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Novel biomarkers for hepatocellular carcinoma: Unraveling the role of piwi-interacting RNAs (piRNAs)

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Abstract

Hepatocellular carcinoma (HCC) represents approximately 90% of primary liver cancers and is characterized by a rising global incidence and high mortality. Alpha-fetoprotein (AFP), the current standard serological biomarker, lacks sufficient diagnostic specificity and sensitivity. This emphasize an urgent need for more robust diagnostic and prognostic biomarkers. Piwi-interacting RNAs (piRNAs) are a class of small non-coding RNAs frequently displaying dysregulated expression across various cancers. Their altered expression profiles suggest piRNAs hold significant potential as auxiliary tools for the diagnosis and prognostic prediction of HCC. This narrative review aims to explore the documented dysregulation of specific piRNAs and to examine their emerging role as potential biomarkers in HCC. Specific piRNAs, such as piR-Hep1 and piR-017724, have emerged as promising biomarker candidates in oncology. Their dysregulated expression and involvement in key pathways -including epigenetic regulation- link them to fundamental cancer processes such as apoptosis, proliferation, invasion, and metastasis. Recent evidence indicates that several piRNAs may facilitate the sensitive and specific detection and prognostication of hepatocellular carcinoma. However, their precise molecular functions and clinical reliability as biomarkers require further extensive validation.

Keywords: piRNA, PIWI, Hepatocellular Carcinoma, Diagnosis, Biomarker.

Introduction

Biomarkers play a crucial role in modern medicine, aiding in the diagnosis and prognostication of disorders such as hepatocellular carcinoma (HCC).[1] HCC constitutes approximately 90% of primary liver cancers and remains a major global health burden, responsible for millions of deaths annually.[2] Current diagnostic and prognostic markers for HCC -primarily biochemical assays measuring factors such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alpha-fetoprotein (AFP)- suffer from limited specificity and sensitivity. This limitation motivates the shift toward molecular biomarkers. Shaped by genetic and cellular processes, molecular markers offer deeper insight into the pathological mechanisms driving HCC progression. Among these, Piwi-interacting RNAs (piRNAs) have gained particular interest due to their regulatory functions and involvement in disease pathways.[3,4]

The search for novel biomarkers with high sensitivity and specificity has increasingly focused on molecular candidates. Such biomarkers offer the potential to restructure HCC diagnosis and prognosis. Since they originate from the interplay of genetic and molecular processes, they can provide detailed information about the underlying mechanisms of HCC progression. Among emerging molecular markers, piRNAs have garnered special attention due to their pivotal roles in gene regulation and disease pathogenesis. piRNAs are short regulatory non-coding RNAs that interact with PIWI proteins; their regulatory capacity enables them to alter gene expression and modify cellular pathways, thereby influencing tissue function.[5–7] For instance, piRNAs can regulate the expression of genes such as *GAPDH* to alter cellular metabolism, or they can modulate signaling pathways such as PI3K and mTOR, subsequently exerting profound effects on cell behavior.[8]

As demonstrated by several studies, piRNA expression is frequently dysregulated in HCC, indicating that specific

piRNAs can contribute to HCC progression, either promoting or suppressing tumorigenesis.[9] Moreover, piRNAs can be secreted from tissues into the bloodstream via exosomes, where they maintain considerable stability. This characteristic makes them strong candidates for liquid biopsy-based diagnostics.[10] Analyzing piRNA profiles in blood samples could facilitate early-stage detection of HCC and enable non-invasive monitoring of disease progression, offering a clear advantage over invasive procedures such as tissue biopsy. Consequently, piRNAs and their associated PIWI proteins have been proposed as potent diagnostic and prognostic biomarkers in HCC.[11]

The expression of specific piRNAs can be either up-regulated or down-regulated depending on their functional role in HCC pathogenesis; piRNAs that facilitate HCC progression are typically up-regulated. Furthermore, the magnitude of piRNA expression (fold-change) often correlates with HCC stage and may enable more accurate tumor staging.[10,12] PIWI proteins, which interact directly with piRNAs, also contribute to HCC progression and are predominantly up-regulated in HCC liver tissue.[11] Although the roles and functions of certain piRNAs and PIWI proteins have been well characterized, the functions of many others in HCC remain incompletely understood and require further investigation.

While numerous studies have cataloged piRNA dysregulation in HCC, a cohesive interpretation of their functional significance and clinical translatability is lacking. This review therefore aims to critically integrate existing data, moving beyond a listing of altered piRNAs to: 1) assess the strength of evidence for their biomarker potential, 2) interpret their dysregulation within the context of established HCC driver pathways, and 3) identify critical contradictions and methodological gaps that define the future research agenda for this field.

Objectives

This narrative review employs a focused search strategy to capture the evolving landscape of piRNA research in HCC. While systematic reviews prioritize exhaustive enumeration, our goal is thematic synthesis and critical appraisal. Consequently, we have prioritized studies that offer mechanistic insight or clinical correlation. We acknowledge that this approach may not capture every published association but is designed to facilitate the integrated analysis necessary to identify overarching biological themes and translational challenges.

Non-coding RNAs and piRNA

The human genome consists of non-coding RNA and coding RNA, which constitute approximately 70% and 30% of all genomic transcripts, respectively. Coding RNAs, comprised of exons or protein-coding transcripts, account for about 1.5% of the human genome, while non-protein-coding RNAs constitute the remaining 27.5%.[13] Non-protein-coding RNAs are classified into two major groups: housekeeping ncRNAs, such as transfer RNA (tRNA) and ribosomal RNA (rRNA); and regulatory ncRNAs. Regulatory ncRNAs include long non-coding RNAs (lncRNAs) -such as circular RNA (circRNA) and enhancer RNA (eRNA)- which are typically more than 200 nucleotides (nt) in length.[14] The second regulatory category comprises small non-coding RNAs (sncRNAs), which are less than 200 nt in length. sncRNAs include: microRNAs (miRNAs), small nucleolar RNAs (snoRNAs),[15] small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), and Piwi-interacting RNAs (piRNAs).[16–20] This classification is illustrated in Figure-1 and summarized in Table-1.

Table-1. Classification of Regulatory Non-Coding RNAs and Their Length

Type of Regulatory RNA	Abbreviation	Full name	Length range
Small non-coding RNA	miRNA	MicroRNA	21–23 nucleotides (nt)
	siRNA	Small Interfering RNA	20–25 nt
	snRNA	Small Nuclear RNA	100–150 nt
	snoRNA	Small Nucleolar RNA	50–300 nt
	piRNA	Piwi-Interacting RNA	24–31 nt
Long non-coding RNA	eRNA	Enhancer RNA	50–2,000 nt
	circRNA	Circular RNA	100–10,000 nt

The universe of non-coding RNAs represents a rich layer of gene regulation, with different classes employing distinct mechanisms. Unlike miRNAs, which primarily regulate mRNA stability via partial complementarity, piRNAs are distinguished by their partnership with PIWI proteins and their primary role in epigenetic and transcriptional silencing, particularly of transposable elements. This fundamental mechanistic difference is

crucial; it suggests that piRNAs may influence oncogenesis not merely by fine-tuning gene expression, but by enforcing genomic stability and controlling large-scale epigenetic programs- a vulnerability frequently exploited in cancer.

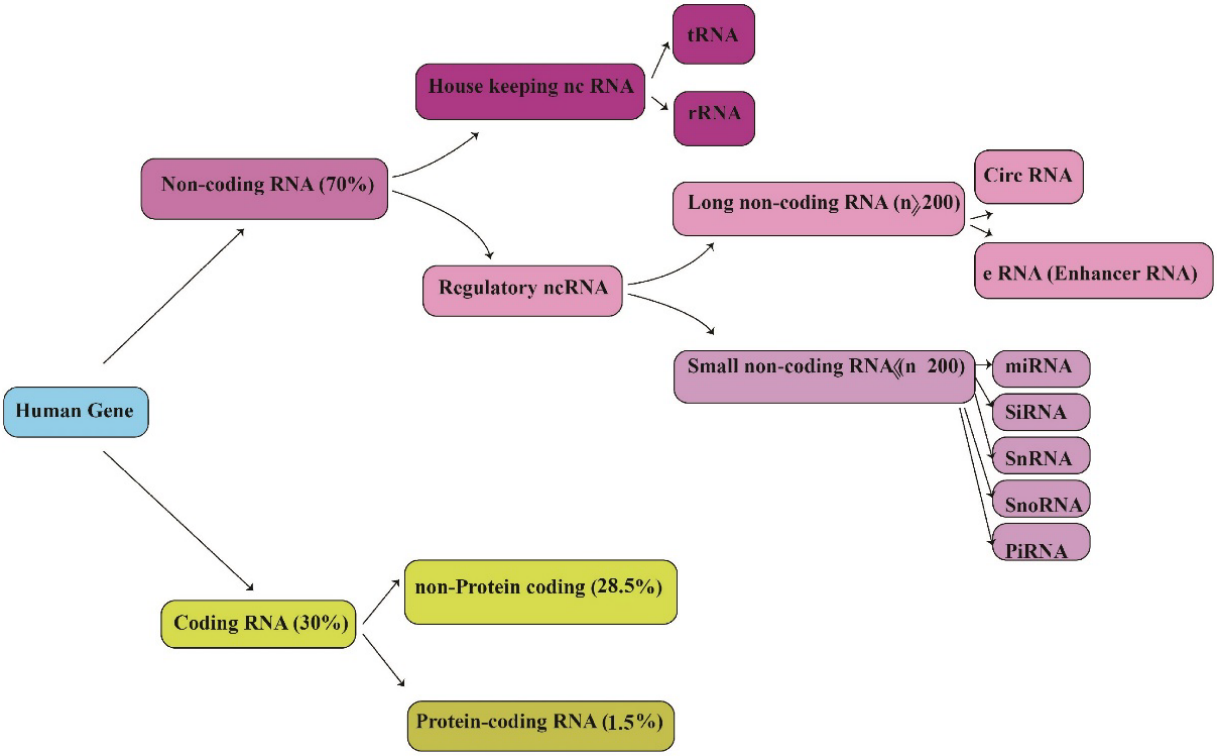

Figure-1. Classification of different RNAs in human genome

piRNAs and PIWI proteins

Piwi-interacting RNAs (piRNAs) were first reported independently by several research groups in 2006 based on studies in mouse and rat germline cells, as well as in flies and *Drosophila melanogaster*.[21–25] They are classified as animal-specific small non-coding RNAs, typically 24–31 nucleotides in length, that bind to P-Element-Induced Wimpy (PIWI) proteins. PIWI proteins, first identified in *D. melanogaster*, belong to the germline-specific Argonaute (Ago) protein family.[26] Consequently, piRNAs are categorized as small regulatory RNAs with recognized functions such as the silencing of transposable elements (TEs) and participation in epigenetic regulation during germline development.

piRNAs exhibit exceptional diversity. Those featuring a 5′ uridine monophosphate and/or a 2′-O-methyl modification at the 3′ terminal exhibit increased stability and resistance to degradation.[27,28] piRNA clusters are transcribed into long primary transcripts. These clusters are categorized as uni-strand or dual-strand clusters. In uni-strand clusters, only one DNA strand is used as a transcription template, whereas in dual-strand clusters, both strands are utilized to generate piRNA precursor transcripts. Furthermore, piRNA precursors can be derived from the 3′ untranslated regions (UTRs) of protein-coding genes or from individual transposon sequences via Dicer-independent pathways.[29–31]

PIWI proteins are regulatory proteins related to the Ago family, belonging to the PAZ/PIWI protein family, which comprises highly conserved RNA-binding proteins. Argonaute proteins incorporate a PAZ domain in the N-terminal region that binds to small non-coding RNAs and a C-terminal PIWI domain that acts as a double-strand-specific RNA endonuclease.[32] PIWI proteins are recognized for their crucial role in maintaining the stability of piRNAs and are responsible for TE repression and the post-transcriptional regulation of mRNAs in the germline.[6] The four PIWI proteins expressed in humans are PIWIL1 (HIWI), PIWIL2 (HILI), PIWIL3, and PIWIL4 (HIWI2).[33]

piRNA and PIWI functions

It is established that, as regulatory RNAs, piRNAs can alter gene expression via diverse mechanisms. For example, piRNAs can exert their effects in both the cytoplasmic and nuclear compartments of cells.[34] They can modify protein expression by regulating protein-coding mRNAs through various mechanisms, inhibit transposable element activity, and alter chromatin structure to apply epigenetic changes that affect the

transcription of specific loci.[34,35] PIWI proteins also contribute directly to gene regulation, TE repression, and chromatin modifications through diverse mechanisms. piRNAs regulate post-transcriptional gene expression by binding to PIWI proteins and influencing mRNA degradation or translation [Figure-2].

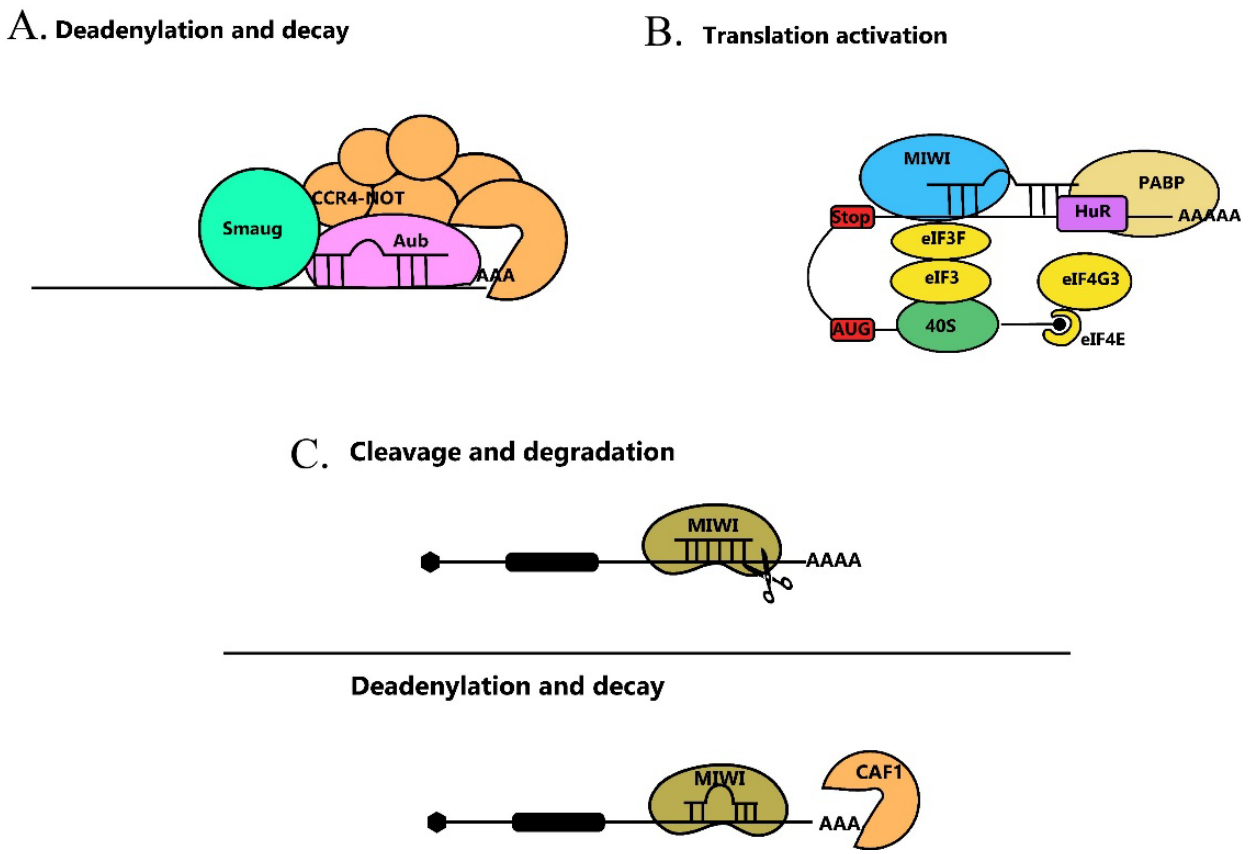

Figure-2. Figure illustrates the mechanisms by which piRNAs influence mRNA stability and expression through a series of molecular interactions. piRNAs can induce mRNA deadenylation and decay via incorporating several proteins such as Smaug, CCR4-NOT and Aub, resulting in reducing protein translation. B) piRNAs can activate and increase translation via loading into MIWI and interacting with the genome. C) piRNAs that are loaded into MIWI can cleavage and decay through deadenylation by CAF1 which subsequently reduces protein expression

The regulation of transcription at a targeted locus is influenced by its chromatin structure. In mammals, this regulation is accomplished through two primary mechanisms: the incorporation of histone variants or post-translational histone modifications, and DNA methylation.[34] PIWI proteins in both mice and flies localize to the nucleus and can repress the transcription of their targets.[36,37] It has been further demonstrated that PIWI proteins in flies can interact directly with chromatin, which may induce chromatin remodeling.[38]

A pivotal function of the PIWI-piRNA complex is the suppression of TE expression in animal germline and somatic cells, which suggests a heritable role for piRNAs in TE control. TE expression can be suppressed by PIWI-piRNA complexes at both the transcriptional and post-transcriptional levels, depending on the specific PIWI protein involved.

Moreover, PIWI can act as an epigenetic activator. In 2007, Yin and Lin demonstrated that in *Drosophila*, the PIWI protein acts as a positive regulator of the 3R-TAS (telomere-associated sequence) located on chromosome 3R. They also found that the absence of PIWI exerts opposing regulatory outcomes. PIWI expresses 3R-TAS in a dose-dependent manner and amplifies the active 3R-TAS signal, implying that PIWI can function as an epigenetic activator in germline cells. The precise mechanism by which PIWI causes these epigenetic alterations requires further study, but it is theorized that PIWI binding leads to transcriptional silencing or activation, which may be associated with effects on the chromatin microenvironment, nuclear sub-localization, and the cofactors with which PIWI interacts.[39]

Several lines of evidence indicate that piRNAs can affect fertility or sterility in male mice. It is suggested that proteins involved in the piRNA pathway, such as MIWI2, Tudor Domain Containing 9 (TDRD9), and the protein

encoded by the *Maelstrom* (MAEL) gene, localize to the nucleus and are associated with *de novo* DNA methylation. This results in the suppression of TEs in regulatory regions within embryonic spermatocytes, a process essential for spermatogenesis.[40,41] Conversely, it has been observed that the demethylation of retrotransposons causes their reactivation, subsequently leading to meiotic failure and sterility.[42] TDRD9 is a protein-coding gene that represses TEs by preventing their mobilization, and MAEL can alter gene expression through histone trimethylation and changes in chromatin state.[43,44] piRNA pathway components such as PIWI, MIWI2, and MILI can have protective effects on germline cells and spermatogenesis in males by suppressing apoptosis.[45] These findings indicate that piRNAs and PIWI proteins can promote TE methylation and act upstream of the methylation machinery, facilitating meiotic progression and post-meiotic differentiation.[46] This pathway supports healthy sperm production and has protective effects on male fertility.

In *Drosophila*, it was observed that the piRNA pathway can increase the deposition of repressive histone marks, which subsequently enhances transcriptional repression. In flies, it was determined that deletion of the PIWI protein's N-terminus results in its nuclear delocalization, an increase in H3K79 and H3K4 di-methylation (which are activation marks), and a reduction in di-/tri-methylation of H3K9 (a repressive mark) over numerous transposons.[47] It has also been observed that PIWI knockdown significantly increases TE transcript levels, indicating that PIWI represses TEs at the transcriptional stage.[34]

PIWI-piRNA complexes are also responsible for TE repression at the post-transcriptional level. It is thought that a piRNA bound to PIWI can recognize complementary target sequences by binding to them, which represses their expression. This concept is supported by observations that PIWI knockdown leads to decreased H3K9 tri-methylation on active transposons, resulting in the loss of TE repression.[38,44,48]

The initial documentation of piRNAs post-transcriptionally regulating protein-coding genes was presented in *D. melanogaster*. It was observed that piRNAs induce deadenylation and decay of mRNAs by guiding the Aubergine (Aub) protein to them and via interaction with Smaug, an RNA-binding protein, and the CCR4-NOT deadenylation complex. CCR4-NOT is a multi-subunit complex present in all eukaryotic cells that contributes to gene expression at different levels, from mRNA synthesis in the nucleus to mRNA degradation in the cytoplasm.[5,49] Therefore, it can be concluded that piRNAs have a significant effect on mRNA expression and stability.[50]

In mice, piRNAs are loaded onto MIWI, which promotes mRNA deadenylation and decay via the CAF1 deadenylase.[51] CAF1 deadenylase is a protein incorporated into the CCR4-NOT complex that can shorten the poly(A) tail of mRNA, leading to mRNA degradation.[52] Additionally, pachytene piRNAs can lead to mRNA cleavage by MIWI in a manner similar to siRNAs.[53,54] In *C. elegans*, regulation of the germline cell transcriptome can occur via imperfect base-pairing, including the regulation of histone genes and ribosomal DNA through transgenerational pathways.[55]

Genic piRNAs are a class of piRNAs produced from specific mRNAs, particularly from regions within their 3′ UTRs.[56,57] The function of genic piRNAs is not yet fully defined. However, as mRNA processing from the 3′ UTR is coupled with translation of the corresponding mRNA, they may contribute to the fine-regulation of protein levels. Furthermore, genic piRNAs can harbor TE sequences, which may allow them to participate in TE inhibition at the post-transcriptional level during postmeiotic stages of spermatogenesis.[58]

Although piRNAs often have inhibitory effects on gene expression, they can also stabilize mRNAs and facilitate their translation; this phenomenon has been discovered in both mice and *D. melanogaster*.[59–62] Based on recent studies, MIWI and pachytene piRNAs activate the translation of specific mRNAs involved in spermiogenesis via incomplete base-pairing. Pachytene piRNAs, which are expressed in the adult mouse testis and are primarily bound to MIWI, constitute the majority of piRNAs expressed during the pachytene stage of germ cell development.[63] This MIWI-dependent gene regulation requires the binding of the Human Antigen R (HuR) protein, an essential regulator of RNA metabolism with a multifaceted role. The HuR protein binds to RNA and to the eukaryotic translation initiation factor 3 subunit F (eIF3F), forming a complex that activates translation in spermatids.[64] In *D. melanogaster* germline cells, it has been shown that Aub's interaction with the poly(A)-binding protein (PABP) and several subunits of eIF3 initiates the translation of *nanos* mRNA, emphasizing the significant conservation of the role of PIWI proteins in translation initiation across species.[65] These pathways and mechanisms are necessary for spermatogenesis. Beyond their role in spermatogenesis, piRNA-mediated gene regulation, the alteration of mRNA expression, and histone modifications may contribute to the inhibition or promotion of cancer progression.

piRNA in Oncogenesis

Given the established involvement of piRNAs in gene regulation, there is increasing interest in their role in human diseases. As elucidated by several studies, dysregulated piRNA expression could either initiate or restrict the onset and progression of numerous diseases, including malignancies such as cancer.[27] Epigenetic changes -including DNA hypomethylation, hypermethylation at specific gene promoters, histone modifications, and the activation of oncogenes (e.g., *cyclin D* and *Ras*)[66,67] alongside the silencing of tumor suppressor genes (e.g., *p16* and *Rb1*)[68] -are central to cancer progression. piRNAs can contribute to cancer progression through multiple pathways, which are classified and further explained below [69] [Figure-3].

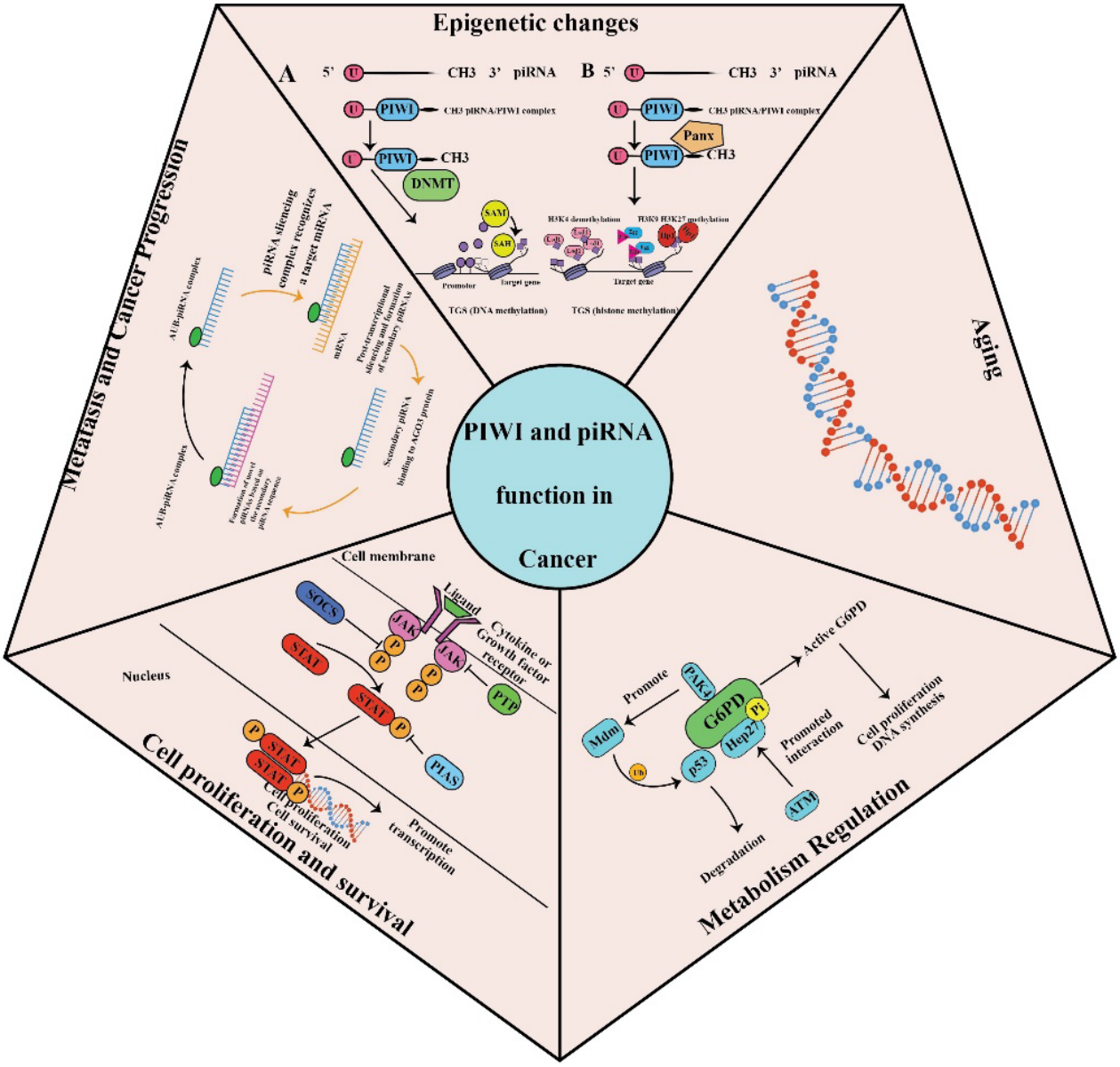

Figure-3. Picture illustrates and summarizes the pathways by which piRNAs affect human genome and contribute to cancer progression

As many studies show, abnormal piRNA expression may result in the unrestricted proliferation of cancer cells via the deregulation of chronic proliferative signaling and the activation of classic pathways such as PI3K/AKT/mTOR. This pathway regulates cell metabolism and growth to support the demands of unlimited cell duplication and proliferation.[70] The oncogenic functions of piRNAs converge on the core hallmarks of cancer. Critically, multiple dysregulated piRNAs -including piR-Hep1 in HCC and piR-004800 in myeloma- appear to co-opt the PI3K/AKT/mTOR signaling axis, a central driver of cell growth and survival.[71] For instance, piR-Hep1 forms a complex with PIWIL2 that can activate the PI3K/AKT pathway, which controls cellular proliferation,

metabolism, and survival via protein phosphorylation. Upregulated piR-Hep1 is present in 46.6% of HCC tumors; furthermore, it was observed that piR-Hep1 inhibition via a locked nucleic acid (LNA) suppresses cell motility and viability. This pattern suggests that disparate piRNAs may function as upstream nodes or amplifiers of this crucial pathway across malignancies. Similarly, the involvement of piRNAs like piR-36026 in inhibiting apoptosis and others like piR-57125 in promoting metastasis indicates that the piRNA landscape does not merely correlate with cancer but actively regulates its defining biological capabilities.[72]

A key mechanism by which piRNAs may contribute to oncogenesis is by conferring resistance to apoptosis.[69] For instance, in breast cancer, piR-36026 appears to function as an onco-piRNA by suppressing the expression of tumor suppressors *SERPINA1* and *LRAT*. While this finding is in another cancer type, it establishes a proof of principle that piRNAs can directly regulate apoptotic pathways. A pressing question for HCC is whether similarly functioning onco-piRNAs (e.g., piR-Hep1) exert their pro-survival effects through analogous inhibition of tumor suppressor genes, a connection not yet fully elucidated in liver cancer.[73]

Tumor metastasis is a critical feature of malignant progression and can be influenced by dysregulated piRNA expression. For example, piR-57125, piR-38756, and piR-30924 are highly associated with tumor metastasis in renal cell carcinomas.[74] Conversely, low expression of piR-017724 can induce HCC progression and malignancy by enhancing cell proliferation, migration, and invasion, potentially through the silencing of *PLIN3*.[12]

Since a major trait of tumors is unrestrained cell growth and proliferation, an upregulated metabolism is required to meet the energy demands of cancer cells. This metabolic reprogramming can be controlled by various factors and is crucial in differentiating malignant cells from normal tissue. In colorectal cancer, upregulated piR-823 can induce the expression of *G6PD*, which suppresses hypoxia-inducible factor-1α (HIF-1α) ubiquitination. This increases glucose consumption in cancer cells and results in a reduction of intracellular reactive oxygen species (ROS) content [75] [Figure-4].

piRNAs also regulate transposable elements (TEs); failure of this regulation can lead to DNA damage and accelerated aging.[76] The accumulation of such damage alongside the aging process reduces normal cellular function and can lead to disorders or malignancies.[69] For example, piR-39980 could prompt neuroblastoma cellular deterioration by altering *JAK3* expression via pathways independent of classical apoptosis.[69] As studies suggest, piRNA expression is highly correlated with malignant tissue phenotype and cancer stage.[77] Therefore, piRNA profiles can be utilized as prognostic and diagnostic tools in various cancers[78] [Table-2]. In this article, we focus specifically on the role of piRNAs as biomarkers in hepatocellular carcinoma.

Table-2. Diagnostic performance (AUROC) of specific piRNAs in low tumor burden HCC

piRNA Name	AUROC Value
piR-1029	0.961
piR-15254	0.868
novel-piR-35395	0.898
novel-piR-32132	0.926
novel-piR-43597	0.935

AUROC: Area Under the Receiver Operating Characteristic Curve.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a type of primary liver cancer that represents the majority (approximately 90%) of all liver cancer cases.[2] Prevalent risk factors for HCC include inflammatory infections such as hepatitis B and C,[79] steatohepatitis related to diabetes or alcoholism, and metabolic disorders such as Wilson disease, tyrosinemia, hereditary hemochromatosis, and alpha-1-antitrypsin deficiency.[80] Additionally, epigenetic alterations that change gene expression may also trigger HCC induction.[81] Although the overall 5-year survival rate for all stages of HCC is approximately 15%, it can increase to up to 70% if the cancer is diagnosed at an early stage.[82]

According to data released by the World Health Organization in 2020, there were 905,677 new cases of liver cancer reported globally, resulting in 830,180 deaths. Liver cancer constituted 4.7% of all newly diagnosed cancer cases and 8.3% of all cancer-related deaths in 2020.[83] It is a prevalent cancer type, ranking among the top three causes of cancer-related deaths in 46 countries and among the top five in 90 countries. The number of new diagnoses is anticipated to increase significantly between 2020 and 2040, with a predicted 1.4 million new cases in 2040.[84]

Current HCC diagnostic methods and their limitations

HCC diagnosis can be carried out by several means, including imaging,[85] radiological screening, histological methods, and biochemical tests. Imaging techniques such as computed tomography (CT) scans or magnetic resonance imaging (MRI) can be used to identify HCC non-invasively. However, these techniques have several limitations, including high cost and a relatively poor ability

to detect HCC in its earliest stages.[86] Although ultrasound is currently the primary radiological screening tool, its limitations -such as operator dependence and poor efficacy in distinguishing between benign and malignant tissues- may affect diagnostic accuracy.[87]

Tissue biopsy can also be used as a diagnostic method, particularly when a definitive diagnosis cannot be made based on imaging alone. In this approach, biopsy findings are interpreted alongside immunohistochemical markers such as glypican-3, HSP70, and glutamine synthetase, achieving up to 100% specificity and 72% sensitivity. While effective, this method requires an invasive procedure and is associated with risks such as pain, hemorrhage, and a small chance of morbidity. In some cases, inadequate or failed sampling may increase diagnostic error rates or necessitate repeated biopsies.[88,89] Needle tract seeding is another potential complication, occurring when malignant cells are disseminated along the biopsy needle tract. This can alter tumor staging and phenotype, potentially converting a resectable tumor into an inoperable one.[90]

Biochemical biomarkers, such as alpha-fetoprotein (AFP), are also used in HCC detection. However, the limited sensitivity and specificity of AFP constitute a major limitation for its standalone diagnostic use.[91] These limitations underscore the need for new diagnostic methods that are less invasive while offering greater specificity and sensitivity. A newly proposed approach for detecting cancers such as HCC involves the analysis of small non-coding RNAs, specifically piRNAs.

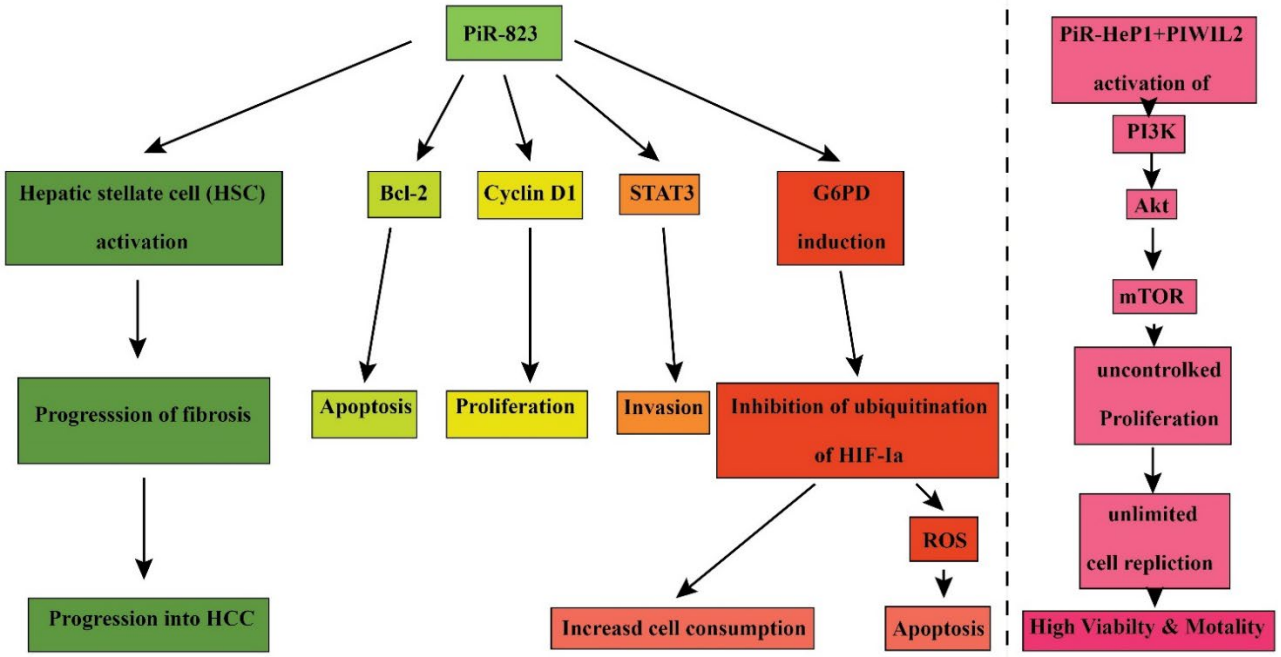

Figure-4. Left chart shows how PiR-823 can contribute to HCC progression by inducing fibrosis, increase cell consumption and apoptosis by activating different pathways. Right chart shows how incorporation of PiR-HeP1 into PIWIL2 results in uncontrolled proliferation and cell replication

piRNA Application in Hepatocellular Carcinoma

The expression of numerous piRNAs is altered in HCC. Specific piRNAs may be downregulated or upregulated depending on their role in either suppressing or promoting cancer progression.[92] According to research by Koduru et al. in 2018, 128 piRNAs were dysregulated in HCC tissue samples (45 downregulated and 83 upregulated), while 56 piRNAs were dysregulated in early-stage hepatocellular carcinoma (eHCC) (46 downregulated and 9 upregulated).[93] In an experiment by Rizzo et al., it was observed that 58 piRNAs were dysregulated in HCC tissue, of which 34 were upregulated and 24 were downregulated.[94] Further research by Rizzo et al. suggests that 30 of the 34 upregulated piRNAs were associated with increased microvascular invasion and histological aggressiveness, while 20 of the 24 downregulated piRNAs were linked to the inhibition of HCC progression, potentially through the control of angiogenic processes.[94]. In a recent study by Rui et al. to identify exosome-derived piRNAs correlated with HCC progression and staging, piRNA was found to be a crucial component in serum exosomes of HCC patients, comprising 23.72% of all exosomal RNA content.[10] They screened 253 differentially expressed piRNAs and concluded that 36 were upregulated and 217 were downregulated in HCC patients.[10] Law et al., observed

that a specific piRNA, piR-Hep1, was upregulated in HKCI-4 and HKCI-8, which are cell lines derived from hepatocellular carcinoma.[72,95]

Collective data from profiling studies reveal a consistent pattern: HCC involves the widespread dysregulation of dozens to hundreds of piRNAs. However, a critical synthesis reveals a major disparity between discovery and validation. While lists are long (e.g., 128 piRNAs identified by Koduru et al.,[93]) only a small subset recurs with functional annotation. For instance, piR-Hep1 emerges as a recurrent oncogenic candidate across independent studies, linked to proliferation via PI3K/AKT signaling. Conversely, piR-017724 is consistently downregulated as a putative tumor suppressor. This contrast between the handful of mechanistically characterized piRNAs and the vast number of unvalidated hits underscores a key field-wide challenge: the imperative to move from high-throughput discovery to focused functional and clinical validation.

Other piRNAs may also serve as biomarkers in HCC diagnosis; however, they may be less specific or sensitive. piR-823 overexpression was initially associated with HCC, but recent studies suggest it can also be upregulated in colorectal cancer, potentially reducing its diagnostic specificity for HCC.[75] It has also been observed that piR-823 is upregulated upon hepatic stellate cell (HSC) activation.[96] Overexpression of piR-823, along with *EIF3B*, promotes TGF-β1 expression, which is a contributing factor to fibrosis progression.[96,97]

In the search for specific and sensitive piRNAs for HCC diagnosis, Wu et al., studied the dysregulation of piR-017724 in both HCC tissues and cells. They observed that piR-017724 was downregulated in HCC cells and tissues, and this low expression was associated with malignancy. HCC patients with stage I-II disease (earlier stages) expressed this piRNA at higher levels than those with stage III-IV disease (advanced stages). Patients with higher piR-017724 expression had a higher survival rate than those with low expression, with a median difference of approximately 27.35 months. HCC patients with low levels of piR-017724 exhibited a remarkably poor prognosis.[12] It was found that knockdown of piR-017724 increases *PLIN3* expression, and based on the "pathological stage map" module of HEPIA2, *PLIN3* expression is inversely related to the pathological stage of HCC.[12] This suggests piR-017724 as a promising biomarker for cancer diagnosis and prognostication [Figure-5].

The search for clinically viable biomarkers has led to the identification of multi-piRNA signatures with superior diagnostic power. Notably, Rui et al. demonstrated that a panel of five exosomal piRNAs could achieve an exceptional area under the receiver operating characteristic curve (AUROC) of 0.986, significantly outperforming individual piRNAs.[10] This underscores a critical principle in biomarker development: combinatorial panels likely capture the biological heterogeneity of HCC better than single molecules. However, this finding awaits external validation in independent cohorts, a necessary step to confirm its generalizability and clinical utility [Table-2]. One advantage of utilizing these piRNAs as biomarkers is their ability to be dysregulated in HCC with low tumor burden. According to Rui et al., these five piRNAs are highly expressed in HCC with low AJCC stages, isolated tumors, or small tumor size compared to non-tumor donors, which was verified by calculating their AUROC values[10] [Table-3]. These findings demonstrate the high sensitivity of this five-piRNA panel, indicating its promise as a biomarker set for HCC diagnosis.

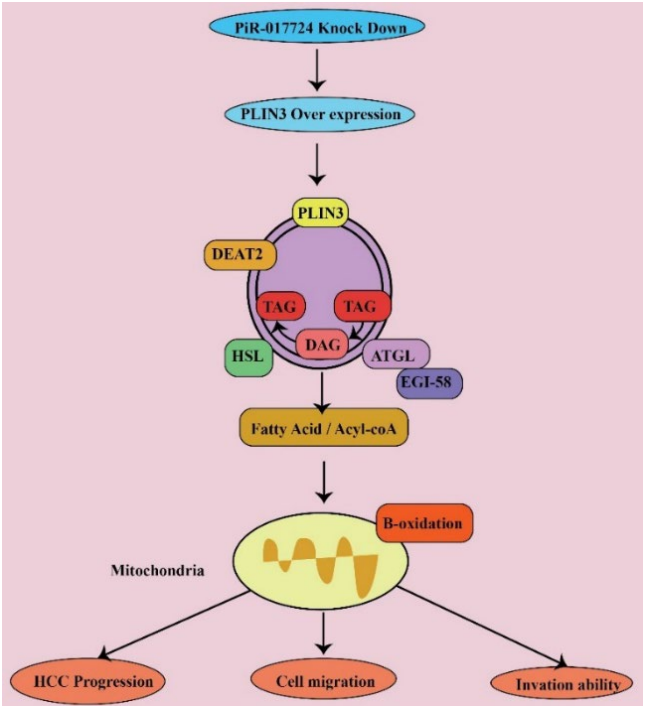

Figure-5. Picture illustrates the underlying mechanism by which PiR-017724 knock down can contribute to HCC progression, cell migration and invasion ability. Overall the PiRNA knock down results in PLIN3 over expression which alters TAG metabolism. This alteration subsequently regulates fatty acid and acyl-coA synthesis and B-oxidation. These metabolic changes contributes to HCC progression.

In the study by Koduru et al., the researchers investigated five piRNAs that were differentially upregulated (piR-28488, piR-7239, piR-5939, piR-1338, and piR-23786) and five that were differentially downregulated (piR-959, piR-

5937, piR-5938, piR-820, and piR-28525) in eHCC, suggesting their potential role as diagnostic biomarkers. In HCC, the upregulated piRNAs identified were: piR-32299, piR-23670, piR-24864, piR-28488, and piR-7239. Conversely, the downregulated piRNAs were: piR-952, piR-820, piR-28525, piR-5938, and piR-5937. It was concluded that the piRNAs dysregulated in eHCC did not show high specificity, despite having high sensitivity. On the other hand, piR-23670 and piR-24864 were specifically altered in HCC. As Law et al. demonstrated, piR-Hep1 expression was increased in HCC cell lines. They also observed that, in addition to piRNAs, the expression of PIWI protein genes was dysregulated in HCC tissue compared to adjacent healthy tissue.[72] piR-Hep1 was upregulated 11.94-fold and 12.83-fold in HKCI-4 and HKCI-8 cells, respectively, compared to the MIHA normal liver cell line. In HCC tissue, this piRNA was upregulated in 80.8% and 46.6% of tumors compared to normal liver and adjacent non-malignant liver, respectively. Its expression also correlated with tumor size.[72]

Rizzo et al. discovered that many piRNAs, including hsa-piR-020498, piR-LLi-30552, hsa-piR-013306, hsa-piR-017724, hsa-piR-020829, and hsa-piR-004309, are upregulated in HCC and could serve as potential diagnostic biomarkers. However, hsa-piR-013306 is the only piRNA that is upregulated specifically in HCC; the others are also expressed in low-grade dysplastic nodules (LGDN), high-grade dysplastic nodules (HGDN), and eHCC, which may limit their diagnostic specificity.[72]

Table-3. Diagnostic performance (AUROC) of selected piRNAs for HCC detection

piRNA Name	AUROC Value
piR-1029	0.878
piR-15254	0.927
Novel-piR-5395	0.986
Novel-piR-2132	0.887
Novel-piR-3597	0.957

AUROC: Area Under the Receiver Operating Characteristic Curve; HCC: Hepatocellular Carcinoma.

PIWI proteins and their role in cancer

In addition to piRNAs, tumorigenesis can be influenced by PIWI proteins. The dysregulation of PIWI proteins in HCC and other cancers is inextricably linked to, yet distinct from, piRNA biology. Their oncogenic roles -in proliferation, apoptosis evasion, and metastasis- suggest they may function as central effectors or even independent drivers. This raises a pivotal, unresolved question: are PIWI proteins primarily dysfunctional carriers for oncogenic piRNAs, or do they possess piRNA-independent functions in hepatocarcinogenesis? The observation that HIWI (PIWIL1) overexpression alone may be insufficient for tumorigenesis in some models favors the former, but the broader pattern of their dysregulation suggests a complex, cooperative role. Disentangling this relationship is essential for understanding whether therapeutic strategies should target the piRNA, the PIWI protein, or their interaction complex.[98]

In gastric cancer, it has been noted that cancer cell proliferation increases following HIWI overexpression,[99] which is also associated with repressed cellular differentiation and an enhanced cell growth state in sarcoma precursors. This effect was inversely correlated with the expression of tumor suppressor genes (TSGs) such as *p15*, *p21*, and *p27*. HIWI may induce these changes via DNA hypermethylation, promoting tumorigenesis.[100] Wang et al., elucidated that HIWI can affect the expression of cell proliferation-, apoptosis-, and cell cycle-related proteins such as p21, cyclin D1, Bcl-2, and Bax in glioma.[103] In hepatocellular carcinoma, HIWI is implicated in the migration of cancer cells. PIWIL2 has been shown to be involved in cell proliferation, colony formation, and attenuated apoptosis *in vitro* via the STAT3/Bcl-XL pathway, potentially through direct binding of PIWIL2 to STAT3.

PIWI proteins can also contribute to cancer cell invasion and metastasis. For example, it was observed that HIWI induces both migration and invasion in glioma cells by upregulating *MMP-2* and *MMP-9* expression. Conversely, the occurrence of metastasis has been correlated with increased PIWIL1 expression in HCC. PIWIL2 and PIWIL4 are upregulated in breast cancer and cervical cancer, respectively, and studies suggest they may play pivotal roles in metastasis and invasion in these cancers. Altogether, this evidence supports the involvement of PIWI proteins in key cancer hallmarks, including cell proliferation, apoptosis evasion, invasion, and metastasis.

PIWI proteins as biomarkers in HCC

Since piRNAs interact with PIWI proteins to exert their effects, the expression of certain PIWI protein genes may also be altered in HCC, indicating a pivotal role in tumorigenesis.[98] As demonstrated by several studies, PIWI proteins are linked to cell proliferation, invasion, metastasis, and apoptosis; consequently, they may serve as applicable diagnostic and prognostic biomarkers in cancer [98] [Table-4].

Table-4. Summary of PIWI proteins in HCC: dysregulation, mechanism, and biomarker potential

PIWI Name	Sample Origin	Dysregulation Type	Change (Fold)	Proposed Mechanism in HCC	Proposed Biomarker Type	[References]
HIWI (PIWIL1)	Tissue	Upregulated	1.9	Apoptosis regulation, metastasis, cell proliferation	Diagnostic & Prognostic	[101, 102]
PIWIL2	HCC Tissue	Upregulated	1.65	Undefined	Diagnostic	[72]
PIWIL2	Adjacent Non-Malignant Tissue	Upregulated	1.52	Undefined	Diagnostic	[72]
PIWIL4	HCC Tissue	Upregulated	8.37	Undefined	Diagnostic	[72]
PIWIL4	Adjacent Non-Tumoral Liver	Upregulated	5.47	Undefined	Diagnostic	[72]

Jiang et al., illustrated that HIWI (PIWIL1) is overexpressed in HCC tissue (65.2% of all collected samples) compared to adjacent healthy tissue (27.2% of samples), with a 1.9-fold increase; a statistically significant difference was observed between intratumoral and peritumoral tissue.[101,102] However, its overexpression did not correlate with patient age, sex, or the histological subtype of the tumor.[102] HIWI also contributes to the high proliferation and growth of HCC *in vitro* and *in vivo*.[103] HIWI expression was differentially increased in HepG2, SMMC-7721, MHCC97L, MHCC97H, and HCCLM3 cells compared to the normal hepatocyte cell line L02, and its expression correlated directly with tumor metastatic potential.[101] Conversely, it was also demonstrated that HIWI overexpression alone did not induce cell proliferation, metastasis, or apoptosis in SMMC-7721 HCC cell lines, primary mouse hepatocytes, xenograft models, or an adenovirus-mediated mouse hepatic gene-expression model. This indicates that HIWI overexpression may be necessary but insufficient for HCC tumorigenesis.[104] It was also discovered that the 1-, 3-, and 5-year overall survival rates were higher in the HIWI-negative expression group (77%, 54%, and 49%, respectively) compared to the HIWI-positive group (61%, 34%, and 34%, respectively).[101] According to Law et al., *PIWIL2* expression was upregulated 1.65-fold in HCC compared to normal liver, and 1.52-fold in adjacent non-malignant tissue compared to normal liver. *PIWIL4* was also upregulated in HCC (8.37-fold) and in adjacent non-tumoral liver (5.47-fold) compared to normal liver.[72]

This evidence suggests that dysregulation of *HIWI* gene expression can be used as both a potential diagnostic and prognostic biomarker [Table-5].

Table-5. Summary of piRNAs in HCC: Dysregulation, Mechanism, and Biomarker Potential

piRNA Name	Origin	Dysregulation Type	Change (Fold)	Proposed Mechanism in HCC	Proposed Biomarker Role	[References]
piR-823	Tissue	Up	–	Promotes liver fibrosis progression leading to cirrhosis and HCC	Diagnostic	[75, 96, 97]
piR-017724	Tissue	Down	–	Inhibits cell proliferation, migration, and invasion; linked to *PLIN3* regulation	Diagnostic & Prognostic	[12]
piR-1029	Blood Serum Exosomes	Up	–	Undefined	Diagnostic	[10]
piR-15254	Blood Serum Exosomes	Up	–	Undefined	Diagnostic	[10]
Novel-piR-35395	Blood Serum Exosomes	Up	–	Undefined	Diagnostic	[10]
Novel-piR-32132	Blood Serum Exosomes	Up	–	Undefined	Diagnostic	[10]

Novel-piR-43597	Blood Serum Exosomes	Up	–	Undefined	Diagnostic	[10]
piR-32299	Tissue	Up	4044.62	Undefined	Diagnostic	[93]
piR-23670	Tissue	Up	2335.40	Undefined	Diagnostic	[93]
piR-24864	Tissue	Up	2072.08	Undefined	Diagnostic	[93]
piR-28488	Tissue	Up	1098.53	Undefined	Diagnostic	[93]
piR-7239	Tissue	Up	949.32	Undefined	Diagnostic	[93]
piR-952	Tissue	Down	517.94	Undefined	Diagnostic	[93]
piR-820	Tissue	Down	78.24	Undefined	Diagnostic	[93]
piR-5937	Tissue	Down	51.29	Undefined	Diagnostic	[93]
piR-28525	Tissue	Down	57.64	Undefined	Diagnostic	[93]
piR-5938	Tissue	Down	56.84	Undefined	Diagnostic	[93]
piR-Hep1	HKCI-4 Cells	Up	11.94	Promotes cell motility and viability	Diagnostic	[72]
piR-Hep1	HKCI-8 Cells	Up	12.83	Promotes cell motility and viability	Diagnostic	[72]
piR-Hep1	Tissue	Up	–	Promotes cell motility and viability; correlates with tumor size	Diagnostic	[72]
hsa-piR-020498	Tissue	Up	–	Undefined	Diagnostic	[94]
piR-LLi-30552	Tissue	Up	–	Undefined	Diagnostic	[94]
hsa-piR-013306	Tissue	Up	–	Undefined	Diagnostic	[94]
hsa-piR-017724	Tissue	Up	–	Undefined	Diagnostic	[94]
hsa-piR-020829	Tissue	Up	–	Undefined	Diagnostic	[94]
hsa-piR-004309	Tissue	Up	–	Undefined	Diagnostic	[94]

Synthesis, contradictions, and future directions

The integrated analysis presented herein supports a model in which specific piRNAs, such as the oncogenic piR-Hep1 and the tumor-suppressive piR-017724, are functionally embedded in the molecular pathogenesis of HCC. However, the translation of this promise into clinical practice is impeded by several critical gaps: 1) Mechanistic Specificity: For the majority of dysregulated piRNAs, their direct mRNA targets or chromatin loci remain unknown; 2) Causation-Correlation Divide: It is often unclear whether piRNA expression changes are drivers or passengers of tumor progression; 3) Technical Heterogeneity: Variability in detection platforms and sample sources impedes direct comparison and meta-analysis across studies; and 4) Therapeutic Neglect: The field has almost exclusively focused on diagnostic potential, neglecting the therapeutic implications of targeting onco-piRNAs or restoring tumor-suppressive piRNAs. These gaps collectively call for a strategic shift from descriptive profiling to hypothesis-driven research. Future efforts must prioritize functional validation, the development of standardized clinical assays, and the exploration of piRNA-directed therapeutics.

Conclusion

piRNAs represent a rapidly evolving class of molecular biomarkers with significant potential to revolutionize the diagnostic and prognostic landscape of HCC. As noted in this review, compelling evidence demonstrates consistent dysregulation of specific piRNAs, exemplified by piR-Hep1, piR-017724, and multi-piRNA panels such as the five-signature set identified by Rui et al., in both tissue and liquid biopsies of HCC patients. Their association with key clinicopathological features -such as tumor stage, metastatic potential, and overall survival- positions them as promising tools to overcome the limitations of current standards like AFP. The intrinsic stability of piRNAs in circulation further enhances their suitability for non-invasive, liquid biopsy-based approaches, aligning with the growing demands of precision oncology.

However, to bridge the gap from promising research to clinical implementation, the field must now embark on a coordinated, multi-faceted roadmap. Key steps include:

Large-Scale, Multi-Center Validation: Priority should be given to validating the most promising piRNA candidates and panels in extensive, prospective cohort studies across diverse populations and etiologies of HCC. This will rigorously assess their clinical sensitivity, specificity, and generalizability, establishing the evidence base required for regulatory consideration and clinical adoption.

Standardization of Detection Protocols: The transition from research assays to clinically reliable tests necessitates the standardization of pre-analytical and analytical workflows. This includes the optimization and harmonization of methods for piRNA isolation from blood-derived exosomes or total serum, quantification (e.g., via RT-qPCR or next-generation sequencing), and data normalization to ensure reproducibility across different laboratories and clinical settings.

Mechanistic Investigation of piRNA Function: Beyond correlation, a deeper understanding of the causative relationship between piRNAs and HCC pathogenesis is essential. Focused research is needed to decipher how specific dysregulated piRNAs mechanistically influence key driver pathways -including PI3K/AKT/mTOR signaling, metabolic reprogramming, and epigenetic modulation- that promote proliferation, invasion, and metastasis. This will not only strengthen their biomarker rationale but also identify nodes for therapeutic intervention.

Exploring Therapeutic Potential: The functional involvement of piRNAs in oncogenesis invites exploration of their therapeutic utility. Research is warranted to investigate strategies aimed at therapeutically inhibiting oncogenic piRNAs or restoring the function of tumor-suppressive piRNAs, utilizing tools such as antisense oligonucleotides (e.g., locked nucleic acids) or small molecule modulators. This offers a potentially novel avenue for targeted HCC therapy.

In summary, piRNAs stand at a promising crossroads in HCC research. Their translation from compelling biological associations to integrated components of clinical management requires a concerted effort focused on validation, standardization, mechanistic deciphering, and therapeutic exploitation. Addressing these priorities will enable the scientific community to harness the full translational potential of piRNAs, ultimately contributing to earlier detection, more accurate prognostication, and improved outcomes for patients with hepatocellular carcinoma.

Practical points in Biochemistry/Nutrition:

PiRNAs (e.g., piR-Hep1) are stable, dysregulated in HCC, and detectable in blood. They show promise as specific, non-invasive diagnostic and prognostic biomarkers, surpassing AFP limitations. Clinical validation and standardization are needed.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Hepatocellular carcinoma: HCC; Piwi-interacting RNAs: piRNAs; Alpha-fetoprotein: AFP; Alanine aminotransferase: ALT; Aspartate aminotransferase: AST; Non-coding RNA: ncRNA; Transfer RNA: tRNA; Ribosomal RNA: rRNA; Long non-coding RNA: lncRNA; Circular RNA: circRNA; Enhancer RNA: eRNA; Small non-coding RNA: sncRNA; MicroRNA: miRNA; Small nucleolar RNA: snoRNA; Small interfering RNA: siRNA; Small nuclear RNA: snRNA; P-Element-Induced Wimpy: PIWI; Argonaute: Ago; Untranslated region: UTR; Nucleotide(s): nt; PIWI-like RNA-mediated gene silencing 1: PIWIL1; Human Piwi: HIWI; PIWI-like RNA-mediated gene silencing 2: PIWIL2; Human Piwi-like: HILI; PIWI-like RNA-mediated gene silencing 4: PIWIL4; HIWI2: HIWI2; Mouse Piwi: MIWI; Mouse Piwi 2: MIWI2; Mouse Piwi-like: MILI; Aubergine: Aub; Human Antigen R: HuR; Poly(A)-binding protein: PABP; Eukaryotic translation initiation factor 3 subunit F: eIF3F; CCR4-NOT Associated Factor 1: CAF1; Tudor Domain Containing 9: TDRD9; Maelstrom: MAEL; Phosphoinositide 3-kinase/Protein Kinase B/Mechanistic Target of Rapamycin: PI3K/AKT/mTOR; Transforming Growth Factor Beta 1: TGF-β1; Signal Transducer and Activator of Transcription 3: STAT3; B-cell lymphoma-extra Large: Bcl-XL; B-cell lymphoma 2: Bcl-2; BCL2-Associated X protein: Bax; Hypoxia-Inducible Factor 1-alpha: HIF-1α; Reactive Oxygen Species: ROS; Glucose-6-Phosphate Dehydrogenase: G6PD; Janus Kinase 3: JAK3; Perilipin 3: PLIN3; Matrix Metalloproteinase-2: MMP-2; Matrix Metalloproteinase-9: MMP-9; Transposable Element: TE; Tumor Suppressor Gene: TSG; Early-stage Hepatocellular Carcinoma: eHCC; American Joint Committee on Cancer: AJCC; Area Under the Receiver Operating Characteristic Curve: AUROC; Computed Tomography: CT; Magnetic Resonance Imaging: MRI; Low-Grade Dysplastic Nodules: LGDN; High-Grade Dysplastic Nodules: HGDN; Hepatic Stellate Cell: HSC; Locked Nucleic Acid: LNA; Reverse Transcription Quantitative Polymerase Chain Reaction: RT-qPCR.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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