.
4. Li N, Xie C and Lu N: Crosstalk between Hippo signaling and miRNAs in tumor progression. FEBS J 284: 1045-1055, 2017.
5. Mori M, Triboulet R, Mohseni M, Schlegelmilch K, Shrestha K, Camargo FD and Gregory RI: Hippo signaling regulates microprocessor and links cell-density-dependent miRNA biogenesis to cancer. Cell 156: 893-906, 2014.
6. Pfleger CM: The Hippo pathway: A master regulatory network important in development and dysregulated in disease. Curr Top Dev Biol 123: 181-228, 2017.
7. Dey A, Varelas X and Guan KL: Targeting the Hippo pathway in cancer, fibrosis, wound healing and regenerative medicine. Nat Rev Drug Discov 19: 480-494, 2020.
8. Kaur S, Najm MZ, Khan MA, Akhter N, Shingatgeri VM, Sikenis M, Sadaf and Aloliqi AA: Drug-resistant breast cancer: Dwelling the Hippo pathway to manage the treatment. Breast Cancer (Dove Med Press) 13: 691-700, 2021.
9. Praskova M, Xia F and Avruch J: MOBKL1A/MOBKL1B phosphorylation by MST1 and MST2 inhibits cell proliferation. Curr Biol 18: 311-321, 2008.
10. Zheng Y and Pan D: The Hippo signaling pathway in development and disease. Dev Cell 50: 264-282, 2019.
11. Nguyen-Lefebvre AT, Selzner N, Wrana JL and Bhat M: The hippo pathway: A master regulator of liver metabolism, regeneration, and disease. FASEB J 35: e21570, 2021.
12. Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, Xie J, Ikenoue T, Yu J, Li L, *et al*: Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes Dev 21: 2747-2761, 2007.
13. Lei QY, Zhang H, Zhao B, Zha ZY, Bai F, Pei XH, Zhao S, Xiong Y and Guan KL: TAZ promotes cell proliferation and epithelial-mesenchymal transition and is inhibited by the hippo pathway. Mol Cell Biol 28: 2426-2436, 2008.
14. Najm MZ, Sadaf, Shingatgeri VM, Saha H, Bhattacharya H, Rath A, Verma V, Gupta A, Aloliqi AA, Kashyap P and Parveen F: Hippo pathway in cancer: Examining its potential. J Curr Oncol 4: 115-120, 2021.
15. Badouel C and McNeill H: SnapShot: The hippo signaling pathway. Cell 145: 484.e1, 2011.
16. Huang YT, Lan Q, Lorusso G, Duffey N and Rüegg C: The matricellular protein CYR61 promotes breast cancer lung metastasis by facilitating tumor cell extravasation and suppressing anoikis. Oncotarget 8: 9200-9215, 2017.
17. Niu J, Ma J, Guan X, Zhao X, Li P and Zhang M: Correlation between Doppler ultrasound blood flow parameters and angiogenesis and proliferation activity in breast cancer. Med Sci Monit 25: 7035, 2019.
18. Yu FX and Guan KL: The Hippo pathway: Regulators and regulations. Genes Dev 27: 355-371, 2013.
19. Han Y: Analysis of the role of the Hippo pathway in cancer. J Transl Med 17: 116, 2019.
20. Mo JS: The role of extracellular biophysical cues in modulating the Hippo-YAP pathway. BMB Rep 50: 71-78, 2017.

21. Varelas X, Sakuma R, Samavarchi-Tehrani P, Peerani R, Rao BM, Dembowy J, Yaffe MB, Zandstra PW and Wrana JL: TAZ controls Smad nucleocytoplasmic shuttling and regulates human embryonic stem-cell self-renewal. Nat Cell Biol 10: 837-848, 2008.
22. Beyer TA, Weiss A, Khomchuk Y, Huang K, Ogunjimi AA, Varelas X and Wrana JL: Switch enhancers interpret TGF-β and Hippo signaling to control cell fate in human embryonic stem cells. Cell Rep 5: 1611-1624, 2013.
23. Liu J, Kang R and Tang D: The KRAS-G12C inhibitor: Activity and resistance. Cancer Gene Ther 2021: Sep 1, (Epub ahead of print).
24. Shen Z and Stanger BZ: YAP regulates S-phase entry in endothelial cells. PLoS One 10: e0117522, 2015.
25. Benham-Pyle BW, Pruitt BL and Nelson WJ: Mechanical strain induces E-cadherin-dependent Yap1 and β-catenin activation to drive cell cycle entry. Science 348: 1024-1027, 2015.
26. Kapoor A, Yao W, Ying H, Hua S, Liewen A, Wang Q, Zhong Y, Wu CJ, Sadanandam A, Hu B, *et al*: Yap1 activation enables bypass of oncogenic Kras addiction in pancreatic cancer. Cell 158: 185-197, 2014.
27. Shibata M, Ham K and Hoque MO: A time for YAP1: Tumorigenesis, immunosuppression and targeted therapy. Int J Cancer 143: 2133-2144, 2018.
28. Mytsyk Y, Dosenko V, Skrzypczyk MA, Borys Y, Diychuk Y, Kucher A, Kowalskyy V, Pasichnyk S, Mytsyk O and Manyuk L: Potential clinical applications of microRNAs as biomarkers for renal cell carcinoma. Cent European J Urol 71: 295-303, 2018.
29. O'Brien J, Hayder H, Zayed Y and Peng C: Overview of microRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne) 9: 402, 2018.
30. Bushati N and Cohen SM: MicroRNA functions. Annu Rev Cell Dev Biol 23: 175-205, 2007.
31. Lee RC, Feinbaum RL and Ambros V: The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 75: 843-854, 1993.
32. Wightman B, Ha I and Ruvkun G: Post-transcriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell 75: 855-862, 1993.
33. Hong Y, Lee RC and Ambros V: Structure and function analysis of LIN-14, a temporal regulator of postembryonic developmental events in Caenorhabditis elegans. Mol Cell Biol 20: 2285-2295, 2000.
34. Lagos-Quintana M, Rauhut R, Lendeckel W and Tuschl T: Identification of novel genes coding for small expressed RNAs. Science 294: 853-858, 2001.
35. Lau NC, Lim LP, Weinstein EG and Bartel DP: An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans. Science 294: 858-862, 2001.
36. Ha M and Kim VN: Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol 15: 509-524, 2014.
37. Croce CM and Calin GA: MiRNAs, cancer, and stem cell division. Cell 122: 6-7, 2005.
38. Hatfield SD, Shcherbata HR, Fischer KA, Nakahara K, Carthew RW and Ruohola-Baker H: Stem cell division is regulated by the microRNA pathway. Nature 435: 974-978, 2005.
39. Borchert GM, Lanier W and Davidson BL: RNA polymerase III transcribes human microRNAs. Nat Struct Mol Biol 13: 1097-1101, 2006.
40. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH and Kim VN: MicroRNA genes are transcribed by RNA polymerase II. EMBO J 23: 4051-4060, 2004.
41. MacFarlane LA and R Murphy P: MicroRNA: Biogenesis, function and role in cancer. Curr Genomics 11: 537-561, 2010.
42. Pong SK and Gullerova M: Noncanonical functions of microRNA pathway enzymes-Drosha, DGCR 8, Dicer and Ago proteins. FEBS Lett 592: 2973-2986, 2018.
43. Han J, Lee Y, Yeom KH, Kim YK, Jin H and Kim VN: The Drosha-DGCR8 complex in primary microRNA processing. Genes Dev 18: 3016-3027, 2004.
44. Wong CM, Tsang FH and Ng IO: Non-coding RNAs in hepatocellular carcinoma: Molecular functions and pathological implications. Nat Rev Gastroenterol Hepatol 15: 137-151, 2018.
45. Valinezhad Orang A, Safaralizadeh R and Kazemzadeh-Bavili M: Mechanisms of miRNA-mediated gene regulation from common downregulation to mRNA-specific upregulation. Int J Genomics 2014: 970607, 2014.
46. Zhang HN, Xu QQ, Thakur A, Alfred MO, Chakraborty M, Ghosh A and Yu XB: Endothelial dysfunction in diabetes and hypertension: Role of microRNAs and long non-coding RNAs. Life Sci 213: 258-268, 2018.
47. Romano G and Kwong LN: MiRNAs, melanoma and microenvironment: An intricate network. Int J Mol Sci 18: 2354, 2017.
48. Fukuda T, Yamagata K, Fujiyama S, Matsumoto T, Koshida I, Yoshimura K, Mihara M, Naitou M, Endoh H, Nakamura T, *et al*: DEAD-box RNA helicase subunits of the Drosha complex are required for processing of rRNA and a subset of microRNAs. Nat Cell Biol 9: 604-611, 2007.
49. Davis BN, Hilyard AC, Lagna G and Hata A: SMAD proteins control DROSHA-mediated microRNA maturation. Nature 454: 56-61, 2008.
50. Alarcón CR, Lee H, Goodarzi H, Halberg N and Tavazoie SF: N6-methyladenosine marks primary microRNAs for processing. Nature 519: 482-485, 2015.
51. Trabucchi M, Briata P, Garcia-Mayoral M, Haase AD, Filipowicz W, Ramos A, Gherzi R and Rosenfeld MG: The RNA-binding protein KSRP promotes the biogenesis of a subset of microRNAs. Nature 459: 1010-1014, 2009.
52. Dinami R, Ercolani C, Petti E, Piazza S, Ciani Y, Sestito R, Sacconi A, Biagioni F, le Sage C, Agami R, *et al*: MiR-155 drives telomere fragility in human breast cancer by targeting TRF1. Cancer Res 74: 4145-4156, 2014.
53. Li L, Li C, Wang S, Wang Z, Jiang J, Wang W, Li X, Chen J, Liu K, Li C and Zhu G: Exosomes derived from hypoxic oral squamous cell carcinoma cells deliver miR-21 to normoxic cells to elicit a prometastatic phenotype. Cancer Res 76: 1770-1780, 2016.
54. Liu C, Kelnar K, Vlassov AV, Brown D, Wang J and Tang DG: Distinct microRNA expression profiles in prostate cancer stem/progenitor cells and tumor-suppressive functions of let-7. Cancer Res 72: 3393-3404, 2012.
55. Fu V, Plouffe SW and Guan KL: The Hippo pathway in organ development, homeostasis, and regeneration. Curr Opin Cell Biol 49: 99-107, 2017.
56. Harvey KF, Zhang X and Thomas DM: The Hippo pathway and human cancer. Nat Rev Cancer 13: 246-257, 2013.
57. Schlegelmilch K, Mohseni M, Kirak O, Pruszak J, Rodriguez JR, Zhou D, Kreger BT, Vasioukhin V, Avruch J, Brummelkamp TR and Camargo FD: Yap1 acts downstream of α-catenin to control epidermal proliferation. Cell 144: 782-795, 2011.
58. Gregory RI, Yan KP, Amuthan G, Chendrimada T, Doratotaj B, Cooch N and Shiekhattar R: The Microprocessor complex mediates the genesis of microRNAs. Nature 432: 235-240, 2004.
59. Chang TC, Yu D, Lee YS, Wentzel EA, Arking DE, West KM, Dang CV, Thomas-Tikhonenko A and Mendell JT: Widespread microRNA repression by Myc contributes to tumorigenesis. Nat Genet 40: 43-50, 2008.
60. Yu T, Ma P, Wu D, Shu Y and Gao W: Functions and mechanisms of microRNA-31 in human cancers. Biomed Pharmacother 108: 1162-1169, 2018.
61. Liu X, Sempere LF, Ouyang H, Memoli VA, Andrew AS, Luo Y, Demidenko E, Korc M, Shi W, Preis M, *et al*: MicroRNA-31 functions as an oncogenic microRNA in mouse and human lung cancer cells by repressing specific tumor suppressors. J Clin Invest 120: 1298-1309, 2010.
62. Wu Y, Li M, Lin J and Hu C: Hippo/TEAD4 signaling pathway as a potential target for the treatment of breast cancer. Oncol Lett 21: 313, 2021.
63. Egawa H, Jingushi K, Hirono T, Ueda Y, Kitae K, Nakata W, Fujita K, Uemura M, Nonomura N and Tsujikawa K: The miR-130 family promotes cell migration and invasion in bladder cancer through FAK and Akt phosphorylation by regulating PTEN. Sci Rep 6: 20574, 2016.
64. Duan J, Zhang H, Qu Y, Deng T, Huang D, Liu R, Zhang L, Bai M, Zhou L, Ying G and Ba Y: Onco-miR-130 promotes cell proliferation and migration by targeting TGFβR2 in gastric cancer. Oncotarget 7: 44522-44533, 2016.
65. Zhang Y, Shen H, Withers HG, Yang N, Denson KE, Mussell AL, Truskinovsky A, Fan Q, Gelman IH, Frangou C and Zhang J: VGLL4 selectively represses YAP-dependent gene induction and tumorigenic phenotypes in breast cancer. Sci Rep 7: 6190, 2017.
66. Cheng L, Wang H and Han S: MiR-3910 promotes the growth and migration of cancer cells in the progression of hepatocellular carcinoma. Dig Dis Sci 62: 2812-2820, 2017.
67. Liu AM, Poon RT and Luk JM: MicroRNA-375 targets Hippo-signaling effector YAP in liver cancer and inhibits tumor properties. Biochem Biophys Res Commun 394: 623-627, 2010.
68. Ruan T, He X, Yu J and Hang Z: MicroRNA-186 targets Yes-associated protein 1 to inhibit Hippo signaling and tumorigenesis in hepatocellular carcinoma. Oncol Lett 11: 2941-2945, 2016.

69. Deng J, Lei W, Xiang X, Zhang L, Lei J, Gong Y, Song M, Wang Y, Fang Z, Yu F, *et al*: Cullin 4A (CUL4A), a direct target of miR-9 and miR-137, promotes gastric cancer proliferation and invasion by regulating the Hippo signaling pathway. Oncotarget 7: 10037-10050, 2016.
70. Higashi T, Hayashi H, Ishimoto T, Takeyama H, Kaida T, Arima K, Taki K, Sakamoto K, Kuroki H, Okabe H, *et al*: MiR-9-3p plays a tumour-suppressor role by targeting TAZ (WWTR1) in hepatocellular carcinoma cells. Br J Cancer 113: 252-258, 2015.
71. Tan G, Cao X, Dai Q, Zhang B, Huang J, Xiong S, Zhang Yy, Chen W, Yang J and Li H: A novel role for microRNA-129-5p in inhibiting ovarian cancer cell proliferation and survival via direct suppression of transcriptional co-activators YAP and TAZ. Oncotarget 6: 8676-8686, 2015.
72. Yu S, Jing L, Yin XR, Wang MC, Chen YM, Guo Y, Nan KJ and Han LL: MiR-195 suppresses the metastasis and epithelial-mesenchymal transition of hepatocellular carcinoma by inhibiting YAP. Oncotarget 8: 99757-99771, 2017.
73. Abd-Aziz N, Kamaruzman NI and Poh CL: Development of microRNAs as potential therapeutics against cancer. J Oncol 2020: 8029721, 2020.
74. Wang V and Wu W: MicroRNA-based therapeutics for cancer. BioDrugs 23: 15-23, 2009.
75. Rupaimoole R and Slack FJ: MicroRNA therapeutics: Towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov 16: 203-222, 2017.
76. Shah V and Shah J: Recent trends in targeting miRNAs for cancer therapy. J Pharm Pharmacol 72: 1732-1749, 2020.
77. Lu PY, Xie F and Woodle MC: In vivo application of RNA interference: From functional genomics to therapeutics. Adv Genet 54: 117-142, 2005.
78. Abbas-Terki T, Blanco-Bose W, Deglon N, Pralong W and Aebischer P: Lentiviral-mediated RNA interference. Hum Gene Ther 13: 2197-2201, 2002.
79. Tong AW: Small RNAs and non-small cell lung cancer. Curr Mol Med 6: 339-349, 2006.
80. Hanna J, Hossain GS and Kocerha J: The potential for microRNA therapeutics and clinical research. Front Genet 10: 478, 2019.
81. Si W, Shen J, Zheng H and Fan W: The role and mechanisms of action of microRNAs in cancer drug resistance. Clin Epigenetics 11: 25, 2019.
82. Samji P, Rajendran MK, Warrier VP, Ganesh A and Devarajan K: Regulation of Hippo signaling pathway in cancer: A MicroRNA perspective. Cell Signal 78: 109858, 2021.
83. Wang ZX, Lu BB, Wang H, Cheng ZX and Yin YM: MicroRNA-21 modulates chemosensitivity of breast cancer cells to doxorubicin by targeting PTEN. Arch Med Res 42: 281-290, 2011.
84. Gong C, Yao Y, Wang Y, Liu B, Wu W, Chen J, Su F, Yao H and Song E: Up-regulation of miR-21 mediates resistance to trastuzumab therapy for breast cancer. Biol Chem 286: 19127-19137, 2011.
85. Zhou L, Qiu T, Xu J, Wang T, Wang J, Zhou X, Huang Z, Zhu W, Shu Y and Liu P: miR-135a/b modulate cisplatin resistance of human lung cancer cell line by targeting MCL1. Pathol Oncol Res 19: 677-683, 2013.
86. Sun C, Li N, Yang Z, Zhou B, He Y, Weng D, Fang Y, Wu P, Chen P, Yang X, *et al*: miR-9 regulation of BRCA1 and ovarian cancer sensitivity to cisplatin and PARP inhibition. J Natl Cancer Inst 105: 1750-1758, 2013.
87. Xu H, Zhao L, Fang Q, Sun J, Zhang S, Zhan C, Liu S and Zhang Y: MiR-338-3p inhibits hepatocarcinoma cells and sensitizes these cells to sorafenib by targeting hypoxia-induced factor 1α. PLoS One 9: e115565, 2014.
88. Feng YH and Tsao CJ: Emerging role of microRNA-21 in cancer. Biomed Rep 5: 395-402, 2016.
89. Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, McLeod H, Klein TE and Altman RB: Doxorubicin pathways: Pharmacodynamics and adverse effects. Pharmacogenet Genomics 21: 440-446, 2011.
90. Tai W, Mahato R and Cheng K: The role of HER2 in cancer therapy and targeted drug delivery. J Control Release 146: 264-275, 2010.
91. González-Alonso P, Zazo S, Martín-Aparicio E, Luque M, Chamizo C, Sanz-Álvarez M, Minguez P, Gómez-López G, Cristóbal I, Caramés C, *et al*: The hippo pathway transducers YAP1/TEAD induce acquired resistance to trastuzumab in HER2-positive breast cancer. Cancers (Basel) 12: 1108, 2020.
92. Lin CW, Chang YL, Chang YC, Lin JC, Chen CC, Pan SH, Wu CT, Chen HY, Yang SC, Hong TM and Yang PC: MicroRNA-135b promotes lung cancer metastasis by regulating multiple targets in the Hippo pathway and LZTS1. Nat Commun 4: 1877, 2013.
93. Mandati V, Del Maestro L, Dingli F, Lombard B, Loew D, Molinie N, Romero S, Bouvard D, Louvard D, Gautreau AM, *et al*: Phosphorylation of Merlin by Aurora A kinase appears necessary for mitotic progression. J Biol Chem 294: 12992-13005, 2019.
94. Dasari S and Tchounwou PB: Cisplatin in cancer therapy: Molecular mechanisms of action. Eur J Pharmacol 740: 364-378, 2014.
95. Gauthier A and Ho M: Role of sorafenib in the treatment of advanced hepatocellular carcinoma: An update. Hepatol Res 43: 147-154, 2013.
96. Wu XZ, Xie GR and Chen D: Hypoxia and hepatocellular carcinoma: The therapeutic target for hepatocellular carcinoma. J Gastroenterol Hepatol 22: 1178-1182, 2007.
97. Tak E, Lee S, Lee J, Rashid MA, Kim YW, Park JH, Park WS, Shokat KM, Ha J and Kim SS: Human carbonyl reductase 1 upregulated by hypoxia renders resistance to apoptosis in hepatocellular carcinoma cells. J Hepatol 54: 328-339, 2011.
98. Trédan O, Galmarini CM, Patel K and Tannock IF: Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst 99: 1441-1454, 2007.