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OVEREXPRESSION OF VIRAL miRs IN HTLV-1, HBV AND HCV INFECTION LEADS TO IMMUNOPATHOGENESIS IN THE DEVELOPMENT OF CANCER

A SUPEREXPRESSÃO DE miRs VIRAIS NA INFECÇÃO PELO HTLV-1, HBV E HCV CONDUZ A IMUNOPATOGÊNESE NO DESENVOLVIMENTO DO CÂNCER

LA SOBREEXPRESIÓN DE miRs VIRALES EN LA INFECCIÓN POR HTLV-1, HBV Y HCV CONDUCE A LA INMUNOPATOGÉNESIS EN EL DESARROLLO DEL CÁNCER

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ABSTRACT

MicroRNAs (miRs) are small non-coding molecules, considered excellent clinical biomarkers; however, they are more unstable in circulation than other classes of nucleic acids. The intricate host-virus interaction, by modulating the miR pathway, generally promotes viral persistence by decreasing immune detection. For data analysis, studies were selected from the NCBI, VHL, LILACS, and SciELO databases that discuss the pathogenesis orchestrated by oncogenic miRs in HTLV-1, HBV, and HCV infections. As a complementary strategy, experimental articles were also selected to serve as the basis for presenting the results. A total of 180 articles were found, and the inclusion criteria encompassed experimental studies, controlled trials, and literature reviews. Among these, six experimental articles were selected to comprise the results of this work, as they met the established criteria. This review elucidated the molecular mechanisms associated with HTLV-1, HBV, and HCV infection. The results show that several miRs are associated with leukemic transformation in the ATL group, reinforcing the potential involvement of these molecules in the pathogenesis of HTLV-1–associated ATL. Additionally, the regulation of these molecules is altered in HBV and HCV infections, in which these hepatotropic viruses deregulate pathways such as NF-κB, PI3K/AKT/mTOR, TP53, and WNT through various mechanisms, leading to uncontrolled hepatocarcinogenesis.

KEYWORDS: *Hepatocellular carcinoma. Hepatitis. Ribonuclease III. Leukemia.*

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RESUMO
Os microRNAs (miRs) são pequenas moléculas não codificantes, consideradas excelentes biomarcadores clínicos; no entanto, são mais instáveis na circulação do que outras classes de ácidos nucleicos. A interação intrincada entre hospedeiro e vírus, ao modular a via dos miRs, geralmente promove a persistência viral ao diminuir a detecção imunológica. Para a análise de dados, foram selecionados estudos das bases de dados NCBI, BVS, LILACS e SciELO que discutem a patogênese orquestrada por miRs oncogênicos na infecção por HTLV-1, HBV e HCV. Como estratégia complementar, também foram selecionados artigos experimentais que serviram de base para a apresentação dos resultados. Foram encontrados 180 artigos, e os critérios de inclusão contemplaram estudos experimentais, ensaios controlados e revisões de literatura. Dentre esses, seis artigos experimentais foram selecionados para compor os resultados deste trabalho, por se enquadrarem nos critérios estabelecidos. Esta revisão elucidou os mecanismos moleculares associados à infecção por HTLV-1, HBV e HCV. Os resultados mostram que diversos miRs estão associados à transformação leucêmica no grupo ATL, reforçando o potencial envolvimento dessas moléculas na patogênese da ATL associada ao HTLV-1. Além disso, a regulação dessas moléculas encontra-se alterada nas infecções por HBV e HCV, nas quais esses vírus hepatotrópicos desregulam vias como NF-κB, PI3K/AKT/mTOR, TP53 e WNT, por meio de diversos mecanismos, levando a uma hepatocarcinogênese descontrolada.

PALAVRAS-CHAVE: Carcinoma Hepatocelular. Hepatites. Ribonuclease III. Leucemia.

RESUMEN
Los microARNs (miRs) son pequeñas moléculas no codificantes, consideradas excelentes biomarcadores clínicos; sin embargo, son más inestables en la circulación que otras clases de ácidos nucleicos. La intrincada interacción entre el huésped y el virus, al modular la vía de los miRs, generalmente promueve la persistencia viral al disminuir la detección inmunológica. Para el análisis de datos, se seleccionaron estudios de las bases de datos NCBI, BVS, LILACS y SciELO que discuten la patogénesis orquestada por miRs oncogénicos en la infección por HTLV-1, HBV y HCV. Como estrategia complementaria, también se seleccionaron artículos experimentales que sirvieron de base para la presentación de los resultados. Se encontraron 180 artículos, y los criterios de inclusión contemplaron estudios experimentales, ensayos controlados y revisiones de literatura. De estos, se seleccionaron seis artículos experimentales para componer los resultados de este trabajo, por cumplir con los criterios establecidos. Esta revisión elucidó los mecanismos moleculares asociados con la infección por HTLV-1, HBV y HCV. Los resultados muestran que diversos miRs están asociados con la transformación leucémica en el grupo ATL, reforzando el potencial involucramiento de estas moléculas en la patogénesis del ATL asociado con HTLV-1. Además, la regulación de estas moléculas se encuentra alterada en las infecciones por HBV y HCV, en las cuales estos virus hepatotrópicos desregulan vías como NF-κB, PI3K/AKT/mTOR, TP53 y WNT, mediante diversos mecanismos, llevando a una hepatocarcinogénesis descontrolada.

PALABRAS CLAVE*: Carcinoma Hepatocelular. Hepatitis. Ribonucleasa III. Leucemia.*

1. INTRODUCTION

MicroRNAs (miRs) have an average length of 18–25 nucleotides and act as guide molecules in post-transcriptional regulation. They can be significantly dysregulated following exposure to infections. In addition, various DNA viruses encode and express functional viral miRs,

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which play a vital role in host–pathogen interactions. Cellular miRs can function as antiviral or proviral components, and their dysregulation occurs across a wide range of infections [2].

Oncogenic viruses are associated with various types of human cancers and have also contributed significantly to the understanding of key molecular mechanisms in cancer biology [3]. Oncogenic viruses dysregulate multiple oncogenic pathways, leading to a loss of cell cycle control. In addition, epigenetic modifications can cause widespread dysregulation of numerous genes, including those associated with well-established cancer hallmarks, while also targeting oncogenic miRs [4].

These molecules have gained prominence due to their prognostic potential and their promise as novel biomarkers. In viral infections—particularly those caused by HTLV-1 (Human T-cell lymphotropic virus type 1), HBV (Hepatitis B virus), and HCV (Hepatitis C virus), which are often asymptomatic—further studies are needed to better understand the mechanisms by which these viruses contribute to oncogenesis. There is a limited number of studies investigating the role of viral miRs in the pathogenesis of HTLV-1, HBV, and HCV. Given that these viruses infect millions of people worldwide, additional research is essential to elucidate the mechanisms underlying virus-induced carcinogenesis, with miRs standing out as key regulators of gene expression and infectious processes [1-3].

Few studies have investigated miRs in HTLV-1 infection, particularly in Adult T-cell leukemia/lymphoma (ATL), as well as the complex pathways involving miRs encoded by HBV and HCV. Thus, this study aimed to review the mechanisms of viral miRs in cellular pathogenesis, the most dysregulated pathways, and the miRs most frequently altered in infections caused by HTLV-1, HBV, and HCV.

2. METHODOLOGY

This is a literature review study. The databases consulted for article retrieval included the National Center for Biotechnology Information (NCBI), the Virtual Health Library (VHL), the Latin American and Caribbean Literature in Health Sciences (LILACS), the Scientific Electronic Library Online (SciELO), as well as the reference lists of selected articles. For data analysis, the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed (Figure 1).

In the initial search, keywords standardized according to the Health Sciences Descriptors (DeCS) were used, including the following terms: hepatocellular carcinoma, hepatitis, Ribonuclease III, and leukemia. No restrictions were applied regarding the publication period or year

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of the articles during the selection and search process. However, the findings concerning the main alterations in miRs during infections caused by the viruses addressed in this study were considered.

Studies addressing the pathogenesis mediated by oncogenic miRs in HTLV-1, HBV, and HCV infections were selected. As a complementary strategy, experimental articles were also included to support the presentation of the results. The eligibility criteria were based on: (i) the methodology employed, (ii) validation of the findings, and (iii) relevance for practical application in model studies.

In the second search, we consulted the reference lists of the selected articles. The eligibility criteria were based on: (i) molecular pathways altered by viral miRs, (ii) oncogenesis mediated by viral miRs, and (iii) the most frequently dysregulated miRs involved in viral oncogenesis. As exclusion criteria in both searches, case reports, technical reports, book chapters, and experience reports were discarded. After the selection process, 180 articles were identified, of which six were experimental studies included in the results section (Chart 1).

The inclusion criteria for the six articles selected for the results section were: (i) the number of patients included in the studies; (ii) inclusion of patients with acute, chronic, symptomatic, or asymptomatic conditions; (iii) miRs most strongly associated with hepatocarcinogenesis; (iv) the type of sequencing used in the methodology; (v) miR expression in T lymphocytes; and (vi) serum exosomal miRs in hepatocellular carcinoma (HC).

The study included experimental studies, controlled trials, and literature reviews. Articles were excluded for the following reasons: duplicates (n = 4), not meeting eligibility criteria (n = 8), lack of validated information, small sample size, or insufficient relevant data (n = 14), not fitting the study theme (n = 82), lack of full-text availability (n = 8), absence of the defined keywords (n = 18), failure to meet eligibility criteria (n = 16), and being outside the scope of the proposed study (n = 8). After the screening process, six experimental articles were selected to compose the results of this work, as they met all predefined criteria (CHART 1).

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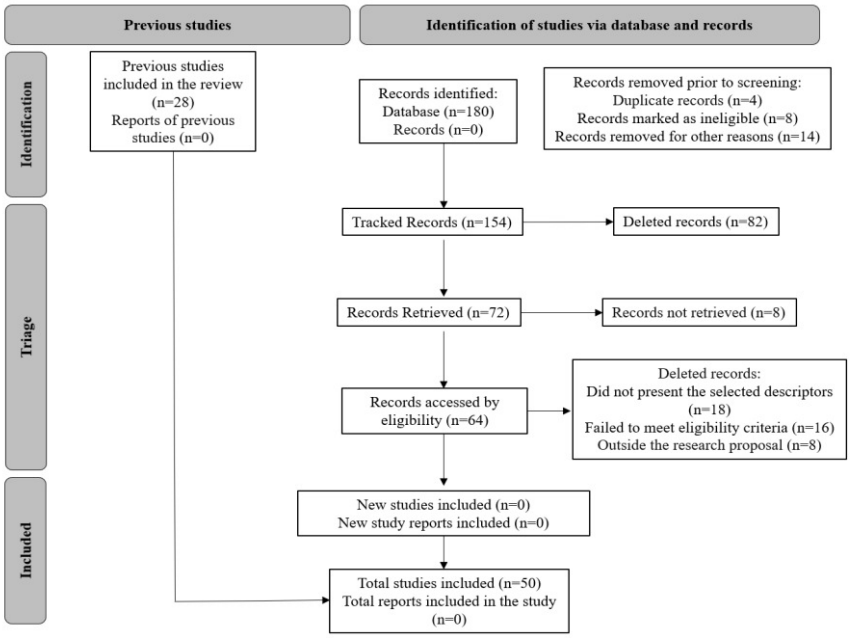
Figure 1. PRISMA flowchart for sorting and selection of base articles



3. RESULTS

CHART 1. Selected experimental articles that present the pathogenic profile according to the information in the title, objective, and main findings

Nº	AUTHORS/YEAR	TITLE	OBJECTIVE	KEY RESULTS	REFERENCES
1	Souza *et al.*, 2020	Small RNA profiles of HTLV-1 asymptomatic carriers with monoclonal and polyclonal rearrangement of the T-cell antigen receptor γ-chain using massively parallel	To investigate cellular small RNA (sRNA) levels in the peripheral blood mononuclear cells (PBMCs) of human HTLV–I infected asymptomatic carriers with monoclonal and polyclonal T cell	In the present study, miR-144-3p was the most notably downregulated miR, consistent with previous studies reporting its low expression in chronic myeloid leukemia, acute myeloid leukemia, and in the PBMCs	6

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		sequencing: A pilot study.	receptor (TCR) γ gene.	of patients with HTLV–I as well as ATL cell lines. In addition, miR-28-5p was another highly expressed miR in the present study.	
2	Nascimento *et al*., 2021	Global expression of noncoding RNome reveals dysregulation of small RNAs in patients with HTLV-1–associated adult T-cell leukemia: a pilot study.	To identify sRNA expression signatures associated with ATL and to investigate their potential implication in the pathophysiology of the disease.	The sequencing identified specific sRNAs signatures associated with ATL patients that target pathways relevant in ATL, such as the transforming growth factor (TGF-β), Wnt, p53, apoptosis, and mitogen-activated protein kinase (MAPK) signaling cascades. Network analysis revealed several miRs regulating highly connected genes within the ATL transcriptome. miR-451-3p was the most	9

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				downregulated miR in active patients.	
3	Wang *et al*., 2013	Hepatitis B Viral RNA Directly Mediates Down-regulation of the Tumor Suppressor miR-15a/miR-16-1 in Hepatocytes.	To analyze the functional interplay between HBV and the miR machinery, hoping to identify potential initiating events for HC development.	HBx RNA mediating the down-regulation of target miRs. Authors found that RNA induce miR tailing and trimming in fly extracts. HBx-induced down-regulation of miR-15a could be rescued efficiently by knocking down c-Myc, but c-Myc down-regulation appears to have a much lesser effect on miR-16-1.	22
4	Zhao *et al*., 2014	The miR-374a-545 Cluster Encoded in the *FTX* lncRNA is Overexpressed in HBv-related hepatocellular Carcinoma and Promotes Tumorigenesis	To examine the expression profiles of the miR-374a-545 cluster and the miR-421/374b cluster derived from the *FTX* transcript in HBV-related HC.	The expression of the miR-374a-545 cluster located in the lncRNA *FTX* is significantly upregulated in HBV-related HC tissue and correlated with a poor prognosis of HC patients.	24

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		and Tumor Progression.		Serum miR-374a-545 originated from tumor tissue and may potentially be utilized as a novel screening and diagnostic marker for HC occurrence in routine clinical practice.	
5	Li *et al*., 2015	HCV induced reduction in miR-181a impairs $CD4^+$ T cell responses via over-expression of DUSP6.	Demonstrate that an HCV-mediated decline of miR-181a expression impairs $CD4^+$ T cell responses via up-regulation of DUSP6 expression.	The findings suggest that a decline of miR-181a expression leads to DUSP6 over-expression and $CD4^+$ T cell dysfunction during HCV infection.	36
6	Cho *et al*., 2020	Exosomal miR-4661-5p–based serum panel as a potential diagnostic biomarker for early-stage HC.	Investigate diagnostic exosomal miR (exo-miR) panel for early-stage HC.	A serum exo–miR–4661–5p–based panel is a potent diagnostic biomarker for early-stage HC and could also be used as a prognostic indicator in patients with HC.	37

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3. MiRs IN THE PATHOGENESIS OF HTLV-1

Modulation of HTLV-1 miRs infection

It has been proposed that, during infection, HTLV-1 dysregulates the host cellular RNA interference machinery, including miRs, through the suppression and degradation of DROSHA mediated by its interaction with the viral TAX protein, as well as through the inhibition of DICER activation via direct interaction with the viral Rex protein. Furthermore, the involvement of miR-26a in multiple biological processes—such as cell proliferation, invasion, differentiation, angiogenesis, and energy metabolism—has been well documented in B-cell chronic lymphocytic leukemia and epithelial malignancies [5].

TAX and HBZ modulate miR expression both directly and indirectly, the latter through disruption of miR biogenesis via DROSHA degradation and DICER repression. However, only a limited number of miR–mRNA interactions have been characterized in HTLV-1-transformed cells. Notably, upregulated miR-93 and miR-130b target the pro-apoptotic gene *TP53INP1*, while HBZ-induced miR-17 and miR-21 repress OBFC2A, a protein involved in apoptosis regulation [6].

A second striking observation is that three different miRs (miR-93, miR-130b, and miR-155), which are overexpressed in ATL cells, target a single transcript, *TP53INP1*. The tumor suppressor *TP53* activates the transcription of *TP53INP1*, thereby inducing G1 cell cycle arrest and promoting apoptosis. The convergence of multiple miRs on a single target reinforces the notion that *TP53INP1* may represent a relevant factor in HTLV-1 leukemogenesis. Additionally, several members of the let-7 miR family are suppressed during HTLV-1 infection [7].

Profile of miRs in HTLV-1-transformed malignant cells

The *MYB* proto-oncogene, which is activated following miR-150-deficient lymphocyte stimulation, is directly regulated by miR-150 through two conserved binding sites in the 3′UTR of the *MYB* mRNA. miR-150 modulates c-Myb protein levels *in vivo*, as demonstrated in experiments where miR-150 was ectopically expressed at moderate levels in B-cell progenitors—cells in which it is not typically expressed—while *MYB* expression is high. This results in a reduction of c-Myb levels, leading to a partial blockade of B-cell development [8].

The dysregulation of miR-150, together with underlying genetic events, contributes to tumorigenesis by activating additional signaling pathways. These alterations may be closely associated with the progression of malignant lymphomas. miR-150 targets CCR6 (CC chemokine

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receptor type 6), a member of the β-chemokine receptor family also known as CD196 (differentiation cluster 196) surface antigen. CCR6, which is preferentially expressed in immature dendritic cells and naïve T cells, plays an essential role in B-lineage maturation; its dysregulation by HTLV-1 is strongly associated with tumorigenesis [9].

Studies suggest that dysregulated expression of miR-155 may have deleterious effects on normal immune function and that elevated levels of miR-155 may contribute to leukemia and lymphoma. Elevated expression of miR-155 has been observed in cells infected by HTLV-I both in vitro and ex vivo. This dysregulated expression supports the idea that miR-155 induction involves NF-κB (nuclear factor kappa B) and JNK (c-Jun N-terminal kinase) signaling pathways, both of which are activated by HTLV-I. In addition, decreased expression of miR-181a results in hyporesponsiveness to TCR signaling and reduced sensitivity to antigens [10].

NF-κB upregulates distinct miRs in TAX-expressing cells, resulting in persistent downregulation of target genes. HTLV-positive cell lines also exhibit elevated levels of miR-34a through activation of its promoter by NF-κB and p53. miR-34a targets SIRT1 (sirtuin 1) and the pro-apoptotic factor BAX, potentially contributing to the proliferation of HTLV-infected cells. In contrast, the pro-apoptotic miR-31, which represses the NF-κB pathway by targeting NF-κB-inducing kinase (NIK), is markedly reduced in ATL. Overall, HTLV-mediated dysregulation of these miRs favors viral replication and cell survival, contributing to oncogenesis in transformed cells [11].

TAX is a mediator to alter the profile of miRs

The T-cell transcription factor profile associated with HTLV-1 integration and TAX expression demonstrates increased activation of substrates and factors involved in chromatin remodeling complexes. TAX downregulates the expression of miRs related to chromatin remodeling. These observations were validated using selected miRs and the HTLV-1-infected T-cell line MT-2. miR-149 and miR-873 were found to directly target p300/CBP-associated factor (PCAF), thereby contributing to oncogenesis [12].

TAX interacts with DROSHA and directs it to specific cellular compartments, such as the proteasome. In the presence of TAX, DROSHA impairs the primary processing of miRs. Furthermore, the addition of DROSHA or antagomiRs against cellular miRs downregulated by HTLV-1 directly recapitulates miR expression changes observed in infected cells. *TAX* is also known to interact with several transcription factors, including CREB (cAMP response element-binding protein), serum response factor (SRF), and NF-κB, as well as with cell cycle-related proteins such as cyclins D2 and D3, mitotic checkpoint regulator MAD1, cyclin-dependent kinases (CDKs), and *TP53* [13].

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The TAX oncoprotein contributes to central nervous system infection by HTLV-1 in $CD4^+$ T cells. These infected T cells subsequently induce the expression of CXCL10 (CXC motif chemokine ligand 10) in astrocytes, promoting the recruitment of inflammatory cells. Resistance mechanisms include reduced phosphorylation of Tyk2 (tyrosine kinase 2) and STAT2 (signal transducer and activator of transcription 2). TAX-mediated competition with the CREB/p300 complex, upstream regulation of SOCS1 (suppressor of cytokine signaling 1), and upregulation of IRF4 (interferon regulatory factor 4), which collectively inhibit interferon (IFN) signaling [14].

HTLV-1 modulates miR expression by transactivating miR-130b and miR-146a promoters, promoting viral replication and oncogenicity. In ATL, miR-93, miR-130b, and miR-155 converge on the *TP53INP1* transcript, while tumor-suppressive miRs such as the let-7 family and miR-34b are downregulated. These combined alterations disrupt key tumor-regulatory pathways, including RAS and MYC signaling, reinforcing the role of HTLV-1–miR interactions in cellular transformation and lymphomagenesis [15].

This interaction also depends on the presence of CREB-binding protein (CBP) acetyltransferases, p300, and p300/CBP-associated factor (p/CAF), which are required for the activation of HTLV-1 gene expression. In addition to TAX interacting with these acetyltransferases to directly activate viral transcription, the recruitment of these factors to the viral long terminal repeat (LTR) promotes covalent modifications of histone tails in adjacent nucleosomes, thereby establishing a transcriptionally favorable chromatin state. In particular, CBP and p300 acetylate histones H2A, H2B, H3, and H4, resulting in conformational changes that facilitate transcription [16].

4. MiRs TARGETING HEPATOCARCINOGENESIS IN HBV INFECTION

HBV-induced miR dysregulation mechanism

During the acute phase, the virus must activate its replication while avoiding destruction by the immune system. In this context, miR-1 may enhance transcription from the central promoter of HBV by downregulating the expression of histone deacetylase 4 (HDAC4). This miR can act in a complementary manner with nuclear HBx to induce epigenetic modifications and amplify the viral genome. miR-372 and miR-373 also support HBV gene expression by targeting nuclear factor I/B, a cellular protein that is an essential regulator in several viral infections [17].

In HBV-infected hepatocytes, the HBx protein has been implicated in cell transformation, in part by antagonizing p53 expression and function. More recently, HBx has been shown to downregulate miR-15a/miR-16-1, an effect that appears to contribute to HBx-induced anchorage-independent cell growth and resistance to apoptosis in hepatocytes. This mechanism has

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been suggested to involve induction of c-Myc, which has previously been shown to mediate transcriptional repression of the miR-15a/miR-16-1 gene cluster in B-cell lymphomas [18].

miR-22 is significantly upregulated in tissues adjacent to HC, consistent with previous studies describing its antiproliferative role in HC. These findings suggest that miR-22 suppresses ERα transcription by directly binding to its 3′-UTR region. Accordingly, increased levels of miR-22 lead to downregulation of ERα expression, which in turn stimulates interleukin-1α (IL-1α) transcription. Enhanced secretion of IL-1α from necrotic hepatocytes activates Kupffer cells, promoting compensatory proliferation and contributing to tumorigenesis [19].

The *FTX* gene gives rise to several RNA isoforms through alternative promoter usage, splicing, and termination. The miR-421/374b cluster and the miR-545/374a cluster are located in different introns and are regulated by distinct promoters. Because each miR cluster contains different regulatory elements, they may be differentially regulated during tumorigenesis. This has been described in HBV-related HC. These findings indicate that the miR-545/374a cluster is significantly upregulated in HC tissue, and its expression correlates with histological differentiation, incomplete tumor capsule formation, and distant metastasis [20].

Mechanism of HBV miRs in cirrhosis

Connective tissue growth factor 2 (CCN2) is overexpressed in the fibrotic liver and can directly promote fibrogenesis in activated hepatic stellate cells. miR-214 regulates CCN2 expression by directly targeting its 3′-UTR region and has been reported to be transferred from hepatic stellate cells to adjacent cells via exosomes. However, miR-214 expression is decreased during chronic liver injury. Exosomal Twist1, which modulates miR-214 expression and contributes to CCN2 suppression in recipient cells, is downregulated during hepatic stellate cell (HSC) activation [21].

miR-26a is frequently downregulated in HC tissues and targets the interleukin-6/signal transducer and activator of transcription 3 (IL-6/STAT3) and MYC/EZH2 pathways. miR-26a is capable of inducing G1 cell cycle arrest and promoting apoptosis. It directly regulates several targets, including cyclin-dependent kinase 8 (CDK8), p21-activated protein kinase 2 (PAK2), and EZH2. Inhibition of CDK8, a coactivator of WNT signaling, results in reduced expression of *MYC*. These regulatory networks are further subverted by HBV-derived miRs, which alter transcription factor activity and contribute to cirrhosis [22].

miR profiles of HBV-associated cirrhotic livers, HC tissue, and corresponding normal liver tissue reveal elevated expression of the polycistronic miR-17-92 cluster and miR-21 in cirrhotic livers and HC tissue. In addition, miRs can modulate the expression of genes involved in the

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regulation of protein phosphorylation, often resulting in activation of signaling pathways implicated in the initiation and progression of cirrhosis toward hepatocarcinogenesis [23].

About 100 miRs, including miR-122, miR-16, miR-223, miR-19b, miR-20a, miR-92a, miR-106a, let-7b, and miR-194, were amplified from HBV patients using TaqMan quantitative reverse transcription polymerase chain reaction (qRT-PCR) assays. The level of serum miRs in HBV patients was significantly higher in hepatitis B 'e' antigen (HBeAg)-positive patients compared to HBeAg-negative patients, with miR-122 and miR-194 being the most differentially expressed. During acute and chronic liver damage, miR-122 was significantly reduced in the injured liver and inversely correlated with liver damage and ALT levels [24].

Hepatocarcinogenesis of miRs in HBV infection

Several miRs regulate hepatocyte proliferation, and miR-21 has been shown to modulate multiple genes involved in the cell cycle and DNA synthesis. miR-21 inhibits DNA synthesis in hepatocytes through its effects on the BTG anti-proliferation factor 2 (BTG2) and Forkhead box M1 (FOXM1). In addition, miR-21 contributes to hepatocyte proliferation by promoting the expression of cyclin D1. Conversely, inhibition of miR-21 impairs progression of hepatocytes into the S phase through RhoB, which is involved in cyclin D1 regulation [25].

Dysregulation of miR-221 and miR-222 has been identified in molecular signatures associated with the progression of hepatic tumorigenesis. These miRNAs have previously been shown to target the cyclin-dependent kinase inhibitors p27 and p57 at the protein level. miR-221 also promotes tumor progression, significantly reducing the mean survival time. In addition, disruption of the PTEN–PI3K–AKT–mTOR signaling axis represents another key event relevant to hepatic tumorigenesis [26].

miR-10b has been reported to function as an onco-miR in various types of cancer. These findings are consistent with previous studies, suggesting that miR-10b may potentially serve as a universal tumor marker. HC exhibit significantly higher levels of miR-10b, and these findings suggest that elevated miR-10b is likely associated with inflammation, which may result from liver tissue injury [27].

Abundant angiogenesis provides the necessary nutrients for tumor growth and metastasis and is therefore essential for the progression of solid tumors. As one of the most common solid tumors, HC is characterized by abnormal and deformed vascular structures. In this context, vascular endothelial growth factor (VEGF) and other members of the VEGF family bind to their

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receptors (VEGFRs) to induce tumor angiogenesis. Alterations in miR-338-3p and miR-497 may promote angiogenesis and metastasis by directly inhibiting VEGFA [28].

5. PROFILE OF miRs IN HCV HEPATOCARCINOMA

Cellular miRs in HCV-mediated liver disease progression

HCV infection aberrantly regulates many miRs in human $CD4^+$ T cells, and miR-181a is upregulated during development to refine T-cell function through DUSP signaling. Since a decline in miR-181a, along with overexpression of DUSP6, is a hallmark of T-cell senescence, miR-181a can efficiently regulate DUSP6 expression. In this context, even a single DUSP6 molecule can significantly impair T-cell receptor sensitivity [29].

exo-miR-4661-5p has been identified as a potential serum biomarker for the diagnosis and prognosis of HC. This miR positively regulates interleukin-10 (IL-10) expression, an anti-inflammatory cytokine encoded by the IL10 gene, which is frequently upregulated in HC patients compared to non-tumor conditions. Increased IL-10 levels are associated with poorer prognosis, suggesting that miR-4661 may contribute to HC progression, potentially in the context of HCV-related oncogenesis [30].

Expression levels of let-7 family members, particularly let-7a-5p, let-7c-5p, and let-7d-5p, are inversely correlated with fibrosis stage severity in patients with HC. Downregulation of let-7 influences the TGF-β signaling pathway in these patients. In addition, miR-27a and miR-27b promote the proliferation of hepatic stellate cells by targeting retinoid X receptor alpha (RXRα), a receptor involved in inhibiting their proliferation. Furthermore, downregulation of miR-449a plays an essential role in modulating YKL40 expression, a factor that induces extracellular matrix synthesis and fibrosis, by targeting components of the NOTCH signaling pathway in HCV-infected patients [31].

The DICER enzyme associates with the RNA-binding protein TRBP during the processing of miR duplexes within the RNA-induced silencing complex (RISC). Activation of NF-κB stimulates DICER promoter activity and induces its expression. In this context, the expression of DICER, along with primary miR such as pri-miR-125b and pri-miR-130a, as well as tumor necrosis factor alpha (TNF-α), is upregulated in response to NF-κB activation. This process triggers both transcriptional and post-transcriptional mechanisms that suppress TNF-α production, involving increased DICER expression and enhanced pri-miR processing, leading to the formation of mature miR [33].

Anti-apoptotic miRs in hepatocellular carcinoma caused by HCV

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Due to the critical role of the p53 and BCL-2 families in regulating the intrinsic apoptotic pathway, miRs can modulate this pathway by altering the expression of proteins from these two families. Accumulating evidence demonstrates that more than 20 miRs directly regulate the pro-apoptotic gene p53 by binding to the 3′ untranslated region (3′-UTR) of its mRNA. For example, one such miR produced by cancer cells is miR-504. This miR binds to two sites within the 3′-UTR region of p53 mRNA, thereby leading to downregulation of this gene [34].

The mechanisms by which miR-363 and miR-582-5p downregulate apoptosis appear to be well established. The Bcl-2 family and caspases play central roles in the regulation of apoptosis. The caspase cleavage cascade is initiated by activation of initiator caspases through either the intrinsic or extrinsic pathways. Caspase-9 is an intrinsic initiator caspase, and its activation occurs following mitochondrial release of cytochrome c. Caspase-3 is an effector caspase that mediates the cleavage of multiple cellular proteins, acting in concert with other effector caspases [35].

Exogenous upregulation of miR-15/16 directly targets the anti-apoptotic BCL2 protein, downregulating its expression and inducing the intrinsic apoptotic pathway. In addition, miR-15a, miR-16, and miR-34 are implicated in the regulation of apoptotic and cell-cycle-related pathways across different cancers. These miRs can subvert cellular regulatory mechanisms, thereby contributing to oncogenesis through alterations in kinase-dependent cyclin profiles. This disruption affects control of the G1/S cell cycle transition, leading to abnormal cellular persistence under conditions of infection-induced dysregulation, such as in HCV-associated hepatic carcinogenesis [36].

Tumorigenesis is associated with the overexpression of anti-apoptotic miRs that promote HC progression. miR-9-5p enhances survival by inhibiting KLF4 and activating AKT/mTOR signaling, leading to increased *Bcl-2* and reduced BAX expression. Similarly, miR-33a promotes cell survival by inhibiting PPARα, while miR-106b suppresses death receptor 4 (DR4), thereby reducing TRAIL-mediated apoptosis. Collectively, these miRs contribute to tumor progression by enhancing anti-apoptotic signaling and impairing programmed cell death [37].

miRs target hepatocyte restriction factors in HCV infection

The let-7 miR family modulates T-cell metabolism to maintain the naïve phenotype of $CD8^+$ T cells. In addition to regulating proliferation and differentiation, let-7 reduces the transcriptional levels of key glycolytic enzymes (Gpd2, Pfk1, Hk2, Tpi, Pkm, and Ldha), glucose transporters (Glut1 and Glut2), and the protein synthesis enzyme Yars, likely through regulation of MYC. Following T-

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cell activation, let-7 levels decrease and *MYC* activity is reduced, leading to a metabolic shift from oxidative phosphorylation to glycolysis that supports an effective cytotoxic T-cell response against virus-infected or antigen-loaded cancer cells [38].

miR-134 and miR-370 target EGFR and PIK3CA, leading to reduced expression of these key regulators and suppression of the PI3K/AKT/mTOR and Raf/MEK/ERK signaling pathways, including downstream components such as p-AKT, p-mTOR, Rictor, p-c-Raf, and ERK1/2. In HER2-overexpressing cells, PI3K inhibition can trigger compensatory HER2/3 dimerization and activate ERK signaling. Overall, these miR-mediated effects disrupt major proliferative signaling networks and may contribute to cell cycle dysregulation and HCV-associated hepatocarcinogenesis [39].

miR-196a plays a significant oncogenic role in cancer by inhibiting tumor suppressor genes. Reports indicate that miR-196a directly targets HOXA5, HOXC8, and Annexin A1 (ANXA1). By inhibiting HOXA5, miR-196a promotes cell invasion. ANXA1 is involved in several physiological processes, including signal transduction, inflammation, phagocytosis, proliferation, differentiation, and apoptosis. In this context, ANXA1 can increase NF-κB activity, thereby promoting cell migration and metastasis [40].

The involvement of RAS (KRAS, NRAS, and HRAS) in human tumors is mainly associated with activating mutations at codons 12, 13, and 61, which lead to the activation of multiple signaling pathways that play a key role in tumor features such as cell proliferation and survival. Given the well-established interaction between let-7 and RAS family members, it is plausible that RAS modulation may also influence additional oncogenes, including c-MYC, Janus kinase (JAK), and STAT3 in HCV-associated HC cells [41].

6. DISCUSSION

In the study by Illumina high-throughput sequencing technology was used to analyze the global expression of the non-coding RNAome in peripheral blood mononuclear cells (PBMCs). Clonal alterations were detected in approximately 10% of cases, and miRs were identified as potential predictive factors in asymptomatic carriers of HTLV-I [6].

miR-144-3p was the most significantly underexpressed miR, which is consistent with previous studies reporting its low expression in chronic myeloid leukemia, acute myeloid leukemia, and in PBMCs of patients with HTLV-I [6]. The importance of TP53 in carcinogenesis is well established, and several miRs have been reported to silence TP53 expression either directly or indirectly. In cases of adult T-cell leukemia/lymphoma (ATL), inhibition of TP53 activity is commonly

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observed. It is possible that genomic instability driven by the integration of HTLV-1 into the host genome leads to the accumulation of multiple mutations [42].

The downregulation of miR-146a, miR-155, miR-150, miR-22, and miR-130b has been reported to affect cell proliferation. The identification of ATL-relevant mRNAs targeted by these miRs includes CREB, TGFBR1, EGR2, NRAS, SMAD2, PIK3R1, E2F2, TP53INP1, and MAP3K1. Furthermore, key signaling pathways implicated in the pathogenesis of ATL—such as TGF-β, Wnt, PI3K, p53, and MAPK—were found to be significantly targeted by differentially expressed miRs in patients with ATL [43].

All these miRs, except hsa-miR-451a and hsa-miR-183, showed significantly reduced expression in patients with ATL. Among them, hsa-miR-150-5p and hsa-miR-146a-5p were some of the most dysregulated miRs in these patients. Additionally, the TGF-β, Wnt, PI3K, p53, and MAPK signaling pathways have been implicated in the pathogenesis of ATL [9]. The viral proteins TAX-1 and HBZ mediate NF-κB dysregulation, while interactions between NF-κB and the miR network contribute to HTLV-1-associated cellular transformation [44].

It was shown that the target site in the HBx transcript is susceptible to miR binding, both in its native sequence context and within the coding region [22]. This finding further supports the proposed role of HBx in the oncogenic transformation of hepatocytes, demonstrating that the viral HBx RNA is capable of regulating the expression of specific miRs, thereby expanding the biological and pathological roles of the HBx oncogene in the HBV genome [45].

In addition to host miRs, HBV has been shown to encode viral miRs, such as HBV-miR-3, which are involved in disease progression. HBV-miR-3 is encoded by nucleotides 373–393 of the HBV genome and is derived from three viral mRNAs (PreC, PreS1, and PreS2). This miR contributes to HC progression by regulating viral replication and inhibiting apoptosis. Moreover, the loss of key components of the miR processing machinery, including DROSHA, TRBP, and AGO2, reduces the production of mature miRs and may contribute to cirrhosis in HBV infection [46].

The expression of the miR-545/374a cluster was analyzed and found to be significantly increased in HC tissues, where it correlated with histological differentiation, incomplete tumor capsule formation, and distant metastasis. Its association with clinical indicators related to HBV infection, including HBeAg and HBV-DNA levels, suggests that the miR-545/374a cluster is positively regulated by HBV infection [24].

It was demonstrated that DUSP6 overexpression induced by HCV and mediated by miR-181a in $CD4^+$ T cells modulates the T-cell receptor (TCR) sensitivity threshold, thereby controlling the intensity of $CD4^+$ T-cell signaling in HCV-infected individuals. This effect is associated with a more pronounced dysfunction in $CD4^+$ T-cell activation, proliferation, and IL-2 secretion [36].

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The results show that a single miR-181a molecule can efficiently regulate DUSP6 expression, and that a single DUSP6 molecule can significantly impair T-cell receptor sensitivity [36]. The deregulation of these miRs contributes to immune evasion and facilitates HCV persistence [47].

Serum exo-miR-4661-5p has clinical implications. This miR was identified as a potential serum biomarker for the diagnosis of HC and was also associated with patient prognosis, with higher serum levels of exo-miR-4661-5p correlating with poorer outcomes in HC patients [37].

Reduced expression of miRs is a frequent event in HC [48], the validation analyses confirmed these findings and demonstrated that panels based on serum exo-miR-4661-5p are powerful diagnostic biomarkers for early-stage HC [37]. This validation represented a strength of the study and supported the development of a new and promising serum exo-miRNA-based panel for HC diagnosis [49].

miRs adjust gene expression by facilitating mRNA degradation and repression of protein synthesis, and an altered expression of miRs has been documented for diseases caused by T cells. Because miRs are encoded and gene expression is strongly influenced by the entry of cytokines into Th cells, miR expression levels are likely influenced by various stimuli present in inflamed tissue and changing micro-environments in different stages of the disease due to HCV [49-50].

7. FINAL CONSIDERATIONS

The data showed that high-throughput sequencing technology used to investigate sRNA levels allowed the identification of potential miR biomarkers in HTLV-1 infection among asymptomatic individuals. However, RT-qPCR validation failed to demonstrate a significant predictive impact of these miRs. Known mature miRs with significantly different expression between the studied groups were associated with leukemic transformation in the ATL group. Additionally, the viral genes Tax and HBZ are known to deregulate the NF-κB pathway, contributing to HTLV-1–associated cellular transformation in adult T-cell leukemia/lymphoma (ATL), in agreement with previous studies.

The negative regulation of miR-15a/miR-16-1 mediated by HBx RNA may represent a mechanism induced by HBx that regulates the expression of specific miRs, thereby enhancing the pathological properties of HBx within the HBV genome. The data also show that the Ftx gene gives rise to multiple miR isoforms, with each cluster being differentially regulated. In particular, the miR-545/374a cluster located within *FTX* is significantly upregulated in HBV-related HC tissues and is associated with poor prognosis.

The findings demonstrate that HCV-induced DUSP6 overexpression mediated by miR-181a in $CD4^+$ T cells recalibrates the TCR sensitivity threshold, thereby modulating the intensity of

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CD4⁺ T-cell signaling. In addition, serum exo-miR panels, such as those including exo-miR-4661-5p, may serve as useful diagnostic biomarkers for early-stage HC and may also have prognostic value in HC patients.

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