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LncRNA PANDAR in Hepatocellular Carcinoma: Expression Patterns, Molecular Mechanisms, Clinical Relevance, and Therapeutic Implications

Mostafa Kamandi [1], Hamideh Feiz Disfani [2,*]

[1] Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Department of Emergency Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[*] ***Corresponding Author:*** Department of Emergency Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Email: feyzh@mums.ac.ir

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Abstract

Context: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, characterized by a poor prognosis due to late-stage diagnosis and limited treatment options. Emerging evidence highlights the pivotal role of long non-coding RNAs (LncRNAs) in tumorigenesis, presenting potential diagnostic and therapeutic targets.

Evidence Acquisition: This narrative review synthesizes current research on PANDAR expression patterns, molecular functions, and clinical relevance in HCC. Studies indicate that PANDAR is upregulated in HCC tumor tissues compared to adjacent non-tumor tissues, suggesting its involvement in tumor progression.

Results: Functionally, PANDAR suppresses apoptosis, promotes cell proliferation, and interacts with key oncogenic pathways, contributing to HCC pathogenesis.

Conclusions: Moreover, its potential as a prognostic biomarker is examined, with evidence linking PANDAR expression to patient survival outcomes. Despite promising findings, challenges remain in fully elucidating PANDAR's molecular mechanisms in HCC. Further research exploring therapeutic interventions targeting PANDAR could open new avenues for personalized treatment strategies.

Keywords: Hepatocellular Carcinoma, LncRNA, PANDAR, Cancer Progression

1. Context

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer and the fourth leading cause of cancer-related death globally (1). The HCC represents a major public health burden, with approximately 841,000 new cases annually, primarily due to its asymptomatic development and the absence of proven early detection methods (2). The disease mainly arises in the context of chronic liver conditions, including infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), cirrhosis, and alcoholic liver injury (3). Current therapies, such as surgical resection, liver transplantation, and therapeutic agents, have limited efficacy, especially for patients diagnosed with stage III and stage IV disease (4). This underscores the urgent need for novel molecular biomarkers that could enhance the early diagnosis, prognosis, and treatment of HCC (5).

Long non-coding RNAs (LncRNAs) have recently been recognized as important regulators in cancer development (6). These non-coding RNAs, typically longer than 200 nucleotides, do not code for proteins but play significant roles in regulating gene expression at multiple levels, including chromatin modification, transcriptional regulation, and post-transcriptional regulation (7). The LncRNAs have been linked to cancer, including HCC, where they regulate key processes such as tumor growth, apoptosis, metastasis, and resistance to treatment (8). Their unique tumor- and cell-line-specific expression patterns make them attractive candidates for novel diagnostic and prognostic biomarkers and therapeutic targets (9).

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Human carcinogenesis is complex and extends beyond genetic changes to include epigenetic changes, which play a crucial role in cancer initiation and progression (10). Epigenetic changes such as DNA methylation, histone modifications, and LncRNA-mediated gene regulation are frequent in HCC (11). Recent studies have demonstrated that such changes can significantly impact tumorigenesis by regulating gene expression and cellular pathways involved in cancer progression (12). Given the growing knowledge of LncRNAs as key contributors to cancer biology, elucidating their roles in HCC is crucial for advancing research and improving clinical outcomes (13).

Hepatocellular carcinoma remains a major health problem with rising incidence rates globally (14). Despite advancements in surveillance techniques such as ultrasound screening and alpha-fetoprotein (AFP) surveillance, most cancers are detected at advanced stages, reducing the effectiveness of curative treatments (15). Additionally, resistance to conventional chemotherapy and targeted agents remains a significant barrier to effective treatment (16). The identification of immune checkpoint inhibitors has provided some promise, but response rates vary among patients (17). Thus, new molecular targets with the potential to improve early diagnosis and therapeutic specificity are urgently needed (18).

The LncRNAs have been implicated in regulating various oncogenic pathways, including Wnt/β-catenin signaling, PI3K/AKT/mTOR, and epithelial-mesenchymal transition (EMT), all of which are essential for HCC development (19). Some LncRNAs act as oncogenes, facilitating tumor growth and metastasis, while others act as tumor suppressors (20). This dual role underscores the complexity of LncRNA regulation and their promise for application in precision medicine (21). The LncRNAs such as highly upregulated in liver cancer (HULC), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), and PVT1 have been found to be significantly dysregulated in HCC and are therefore attractive candidates for continued investigation as biomarkers or therapeutic targets (22).

This review aims to summarize the role of LncRNAs in HCC, detailing current evidence on their mechanisms of action and potential use as biomarkers and therapeutic targets. By discussing the cross-talk between LncRNAs and key oncogenic pathways, this review highlights the significance of these non-coding RNAs in HCC development. Furthermore, the review discusses the opportunities and challenges in translating LncRNA research into clinical practice. Through the analysis of well-characterized LncRNAs with established clinical relevance, this work contributes to ongoing efforts in formulating LncRNA-based diagnostic reagents and therapeutic strategies for HCC. Additionally, we will discuss the potential of RNA-based therapies, including antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs), in targeting oncogenic LncRNAs to disrupt tumor development. By integrating findings from high-impact research and clinical trials, this review aims to bridge the gap between basic research and clinical practice, ultimately translating into improved patient outcomes in HCC.

2. Long Non-coding RNA PANDAR: Molecular Mechanisms and Tumorigenesis

Long non-coding RNAs have garnered extensive interest due to their critical functions in regulating cellular processes, including cell proliferation, apoptosis, and differentiation. Once considered non-functional "junk" DNA, these molecules are now recognized as crucial regulators of gene expression through various mechanisms. PANDAR (P53-activated non-coding antisense RNA) is a significant LncRNA identified as a key regulator of the p53 signaling pathway, a vital network responsible for orchestrating the cell's response to DNA damage and other forms of stress (23). The p53 pathway is critical to cellular homeostasis, orchestrating DNA repair mechanisms, inducing cell cycle arrest, and promoting apoptosis — each essential for maintaining genomic integrity. In response to DNA damage, p53 becomes activated, leading to the transcription of genes involved in either repairing the damage or eliminating the damaged cell via apoptosis.

In this context, PANDAR was first described as a key modulator of the apoptotic function associated with p53. In response to genotoxic stress, including radiation or chemotherapy exposure, there is heightened expression of PANDAR, which impacts the apoptotic response (24). The binding of PANDAR to NF-YA, a component of the NF-Y transcription factor family, is integral to its inhibitory apoptotic role. NF-YA is recognized as a central repressor in regulating pro-apoptotic gene expression, such as BAX, which is crucial for apoptosis initiation. It has been shown that under stress conditions, PANDAR upregulation binds NF-YA and inhibits NF-YA's capacity to repress BAX expression (25). Therefore, PANDAR inhibits apoptosis by preventing the activation of important pro-apoptotic factors. This capacity enables cells to survive and proliferate even in the presence of DNA damage. This survival advantage is particularly relevant to oncology, where the avoidance of programmed cell death

provides tumor cells with a proliferation advantage, facilitating their escape from one of the primary defense mechanisms employed by the body against tumor development (26).

3. PANDAR's Role in Cancer: A Tumor-Promoting Factor

PANDAR (P53-activated non-coding antisense RNA) has been identified as a significant oncogenic LncRNA involved in regulating cancer cell survival, chemoresistance, and tumor growth. This LncRNA influences cellular activities by regulating apoptosis, allowing cancer cells to evade programmed cell death typically triggered by DNA damage or chemotherapeutic drugs. By suppressing apoptotic pathways, PANDAR provides neoplastic cells with a survival advantage, facilitating unchecked proliferation and enhancing resistance to therapy. PANDAR's ability to maintain cancer cell viability under stressful conditions supports its designation as a tumorigenic factor or oncogene (27).

Colorectal cancer (CRC) exemplifies PANDAR's involvement in tumorigenesis. Research consistently demonstrates that PANDAR is overexpressed in CRC-affected tissues, with expression levels associated with decreased apoptosis of neoplastic cells. This anti-apoptotic function enables cells to evade intrinsic cellular death mechanisms, enhancing tumor growth potential. Furthermore, PANDAR's role in chemoresistance has been observed in CRC, where elevated PANDAR expression correlates with unfavorable chemotherapy responses (21). Inhibition of apoptosis not only favors tumor growth but also leads to treatment failure, making PANDAR a target for drug resistance reversal therapies.

Similarly, in non-small cell lung cancer (NSCLC), PANDAR expression is significantly higher in tumor tissues compared to normal lung tissues, where it inhibits apoptosis and facilitates disease progression. Sustained PANDAR expression has been correlated with poorer clinical outcomes, including reduced survival rates in NSCLC patients (28). Through its association with NF-YA and inhibition of pro-apoptotic genes, PANDAR enhances cell viability and inhibits apoptotic pathways that would otherwise limit tumor growth.

Given PANDAR's role in facilitating cancer cell survival and chemoresistance, it has become a focus for therapeutic targeting. Strategies targeting PANDAR's activity may sensitize cancer cells to chemotherapy, re-sensitize drug-resistant cells, and enhance treatment outcomes, thereby improving patient survival in cancers such as CRC and NSCLC (29). Given its pervasive role in promoting cellular survival, targeting PANDAR holds promise as a master therapeutic strategy against cancer and in overcoming resistance to standard therapies (30).

4. PANDAR in Hepatocellular Carcinoma: Implications for Tumor Progression

In HCC, a highly aggressive liver cancer often diagnosed at late stages, the role of PANDAR is particularly evident. The HCC has a poor prognosis and high recurrence rate, especially in the context of liver cirrhosis and chronic hepatitis infection. In these cases, PANDAR overexpression is noted as a feature of HCC tissues, occurring at much higher levels in tumor tissue compared to adjacent non-tumor liver tissues. The high level of PANDAR expression indicates the critical involvement of this LncRNA in the malignancy of liver cells and tumorigenesis. Research has shown that PANDAR is associated with chemoresistance in HCC, promoting cell survival via inhibition of apoptotic pathways (30). The chemotherapy resistance caused by PANDAR complicates the treatment of liver cancer, making it increasingly difficult to target and destroy HCC cells (31).

PANDAR overexpression also correlates with worse overall survival and increased recurrence risk in patients with HCC, making it a valuable prognostic indicator. Thus, PANDAR is not only a marker of disease severity but also a predictive marker of chemotherapy resistance and unfavorable clinical outcomes (32). PANDAR's dual functions of facilitating tumor survival and inducing chemoresistance render it an attractive candidate for new therapeutic approaches aimed at reversing chemotherapy resistance in HCC. Inhibition of PANDAR expression or its downstream function may sensitize liver cancer cells to conventional chemotherapy drugs and enhance treatment response in otherwise non-responsive patients (33).

5. PANDAR and Epithelial-to-Mesenchymal Transition: Promoting Invasiveness

Recent studies highlight another function of PANDAR in cancer: Its role in the EMT. The EMT is a biological process in which epithelial cells lose their tight junctions, polarity, and adhesive properties, acquiring a mesenchymal phenotype that favors increased migration, invasiveness, and metastatic potential (34). This process is central to the metastatic spread of cancer cells from the primary tumor to distant organs, a hallmark of late-stage cancer. In HCC, PANDAR has been shown to induce EMT by interacting with chromatin-modifying enzymes and transcription

factors such as Snail, Slug, and ZEB1 (34). These transcription factors are key regulators of mesenchymal markers such as N-cadherin and vimentin, which play significant roles in cellular motility and invasiveness (35). They inhibit the production of epithelial markers such as E-cadherin, resulting in the loss of epithelial characteristics and the acquisition of mesenchymal characteristics.

PANDAR's ability to regulate these transcription factors makes it a potent inducer of the EMT process, thereby promoting the migration, invasion, and metastasis of tumor cells in HCC. PANDAR's regulation of EMT adds another layer of complexity to its involvement in liver cancer. By promoting both tumor growth and metastatic potential, PANDAR enables cancer cells to escape not only chemotherapy-induced apoptosis but also other therapeutic modalities, including targeted therapy and immunotherapy. Furthermore, PANDAR's involvement in EMT suggests that it can be at the forefront of early tumor dissemination, which may explain the aggressiveness of the disease (36). The metastatic potential conferred by PANDAR underscores the importance of this LncRNA as a therapeutic target for anti-metastatic therapy. Inhibiting PANDAR's ability to promote EMT may restrict the invasive potential of liver cancer cells, inhibit metastasis, and enhance patient survival.

6. PANDAR Expression in Hepatocellular Carcinoma: Evidence from Clinical Studies

Recent publications have explored the involvement of PANDAR in HCC and revealed that its overexpression in neoplastic tissues is associated with enhanced tumor aggressiveness and unfavorable clinical prognosis (37-39). A seminal study involving 24 HCC patients demonstrated that PANDAR expression was notably elevated in tumor tissues compared to adjacent non-tumor tissues, showing a 2.04-fold change ($P = 0.038$). This increase in PANDAR levels aligns with findings in other cancers, where PANDAR overexpression is associated with more aggressive tumors, including greater metastasis, chemoresistance, and worse patient survival. Such findings underscore the potential of PANDAR as a prognostic biomarker for liver cancer progression (40, 41).

In addition to examining PANDAR expression in tumor tissues, the research also investigated its association with various clinicopathological variables, including tumor size, tumor grade, vascular invasion, and survival rates. Notably, although PANDAR expression was not significantly associated with most of these variables, a peculiar observation was made in liver transplant patients. In this subgroup, PANDAR expression levels were dramatically higher than in those who underwent lobectomy ($P = 0.045$). The high expression level of PANDAR in transplant patients is particularly interesting, as it suggests a potential role for PANDAR in liver regeneration during transplantation, which may have implications for tumor recurrence. This result presents a promising avenue of research to determine if PANDAR expression can be utilized as a biomarker to monitor liver regeneration and facilitate the early detection of tumor recurrence in patients post-transplantation (42-44).

Although this study suggests an association of PANDAR overexpression with a more aggressive HCC tumor phenotype, large-scale cohort studies are needed to validate this and establish PANDAR as a firm prognostic marker for HCC progression and treatment outcomes. Future studies with longitudinal designs and larger patient cohorts are necessary to ascertain the potential of PANDAR expression as a prognostic indicator for tumor recurrence following surgical procedures, such as liver transplantation and resection. Furthermore, whether PANDAR can be targeted therapeutically should be investigated, as inhibition of PANDAR could potentially enhance sensitivity to chemotherapy and reduce metastasis in hepatocellular cancers (45).

7. Comparison with Other Long Non-coding RNAs in Hepatocellular Carcinoma

Within the intricate network of HCC, LncRNAs have emerged as key regulators of tumor growth, metastasis, and therapeutic resistance. Among the numerous LncRNAs involved in HCC, PANDAR is notable for its distinctive mechanism of action and significant contribution to the regulation of apoptosis and cell viability. To contextualize its function, it is instructive to compare PANDAR with other well-characterized LncRNAs, such as MALAT1, HOTAIR, and HULC, which have been found to play essential roles in the development of liver cancer (46, 47).

8. Metastasis-Associated Lung Adenocarcinoma Transcript 1: A Prominent Oncogene in Hepatocellular Carcinoma

Metastasis-associated lung adenocarcinoma transcript 1 is one of the most extensively studied LncRNAs in cancer biology, including HCC. Like PANDAR, MALAT1 promotes tumor growth and metastasis. MALAT1 has been shown to regulate cell cycle progression, thereby enhancing cell proliferation and inhibiting apoptosis. It is upregulated in most HCC cases and is

associated with poor prognosis, metastasis, and chemoresistance (48). Furthermore, MALAT1 is involved in controlling various epigenetic processes, such as chromatin remodeling, which may contribute to drug resistance and tumor development.

Similarly, PANDAR, like MALAT1, is involved in pro-tumorigenic functions; however, it achieves this through a different pathway, namely by interacting with the p53-NF-YA axis to inhibit apoptosis. While MALAT1 is primarily effective in cell cycle regulation and inhibition of apoptosis via chromatin remodeling, PANDAR exerts its effects through interaction with transcription factors like NF-YA. This highlights the specific role of PANDAR in promoting cell survival under conditions of DNA damage and stress (49, 50).

9. HOX Transcript Antisense Intergenic RNA: Chromatin Remodeling and Metastasis

HOX transcript antisense intergenic RNA (HOTAIR) is a well-characterized LncRNA that shares several characteristics with PANDAR, including its ability to promote metastasis and tumor progression. HOTAIR functions as a chromatin remodeling factor and has been found to epigenetically suppress the transcription of tumor suppressor genes, leading to invasive and metastatic characteristics in several cancers, including HCC (51). Epigenetic regulation of genes involved in cancer is known to involve control of histone modification and DNA methylation.

PANDAR, however, induces metastasis and tumor progression through a somewhat different pathway. It is associated with the regulation of the EMT, a process whereby cancer cells gain invasive properties and migrate to distant organs. While both HOTAIR and PANDAR are involved in metastatic potential, PANDAR does so through the regulation of transcription factor interactions (e.g., Snail, Slug) that drive EMT, whereas HOTAIR is primarily involved in chromatin organization and gene repression. Thus, while HOTAIR plays a greater role in long-term epigenetic control, PANDAR facilitates short-term cellular events like EMT that directly contribute to metastasis in cancers such as HCC. This postulation highlights the intricacy of LncRNA functions in tumor progression, where each LncRNA may target multiple aspects of cellular plasticity and pathways of tumor progression (52).

10. Highly Upregulated in Liver Cancer: Role in Lipid Metabolism and Chemo Resistance

Another important LncRNA in HCC is HULC, which plays a role in lipid metabolism and chemoresistance. Highly upregulated in liver cancer is frequently upregulated in HCC tissues and has been shown to enhance liver cancer formation by modulating lipid metabolism, supporting cell growth, and preventing apoptosis. Furthermore, HULC is associated with the acquisition of chemoresistance through its regulation of drug efflux pumps and anti-apoptotic proteins, rendering HCC cells less sensitive to chemotherapy-induced cell death (50-52).

Similar to HULC, PANDAR also plays a role in chemoresistance but via an alternative mechanism. PANDAR primarily inhibits apoptosis by binding to NF-YA, which in turn inhibits the activation of pro-apoptotic molecules like BAX. This function positions PANDAR as a key player in chemoresistance in HCC, especially in tumors that are already genetically mutated or under treatment stress. Unlike HULC, which influences lipid metabolism and drug transportation, PANDAR functions by directly involving the pathways of cell death, making it an even more attractive target for therapies aimed at reversing chemoresistance (51).

11. Therapeutic Implications of Targeting PANDAR

Due to its anti-apoptotic function and tumor-promoting role, PANDAR represents a potential therapeutic target against HCC. Strategies to suppress PANDAR expression could restore apoptotic mechanisms in HCC cells, making them more responsive to conventional chemotherapy or targeted therapies. Research on RNA-targeting therapeutic strategies, including siRNAs and ASOs, has demonstrated potential in downregulating PANDAR expression in preclinical models, resulting in decreased tumor growth and enhanced apoptosis in various cancers other than HCC.

Another strategy involves disrupting the regulatory interaction between PANDAR and the transcription factor NF-YA. PANDAR interacts with NF-YA, inhibiting the activation of pro-apoptotic genes, a mechanism implicated in the development of chemoresistance. By blocking this interaction, it may be possible to enhance the apoptotic sensitivity of liver cancer cells, circumventing one of the greatest barriers to successful treatment. PANDAR-targeted treatments combined with traditional chemotherapy drugs, such as sorafenib — the first-line treatment for advanced HCC — could enhance treatment outcomes and improve patient survival.

12. Challenges and Future Directions

Despite the promising findings surrounding PANDAR in HCC, several challenges exist. The primary challenge is the limited number of large-scale studies confirming

the clinical utility of PANDAR as a diagnostic and prognostic biomarker. Most studies, including the one under review, involve comparatively small patient populations, limiting the generalizability of their findings. Larger multi-center studies are necessary to validate the clinical utility of PANDAR and examine its use in different subtypes of liver cancer.

Another challenge is the molecular heterogeneity of HCC. The heterogeneity of liver cancer, due to genetic, epigenetic, and environmental factors, means that PANDAR expression may vary between patients. It is necessary to discern the individual genetic and molecular contexts under which PANDAR exerts its tumorigenic effects to devise personalized therapeutic strategies.

Finally, therapeutic targeting of PANDAR also faces technical challenges, particularly in drug delivery to the liver. Recent advances in nanotechnology and RNA therapy have the potential to circumvent these hurdles and offer new hope for HCC therapy.

13. Conclusions

Long non-coding RNAs PANDAR represents a promising biomarker for the diagnosis and prognosis of HCC. Its elevated expression in HCC tissues and its role in regulating apoptosis and tumor growth highlight its potential as a therapeutic target. While further research is needed to validate these findings and explore the molecular mechanisms underlying PANDAR's role in HCC, the evidence suggests that PANDAR could play a critical role in improving the diagnosis, prognosis, and treatment of liver cancer. As research into LncRNAs continues to expand, PANDAR may emerge as a key player in the development of personalized medicine for liver cancer, offering new opportunities for improving patient outcomes.

Footnotes

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