MicroRNA signatures as predictive biomarkers in transarterial chemoembolization-treated hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide. Unfortunately, many patients are diagnosed at a late stage with a delay in the optimal timing for tumor resection. Transarterial chemoembolization (TACE) is currently considered the standard of care for patients with unresectable HCC Barcelona system class B classification. However, the treatment response of HCC patients to TACE varies widely, and there is no reliable marker for predicting a patient’s response to TACE. Thus, the identification of patients who are sensitive or resistant to TACE is important for individualized therapy. Recently, our understanding of cancer cell biology has progressed enormously. Much of this progress has been driven by technological advances enabling previously unachievable studies to be performed and yield a constantly evolving picture of the regulatory role of noncoding RNAs (ncRNAs) in tumor biology. Micro-RNAs (miRNAs) are a class of ncRNA molecules that regulate nearly one-third of all protein-coding RNAs. The existing literature indicates that the deregulation of miRNAs can contribute to tumorigenesis and metastasis in multiple cancers, including HCC, via the control of cell proliferation, apoptosis, invasion, or metastasis. Analysis and evaluation of this type of regulatory RNA could shed new light on the behavior of many cancers and provide new diagnostic and prognostic biomarkers as well as pharmacological targets for novel treatment strategies. To this end, this review highlights the expression and functional roles of miRNAs in TACE-treated HCC and explores the potential applications of miRNAs as diagnostic markers and therapeutic targets.

KEYWORDS

biomarkers, gene expression, HCC, microRNAs, TACE

Abbreviations: ADAM17, a disintegrin and metalloprotease 17; ALT, alanine transaminase; AST, aspartate transaminase; BCLC, Barcelona clinic liver cancer; EGFL7, EGF-like domain multiple 7; EMT, epithelial-mesenchymal transition; ERK, extracellular-signal-regulated kinase; HBV, hypoxia-inducible factor 1α (HIF-1α); HCC, hepatocellular carcinoma; JNK, c-Jun N-terminal kinase; miRNAs, microRNAs; ncRNAs, noncoding RNAs; NRF2, nuclear factor erythroid related factor 2; PPARGC1A, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SOX2, SRY (sex-determining region Y)-box 2; TACE, transarterial chemoembolization; WNT, wingless/integrated.

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Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality worldwide, with a high incidence in Eastern Asia and sub-Saharan Africa. Multiple HCC treatment modalities, such as chemotherapy, irradiation, resection, and radiofrequency ablation, are available, although selective transarterial chemoembolization (TACE) using chemotherapeutic agents—doxorubicin and cisplatin—is usually performed.3,4

According to the Barcelona clinic liver cancer (BCLC) guidelines, TACE is the standard treatment for intermediate HCC.5 However, increasing evidence suggests that TACE may also be used to treat patients with early or advanced HCC.6 Although TACE may result in a favorable clinical course,7 the long-term prognosis varies substantially among patients with TACE-treated HCC because of the heterogeneous pathogenic nature of the disease and differences in disease etiology, liver function, and tumor burden.8 Furthermore, the prognosis might remain unfavorable due to chemotherapy resistance and the high recurrence rate.9 Thus, identifying noninvasive predictive biomarkers is necessary to improve the prognosis of this disease and evaluate the effectiveness of TACE.10,11

Recent studies provide clear evidence that microRNAs (miRNAs) are abundant in the liver and modulate a diverse spectrum of liver functions.12 Deregulation of miRNA expression may be a key pathogenic factor in multiple liver diseases and could be a potential predictive biomarker.12,13

In the following sections, we will address the role of miRNAs and the differential miRNA expression signature in HCC to provide a better understanding of the predictive value of miRNAs in TACE-treated HCC.

1.1 | MicroRNAs: key players in HCC

MiRNAs are small (20-24 nucleotides) noncoding RNA (ncRNA) molecules that regulate gene expression post-transcriptionally by various mechanisms.12 Although the most common mechanism is translational repression resulting from miRNA binding to the 3’UTR of an mRNA, mechanisms involving mRNA destabilization and degradation have also been described.14 MiRNAs control cellular processes in carcinogenesis, including proliferation, cell cycle regulation, apoptosis, invasion, angiogenesis, and metastasis.15 Several miRNAs have been reported to be involved in HCC development, progression, and theranostics.12,16-19 Given that they are extremely stable in bodily fluids, including serum or plasma, where they are associated with RNA-binding proteins or packaged into various microparticles, circulating miRNAs have potential applications as minimally invasive biomarkers for HCC diagnosis and prognosis.17 A literature search of multiple databases up to June 2019, including PubMed, Scopus, Google Scholar, and Web of Science, within relevant disciplines, was conducted. The relevant studies from the search results are summarized in Table 1.

1.2 | MicroRNA-122 (miR-122)

MiR-122 is a liver-specific miRNA. Several studies have demonstrated that an increased level of circulating miR-122 is associated with hepatic injury and increased alanine transaminase (ALT) levels induced by several pathologies, such as alcohol-induced, drug-induced, and inflammatory liver diseases.20-22 Recently, Suehiro et al revealed that miR-122 might serve as an important post-TACE predictive biomarker, showing that the pre-TACE exosomal miR-122 expression levels were significantly associated with the aspartate transaminase (AST) and ALT levels and negatively correlated with the Child-Pugh score.13 Given that exosomal miRNA levels mirror those in the parental cells, Suehiro et al concluded that exosomal miR-122 levels could reflect residual liver function and capacity, as well as the liver fibrosis rate. These results followed other studies showing that miR-122 is associated with the liver fibrosis rate23-25 and the viral replication rate.27-29 Furthermore, Kim et al showed that high pre-TACE plasma miR-122 levels could be an independent risk factor for early TACE refractoriness in patients with unresectable hepatitis B virus (HBV)-associated HCC. Significant additive power in predicting liver transplant-free survival was found when the miR-122 and alpha-fetoprotein (AFP) levels were combined with the baseline model consisting of age, gender, and different tumor parameters.30

A low exosomal miR-122 ratio (post-/pre-TACE levels) was shown to be an independent factor for poor prognosis in HCC patients with liver cirrhosis.31 Also, serum miR-122 levels were shown to be negatively correlated with the Model for End-Stage Liver Disease score31 and to be associated with poor prognosis in patients with decompensated liver disease.32 Moreover, in HCV-induced fibrosis, a decrease in the level of circulating miR-122 reflects the development of liver fibrosis and the loss of viable liver cells.33 Although the mechanisms of action and functions of miR-122, especially post-treatment, are not well known, some investigators have speculated that under the hypoxic conditions occurring after embolization, miR-122 may induce hypoxia-inducible factor 1α (HIF-1α) expression in noncancerous liver tissue and cancer cells.11 HIF-1α and vimentin are miR-122 targets in hepatocytes.34 Furthermore, changes in miR-122 levels may be associated with epithelial-mesenchymal transition (EMT), as miR-122 has been found to inhibit EMT by targeting the Snail (a zinc finger transcriptional repressor) and Wingless/Integrated (WNT)/β-cadherin signaling pathways.35 Additionally, miR-122 plays a key role in mitochondrial metabolism by indirectly regulating mitochondrial genes, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α),36 and it can inhibit angiogenesis and intrahepatic metastasis by suppressing the expression of a disintegrin and metalloproteinase 17 (ADAM17), among other genes.37 Phosphoinositide 3-kinase and Bcl-w have also been identified as miR-122 targets; these proteins mediate the downregulation-associated escape from apoptosis through the activation of the receptor tyrosine kinase survival pathway and anti-apoptotic signaling, respectively.38 Additionally, miR-122 was reported to regulate cell cycle checkpoints by targeting cyclin G1.39
TABLE 1  Summary of the literature concerned with trans-arterial chemoembolization-treated hepatocellular carcinoma and miRNAs

| First author       | No. patients | Type of sample | Dysfunction pattern of expression levels                                                                 | Year | PMID      |
|--------------------|--------------|----------------|----------------------------------------------------------------------------------------------------------|------|-----------|
| Suehiro T et al    | 75 before and after TACE | Exosomal microRNAs | miR-122 significantly decreased after TACE miR-21 expression levels did not significantly change            | 2018 | 30 127 924|
| Kim SS et al       | 198          | Plasma         | Combination of plasma miRNA-21, -26a, and -29a-3p expression could predict early TACE refractoriness in patients with TACE-treated HCC | 2018 | 29 215 815|
| Xiang LY et al     | 100          | HCC tissues    | The loss of tumor suppressor miR-126 in hepatitis B virus-related hepatocellular carcinoma cells contributes to the development of metastases through the upregulated expression of its target gene, ADAM9 | 2017 | 28 639 884|
| Kim SS et al       | 177          | Plasma         | High expression levels of plasma miR-122 are associated with early TACE refractoriness in HCC patients treated with TACE | 2017 | 27 194 671|
| Lu YL et al        | 411          | Liver tissues (HCC and noncancerous) | Decreasing microRNA-126a expression may be beneficial for post-operative adjuvant TACE treatment in HCC | 2016 | 27 796 321|
| Qiu GP et al\(^a\) | 507          | Whole blood    | MiR-196a2 rs11614913 and miR-499a rs3746444 were significantly associated with a curative effect and a positive prognosis of TACE for primary HCC | 2016 | 27 525 669|
| Jia HL et al\(^b\) | NA           | –              | It was found and confirmed that interferon could prevent a postoperative recurrence, and those with low expression of miR-26a are more likely to benefit | 2016 | 27 470 884|
| Cui L et al        | 125 before and 30 days after TACE | Serum | Serum miR-335 can be used as a molecular marker to predict the treatment response and clinical outcome in HCC patients receiving TACE | 2015 | 26 305 026|
| El-Halawany MS et al | 15         | FFPE tissues   | A set of 12 miRNAs have been identified to be significantly upregulated in TACE-treated HCC nonresponders group | 2015 | 25 811 030|
| Liu J et al        | 97           | Plasma         | Circulating miR-1285-3p and miR-4741 was predictive of response to TACE therapy in HCC | 2015 | 25 230 788|
| Zhan M et al       | 113          | Serum          | Serum miR-210 may represent a novel biomarker for predicting the efficacy of transarterial chemoembolization and overall survival for patients with HCC | 2014 | 24 935 355|
| Pan Y et al\(^a\)  | 331          | Whole blood    | rs9909601 in the pseudogene E2F3P1 may be a genetic marker for HCC prognosis in Chinese | 2014 | 25 013 402|
| Liu M et al        | 136          | Serum          | Serum miR-200a can potentially guide individualized treatment for HCC patients with a high risk of TACE treatment failures. | 2014 | 25 275 448|

Abbreviations: ADAM: a disintegrin and metalloproteinase; FFPE, formalin-fixed paraffin-embedded; E2F3P1, E2F transcription factor 3 pseudogene 1; HCC, hepatocellular carcinoma; NA, not applicable; TACE, transarterial chemoembolization.

Note: [Data source: COREMINE Medical (http://coremine.com/medical/) and literature search].

\(^a\)This research was concerned with miRNAs gene variants evaluation, which differs from the review theme, which covers miRNAs expression analyses in hepatocellular carcinoma cases subjected to TACE therapy. It is included in the table list as a related issue to the review subject, but it is not included in the main review text.

\(^b\)Article in the Chinese language. The authors could not access the full text.
1.3 | MicroRNA-126 (miR-126)

MiR-126 was reported to play a significant role in developmental angiogenesis and vascular integrity. Previous in vitro and in vivo studies demonstrated miR-126 downregulation in HCC cells. Chen et al demonstrated that the expression of miR-126 is lower in the tissues of HCC patients with recurrence after liver transplantation than in patients with no recurrence. However, both transfection of HepG2 cells with full-length HBV and preoperational TACE treatment in HCC patients were shown to significantly induce miR-126 expression, although no underlying mechanisms were elucidated. Notably, previous studies did not specify whether patients who had received preoperative TACE treatment (and/or other therapeutic approaches) were excluded.

Recent findings by Xiang et al revealed that miR-126 downregulation in tumor cells might contribute to the development of metastasis and early recurrence in HBV-related HCC. Several emerging molecular targets have been suggested to mediate the potential mechanism underlying the effects of miR-126 in HCC. Dere-expression of miR-126 expression promotes HCC metastasis and neoangiogenesis by targeting LRP6 and PIK3R2, respectively. Restored expression of miR-126 in HCC cells was reported to lead to a decrease in the proliferation rate through targeting EGF-like domain multiple 7 (EGFL7) and sex-determining region Y (SRY)-box 2 (SOX2). Furthermore, attenuation of cell migration and invasion was demonstrated to be mediated through a disintegrin and metalloproteinase 9 (ADAM9) upregulation.

1.4 | MicroRNA-1268a (miR-1268a)

MiR-1268a has been implicated in embryogenesis and cell differentiation. The genetic variables in its seed region were found to be correlated with tumor angiogenesis and to be involved in HCC carcinogenesis. Also, decreasing levels of miR-1268a expression were found to be strongly associated with poor outcome in HCC. Interestingly, upon stratifying HCC patients by different levels of miR-1268a expression and investigating the effects of TACE on HCC prognosis in the differential expression strata, Lu and colleagues revealed that TACE treatment could significantly improve the survival of HCC patients with low miR-1268a tissue expression but not those with high miR-1268a expression; this finding suggests that miR-1268a expression could modify the sensitivity of tumor cells to TACE treatment and therefore implies that miR-1268a expression is a useful marker for the selection of patients for TACE treatment.

1.5 | MicroRNA-1285-3p (miR-1285-3p)

The expression of the differentially expressed plasma miR-1285-3p was consistently downregulated in HCC patients with a poor response to TACE than those with a good response to TACE. Also, miR-1285-3p might directly target the JUN oncogene in HCC cells, which has been implicated in both the extracellular-signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling pathways that impact cancer cell proliferation as well as migration. This last finding could partially explain the observed association of low levels of miR-1285 (which could act as a potential tumor suppressor in HCC patients) with a poor response to TACE due to JUN derepression via miR-1285 and enhanced JUN pathway activation in the HCC lesions of these patients.

1.6 | MicroRNA-200 (miR-200)

The miR-200 family has been identified as a potential diagnostic marker in HCC. Liu et al. found that among the 11 analyzed miRNAs (miR-122, miR-199a-5p, miR-221, miR-201, miR-101-3p, miR-200a, miR-214, miR-222, miR-223, miR-19a, and miR-224-5p), miR-200a was a robust classifier for predicting the prognosis of TACE-treated HCC patients and outperformed the combined classifier of AFP and satellite nodules as a biomarker with a positive predictive value. Furthermore, when the researchers combined AFP, satellite nodules, and miR-200a for prognosis prediction, the predictive probability was further improved, confirming the potential role of miR-200a in predicting the prognosis of TACE-treated HCC. Additionally, Liu et al. found that HCC patients with increased serum miR-200a expression after TACE therapy had shorter survival rates. Thus, serum miR-200a may also be a marker indicating disease severity-dependent changes in HCC patients.

MiR-200 family members were shown to regulate EMT in different cell systems and play important roles in HCC migration by regulating E-cadherin expression. Petrelli et al showed that the upregulation of the miR-200 family and activation of the nuclear factor erythroid-related factor 2 (NRF2) pathway were among the most prominent early molecular changes in HCC. Furthermore, Au et al. showed that miR-200a directly regulated ankyrin repeat and SOCS box-containing 4 (ASB4) in HCC and that its level was associated with that of serum AFP. The findings of the above studies emphasize the important role of miR-200a in HCC.

1.7 | MicroRNA-21 (miR-21)

MiR-21 is considered a typical “oncomiR”. This miRNA is associated with a wide variety of cancers, including liver cancer, and is a potential diagnostic biomarker for early HCC. However, few studies have evaluated the prognostic value of miRNA-21 for HCC, especially after TACE. Although exosomal levels were associated with prothrombin time and the Child-Pugh score, circulating miR-21 levels did not significantly change after TACE therapy for HCC. Another study reported that higher levels of miRNA-21 were associated with shorter postoperative survival in patients with HCC. In contrast, other researchers found that serum miRNA-21 levels were not significantly associated with survival after TACE. However, the recent findings of Kim et al showed that high pretreatment plasma miRNA-21 levels, as part of a
panel with miR-26a and miR-29a-3p levels, could predict early TACE refractoriness in patients with TACE-treated HCC.8

1.8 | MicroRNA-210 (miR-210)

MiR-210, the miRNA most frequently upregulated in response to hypoxia, has been identified to be induced by HIF-1α and to play an important role in the development and progression of many solid tumors.61,62

For example, Zhan et al63 showed that serum miR-210 levels increased significantly 4 weeks after TACE in nonresponders, whereas no significant change was observed in responders. These researchers concluded that serum miR-210 might represent a novel biomarker for predicting TACE efficacy and overall survival in TACE-treated HCC patients. This conclusion was consistent with those of previous studies reporting that circulating miR-210 levels are associated with chemotherapy sensitivity in patients with human epidermal growth factor receptor (HER)-2+ breast cancer64 and with treatment response in patients with metastatic castration-resistant prostate cancer.65

MiR-210 was reported to be overexpressed in HCC63,66 and mediate the migration and invasion of hypoxia-induced HCC cells.62 Additionally, a strong correlation between baseline serum miR-210 levels and vascular invasion, tumor size, tumor differentiation, and BCLC stage was observed, and miR-210 expression tended to

FIGURE 1 Functional enrichment analysis of HCC-related miRNAs. HCC, hepatocellular carcinoma

RAW TEXT
increase with the progression of BCLC stage (stage C patients > stage B patients > stage A patients > healthy control subjects) in TACE-treated HCC patients.63

1.9 | MicroRNA-26a (miR-26a)

MiRNA-26a is an emerging key regulator of carcinogenesis and tumor progression8 and is consistently downregulated in HCC.67 Kim et al found that a high miR-26a plasma level (≥ 1.5) was associated with overall TACE refractoriness in univariate analysis and with early TACE refractoriness in multivariate analysis with miR-21 and -29a-3p plasma levels.8 Additionally, El-Halawany et al68 identified miR-26a as one of a set of 12 miRNAs significantly upregulated in the TACE-treated HCC nonresponder group. However, this result contradicts previous reports showing that patients with HCC and low miRNA-26a expression levels had shorter overall survival times than those with high expression levels.67 The discrepancy between these findings might be partly due to the different cellular contexts of the tumors and different study populations.8

Concerning the molecular mechanism by which miRNA-26a performs its regulatory function, several studies reported that miR-26a suppressed tumor growth and metastasis in HCC through interleukin-6-mediated signal transduction and activation of transcription three signalings and exerted an anti-angiogenic function by inhibiting hepatocyte growth factor-cMet signaling.69,70 Moreover, miRNA-26a induced cell cycle arrest at the G1 phase in human HCC cells, partly through the direct downregulation of cyclin D2 and cyclin E2 expression.71 Furthermore, therapeutic delivery of miRNA-26a using an adeno-associated virus inhibited liver cancer cell formation while also inducing tumor-specific apoptosis and providing important protection from disease progression without toxicity.71

1.10 | MicroRNA-29a (miR-29a-3p)

MiRNA-29a may act as either an oncogene or a tumor suppressor gene, and reports about the association between miRNA-29a and HCC pathology are conflicting. Zhu et al reported that miRNA-29a-3p expression was downregulated in HCC tissues compared to adjacent
noncancerous liver tissues. Its high levels in HCC tissues were correlated with early tumor recurrence after HCC surgery, especially in patients with BCLC stage 0/A disease.72 Another study proposed that high serum miR-29a-3p expression levels were associated with poor overall survival and progression-free survival in patients with HCC treated with resection or local ablation.73 In contrast, Xiong et al demonstrated downregulation of miR-29 (miR-29a-3p/b/c) expression in HCC tissue, supporting its potential tumor-suppressive role.74 The reason for the discrepancy in the findings above is not clear, but “a deeper investigation into different miRNA-29 family members would likely explain the varied reports”, as suggested by Kim et al.8 MiRNA-29a-3p is the counterpart of miRNA-29a-5p in the development and progression of cancers.

Consequently, in the study by Kim et al.8 low pretreatment miRNA-29a-3p levels tended to be associated with early and overall TACE refractoriness, consistent with a study by Parpart et al demonstrating that downregulation of miRNA-29a-3p was associated with poor overall survival in AFP-positive HCCs. AFP inhibited miRNA-29a expression and induced DNA methyltransferase 3A expression through the binding of c-MYC to the miRNA-29a/b-1 transcript.75 Notably, the level of miR-29a-3p alone failed to show statistically significant predictive power for early TACE refractoriness, in contrast to the panel combining miR-29a-3p, miR-21, and miR-26a, which was suggested to be a predictive factor for early TACE refractoriness, supporting the view that this multi-biomarker panel could have stronger diagnostic and prognostic power than miR-29a-3p alone.8

1.11 | MicroRNA-335 (miR-335)

miR-335 can act as an oncogene or tumor suppressor in several types of cancers. As a suppressor of tumor metastasis, miR-335 has been shown to act by regulating several classical signaling pathways.76-79 Moreover, this miRNA has been found to predict sensitivity to anticancer treatment in some types of cancer, suggesting its involvement in the development of chemoresistance.80 Cui and colleagues81 found decreased serum miR-335 expression levels in patients with HCC. Patients with low miR-335 levels exhibited unfavorable clinicopathologic features (high AFP levels, vascular invasion, cirrhosis, and large tumor volumes) and a poor TACE response. These researchers also found that the serum miR-335 level was an independent determinant of both overall survival and time to progression (defined as the interval between treatment and either disease progression or the final observation of patients without disease progression) in these patients, even when considered in the context of other validated clinical prognostic factors. Collectively, these findings indicate that the expression level of miR-335 could provide prognostic information in TACE-treated HCC patients independent of a comprehensive panel of other established clinical predictors.

1.12 | MicroRNA-4741 (miR-4741)

miR-4741 was one of the 19 circulating miRNAs identified through miRNA microarrays by Liu et al.52 to be significantly differentially expressed between the TACE-responsive and the TACE-nonresponsive cohort. In the validation stage of the previous study, miR-4741 expression was significantly downregulated in plasma samples of HCC patients with a poor response to TACE than that in patients with a good response (4.6-fold, P = .001). Interestingly, subsequent studies identified miR-4741 as one of the miRNAs in a panel of miRNAs associated with differentiation and HBV infection in HCC cell lines. MiR-4741 expression was upregulated in HBV-positive HCC cells relative to that in HBV-negative HCC cells (2.5-fold, P = .009).82

1.13 | Other microRNAs

By comparing the pretreatment miRNA expression profiles in advanced-stage HCC patients and the patients’ responses to TACE treatment, El-Halawany et al.68 identified a set of 12 miRNAs significantly upregulated in the nonresponder group. This miRNA panel included miR-10a, miR-23a, miR-24, miR-26a, miR-27a, miR-30c, miR-30e, miR-106b, miR-133b, miR-199a-3p, and miR-200b. These findings highlight “the potential implications of pretreatment miRNAs expression profiling in the prediction of the patients’ response to TACE treatment in liver cancer”, as concluded by the researchers.

The existing literature indicates that miR-10a can mediate the metastatic properties of HCC by targeting the Eph tyrosine kinase receptor EphA4, thereby regulating the EMT process and cell adhesion.83 Overexpression of the miR-23a-miR-27a-miR-24-2 cluster could promote hepatic metastasis by stimulating cell growth and attenuating, transforming growth factor-beta (TGF-β)-induced apoptotic cell death.84 Also, miR-30 expression was found to be higher in HCC patients with cancer metastasis than in those without,85 and miR-30 was found to inhibit TGF-β-mediated EMT in hepatocytes by targeting Snail1.86 MiR-106b is involved in the TGF-β signaling pathway, and its overexpression is implicated in HCC metastasis via the activation of the EMT process.87 Also, miR-133a could mediate TGF-β-dependent derepression of collagen synthesis in hepatic stellate cells during liver fibrosis.88 Finally, miR-199a-3p can regulate mamalian target of rapamycin (mTOR) signaling, which is required for tumor cell motility/cancer invasion, as well as c-Met, which codes for a transmembrane tyrosine kinase receptor that binds hepatic growth factor and plays an important role in metastatic ability.89

1.14 | Functional enrichment analysis

Application of DIANA-miPath v3.0 (http://diana.imis.athena-innovation.gr/)90 to decipher the functional roles of the miRNAs analyzed in the present review revealed that the miRNA panel was enriched in precursor carcinogenic risk factors for HCC, such as viral carcinogenesis (hsa05203, P = 3.29e-05) and hepatitis B infection (hsa05161, P = 4.54e-05). Also, these miRNAs target genes involved in hallmark biological processes of cancer, such as ECM-receptor interaction (hsa04512, P = 3.57e-16), the hippo signaling pathway (hsa04390, P = 1.30e-05), adherens junctions (hsa04520, P = .008),...
the TGF-β signaling pathway (hsa04350, \( P = 1.92e-05 \)), the p53 signaling pathway (hsa04115, \( P = 0.02 \)), and signaling pathways regulating the pluripotency of stem cells (hsa04550, \( P = 3.29e-05 \)). Furthermore, these miRNAs were enriched in the cancer-related pathways as “pathways in cancer” (hsa05200, \( P = 2.39e-04 \)), and “proteoglycans in cancer” (hsa05205, \( P = 6.34e-12 \)) (Figure 1).

2 | CONCLUSION AND FUTURE PERSPECTIVES

Several attempts have been made worldwide to predict the state of TACE refractoriness or failure (the time point when repeated TACE loses its efficacy).\(^9\)\(^1\)\(^-\)\(^9\)\(^5\) Despite the various definitions of TACE refractoriness, most studies recommend switching the treatment modality from repetitive TACE to other treatments such as sorafenib monotherapy/combined therapy with TACE or hepatic artery infusion chemotherapy.\(^9\)\(^1\)\(^9\)\(^3\)\(^9\)\(^5\)\(^9\)\(^6\)

The present review revealed that a high miRNA expression signature, especially in the plasma/serum of TACE-treated HCC patients, could predict early TACE refractoriness or response. Therefore, if there is a high probability of early TACE refractoriness, considering timely changes in the treatment modality from repetitive TACE to sorafenib or combination therapy might improve results. Additionally, the establishment of standardized miRNA quantification methods may be crucial for the stratification of treatment modalities in HCC patients.

Furthermore, targeted treatments that increase the endogenous levels of downregulated miRNAs or decrease the levels of upregulated miRNAs implicated in the poor prognosis of TACE-treated HCC patients (Figure 2) might be new therapeutic options.\(^8\) However, it is appropriate to prospectively validate these suggestions in a large-scale randomized controlled clinical trial to confirm these findings before immediate clinical implementation. Hence, advances in scientific research, along with overcoming the current limitations, will pave the way towards truly personalized therapies and clinical applications of miRNAs in diagnosis, prognosis, and therapy, a major step forward in cancer epigenetics.

AUTHORS’ CONTRIBUTION

Performing the data search and preparing the primary draft conducted by Manal S Fawzy and Eman A Toraih. Manal S Fawzy edited the manuscript. All authors reviewed, commented, and approved the final draft.

CONFLICT OF INTEREST

The authors declare no competing interests.

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