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Review

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# The oncogenic role of Holliday junction recognition protein in hepatocellular carcinoma

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**Abstract**

The relationship between centromere dysfunction leading to numerical chromosomal changes and cancer is well-known. Holliday Junction Recognition Protein (HJURP) is a chaperone of the centromere-specific protein, Centromere Protein A (CENP-A), and is considered a critical factor in determining centromere identity. There are researches showing that CENP-A is overexpressed in many types of human cancer. However, the role and dynamics of HJURP in tumorigenesis have only recently been clarified. In this review, the connection between HJURP and liver cancer, as well as the role of HJURP in cancer development, has been summarized.

**Keywords:** CENP-A, Chaperone, HJURP, hepatocellular carcinoma, liver cancer, prognosis

## 1. Introduction

Today, liver cancer remains a significant global health concern due to its high incidence and mortality rates. Cirrhosis, chronic liver disease, viral hepatitis and excessive alcohol consumption are the main risk factors for liver cancer (1-3). Hepatocellular carcinoma (HCC) is the most prevalent type of liver cancer, representing around 75-90% of all cases. Smoking, type 2 diabetes, viruses, aflatoxin-contaminated food products, excessive alcohol consumption, and obesity are among the primary risk factors for HCC (Figure 1) (3).

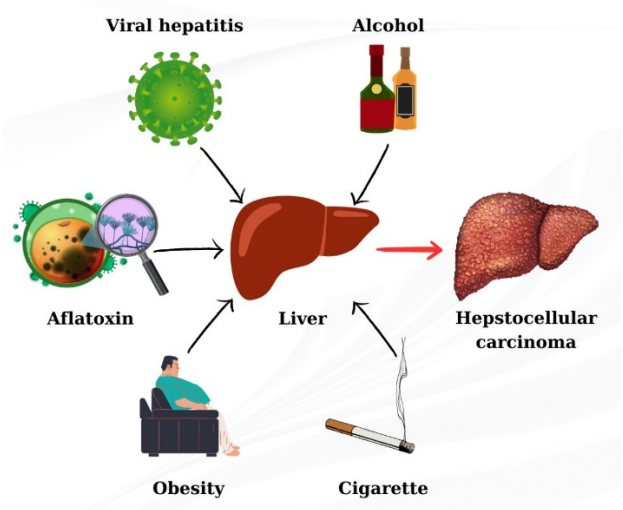


**Fig.1.** Various risk factors contributing to hepatocellular carcinoma development

Despite various treatment approaches, the general 5-year survival rate observed in patients with liver cancer, due to delayed diagnosis and advanced stages, does not exceed 20%. Surgery is the primary treatment option for early-stage HCC. Liver transplantation can also be performed in patients who are not suitable for surgical resection and have liver dysfunction. The ablation therapy is also considered for the patients with early-diagnosed HCC (4). Due to its anti-proliferative and anti-angiogenic effects, sorafenib, recognized for its role as a potent tyrosine kinase inhibitor (TKI), is used as a long-term first-line treatment in patients with advanced HCC or cases that have relapsed and show poor progression after regional therapy. A distinct kinase inhibitor, lenvatinib, is noted for its reduced incidence of hand-foot skin reactions when compared to sorafenib, while it has an increased incidence of hypertension, proteinuria, and anorexia (5). Ramucirumab, a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist, represents the first application of biomarker-based therapy for advanced patients and serves as a highly successful second-line treatment option demonstrating favorable responses. Likewise nivolumab, a humanized anti- programmed cell death protein 1 (PD-1) monoclonal antibody and an immune checkpoint inhibitor, demonstrates promising potential for treating patients with advanced HCC. Durvalumab, another inhibitor developed in recent years, is a programmed death-ligand 1 (PD-L1) monoclonal antibody that works by enabling the

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recognition of cancer cells by the immune system and stands out with its clinical phase study results. Positive results of the clinical phase I/II study of durvalumab and tremelimumab combined treatment have been reported (5, 6).

Chromosomal instability (CIN) is the most frequently encountered pathology in HCC cells. Additionally, various mechanisms, including errors in chromosomal segregation, defects in DNA repair processes, and the inhibition of the tumor suppressor gene *p53* are correlated with HCC (7). The segregation errors occurring during mitotic division result in cells characterized by an abnormal chromosome count, known as aneuploidy, which is largely associated with cancer (8). The errors that occur during cell division result in the activation of p53. Activation of p53 occurs following inappropriate chromosome segregation and leads to cell cycle arrest, senescence or apoptosis. Therefore, p53 depletion often contributes to aneuploidy in cancers (8, 9). P53, which is crucial for preserving genomic stability, serves as the primary checkpoint during cell division, inducing cell cycle arrest upon detecting DNA damage and promoting apoptosis in the event that the issue is unresolved. In addition, it is known that *p53*, one of the most frequently mutated tumor suppressor genes in cancers, has a strong relationship with HCC pathogenesis and is one of the most frequently mutated genes (10-12).

One of the critical points in ensuring chromosomal stability is the centromere. The centromere functions for kinetochore construction, kinetochore-microtubule connection, and the spindle assembly checkpoint (SAC). As detailed in the following sections, Constitutive Centromere Associated Network (CCAN) proteins, such as CENP-C and CENP-N, and the CENP-A nucleosome form a complex to bring together the kinetochore and kinetochore-associated proteins to ensure normal segregation of chromosomes (13). The histone H3 variant specific to the centromere, known as CENP-A, is found to be overexpressed in aggressive cancer cells (14, 15). Additionally, the relationship between the levels associated with the centromeric chaperone Holliday Junction Recognition Protein (HJURP) and CENP-A has shown that HJURP is essential for the localization of CENP-A at centromeres and serves a crucial function in the completion of CENP-A nucleosome formation (16, 17). The high expression of CENP-A and its chaperone HJURP correlates with one another and results in cancer prognosis in cells lacking p53. The accumulation of CENP-A causes mitotic errors, loss of centromere function, and CIN, characteristic features of cancer (18).

Despite the availability of various alternative therapeutics, the expected outcome and survival rates in patients with HCC are not very high. Therefore, identifying the biomarkers to facilitate early diagnosis and investigation of the new target molecules remains important for achieving better outcomes in HCC patients. Since genomic instability is a significant parameter driving the formation and advancement of HCC, elucidating the mechanisms that trigger genomic instability is considered crucial for identifying new biomarkers and target molecule s. Consequently, there is a significant need to identify new proteins with low or absent expression in normal liver cells but elevated expression in HCC as diagnostic markers. Furthermore, developing new treatment strategies by targeting these proteins is possible.

In this review, we concentrated on the potential for CENP-A and its chaperone HJURP, that play a key role during mitotic segregation, as diagnostic, prognostic, and therapeutic cancer markers in liver cancer.

## 2. Nucleosome Formation and Histone Chaperones

Eukaryotes maintain their genomes through a densely packed nucleoprotein complex called chromatin within the cell nucleus (19, 20). Nucleosomes, the fundamental units of tightly organized chromatin, are formed by wrapping a ~147 base pair DNA sequence in the vicinity ofa histone octamer, which includes an H3-H4 histone heterotetramer surrounded by H2A-H2B histone heterodimers on both sides. This formation is completed by incorporating linker DNA and a linker histone (21, 22). The formation of the nucleosome complex is a extremely complex process that involves the coordinated action of many proteins within the cell. Central to nucleosome formation are ATP-dependent chromatin remodeling complexes and ATP-independent histone chaperones (23). The remodeling of chromatin structure is necessary to ensure the continuity of eukaryotic cells. Nucleosome formations occur repeatedly in various processes, such as DNA replication. Following DNA replication, ancestral histones together with newly synthesized histones ensure the formation of replication-dependent nucleosomes, while replication-independent nucleosome formation occurs during gene transcription (24, 25).

Histone proteins have a positive charge, making them prone to easily bind to negatively charged DNA. Nevertheless, they also possess the ability to interact undesirably with all nucleic acids and various cellular components (26). It is recognized that histones precipitate when mixed with DNA in solution at physiological ionic strength, provided that proteins known as chaperones are absent. First described by Laskey et al. as nuclear proteins that inhibit improper interactions between histones and DNA in frog oocyte extracts (27), chaperones ensure the proper folding of histones and prevent their positive charges from engaging in nonspecific interactions (28, 29). Histone chaperones are a family of histone-binding proteins that maintain non-nucleosomal histone-DNA interactions. They separate core histones from DNA until a proper nucleosomal arrangement is achieved and, together with ATP-dependent chromatin remodelers, reshape nucleosomes to resolve chromatin structure and provide accessible DNA templates for cellular processes (19). Generally, histone chaperones are a highly conserved family of proteins participating in chromatin-linked cellular processes, including

histone and nucleosome biosynthesis/biodegradation, remodeling, central dogma mechanism, and DNA repair. Unlike ATP-dependent chromatin remodeling complexes that interact with DNA, chaperones function as histone-binding proteins. Depending on their selectivity for targeted histones, they can have broad functions in many biological processes central to chromatin structure, including the eukaryotic FACT (facilitates chromatin transcription) complex, or very specific, limited functions, such as Scm3 in yeast and HJURP in humans, which facilitate the formation or maintenance of centromeric chromatin (26). Histone chaperones, classified according to the histone substrates they bind to, are often categorized as H3–H4 or H2A–H2B chaperones based on their binding to H3-H4 or H2A-H2B oligomers. Some, such as FACT, are known to bind to both hetero-oligomers with dissimilar domains. A few histone chaperones can bind to specific histones (canonical or variant) alone, and this binding pattern often contributes to the chaperone's localization and/or functions (30, 31). They perform different functions at various stages of nucleosome formation. Initially, histone proteins are produced in the cytosol and subsequently transferred to the nucleus for nucleosome assembly. Certain histone chaperones, like Nap1, facilitate this transport by partially regulating the importin-histone interaction. Second, during stress conditions, a soluble histone pool must be maintained continuously, and some histone chaperones, like nuclear autoantigenic sperm protein (NASP), act as a histone reservoir and respond to histone demand. Histone chaperones and histone-binding proteins including RbAp46 and Asf1 ensure the continuity of interactions between histones and histone-modifying enzymes by directly regulating the enzymatic activity of these enzymes. Finally, histone chaperones are immediately involved in the deposition of histones onto DNA for nucleosome formation (31). They also act as necessary regulators of chromatin structure and function, often being misregulated in cancer, with significant effects on tumor growth and survival rates (32).

Both genetic and epigenetic changes contribute to cancer pathogenesis. Research indicates that histone associated proteins, effector proteins, and chromatin remodelers play a role in the initiation and advancement of cancer (33). The centromeric nucleosomes possess a kinetochore, the region where chromosomes attach to spindle microtubules during mitotic division. The seamless transfer of genetic material to daughter cells during cell division is achieved by the specific binding of chromosomes to spindle microtubules (34). The centromeres and kinetochores play a critical role in the separation of chromatids that make up the chromosomes during division. Consequently, the errors in centromere and/or kinetochore formation lead to various chromosomal aberrations in the form of chromosomal gains and losses (aneuploidy) and are the primary course of chromosomal instability observed in cancer cells (35-37). The centromeres and kinetochores, together with centromeric chromatin, consist of inner and outer kinetochore structures. The structural core component for centromeric chromatin and kinetochore formation is the histone H3 variant CENP-A. The assembly of CENP-A depends on the HJURP chaperone brought to the centromere by the MIS18 complex. This assembly also requires several CCAN components, such as CENP-C, CENP-H/-I/-K, and CENP-N/-L/-M complexes. Errors associated with CENP-A result in chromosome segregation defects and aneuploidy. Notably, high expression of CENP-A, HJURP, and certain centromeric proteins has been linked with poor prognosis in some cancers, such as liver cancer (38-40).

## 3. CENP-A Nucleosome and Hepatocellular Carcinoma

During cell division, the centromere, which is responsible in the accurate transmission of the chromosome set to daughter cells, functions with a complex called the kinetochore. This complex assembles centromeric DNA and consists of over 90 proteins, ensuring proper attachment of spindle fibers to the chromosome (41, 42). Loss of centromere structure and/or function leads to chromosome segregation errors, which often result in the formation of micronuclei and aneuploidies linked with the presence of abnormal chromosomes in the cell. Consequently, the accumulation of these errors causes chromosomal instability in cells, leading to cancer (18, 43).

The centromere consists of two regions: the core centromeric chromatin and the pericentric heterochromatin. In the course of the cell cycle, the centromere is formed by a protein complex known as CCAN, which includes 16 centromere proteins (e.g., CENP-C, CENP-H, CENP-I, CENP-K, CENP-U, CENP-W, and CENP-X) (44). The arrangements of the kinetochore structure during mitosis is thought to involve the CCAN proteins (44). The formation of kinetochore at the centromere during cell division and the attachment of spindle fibers to the kinetochore are important for a healthy cell cycle. The formation of the kinetochore complex at the centromere, which has a special importance for the occurrence of a normal mitotic phase, is determined by the localization of the histone H3 variant CENP-A, and CENP-A stands out as an important protein that confers epigenetic identity to the centromere (39, 45). In addition, CENP-A nucleosomes are centromere-specific, distinguishing them from other H3 nucleosomes found in chromatins (44).

CENP-A and other proteins interact with spindle microtubules to form a network with chromatin, bridging the centromeric chromatin and the mitotic kinetochore (46, 47). The position of centromeres on chromosomes should be maintained through cell generations, making the retention of CENP-A in centromeric chromatin essential. Indeed, CENP-A levels at centromeres are stable across numerous cell divisions (39). Loss of CENP-A, which is necessary for the localization of all kinetochore components, leads to disruptions in kinetochore function, improper chromosome segregation, and subsequent impairments in cell viability and function. Therefore, the continuity of centromere characteristics and function is proportional to the presence of CENP-A

nucleosomes on each chromosome (42). Additionally, overexpression of CENP-A, leading to mislocalization to non-centromeric regions, has the potential to form ectopic kinetochores or weaken normal kinetochores, causing chromosomal segregation errors and genomic instability (45).

Cancer requires a process involving the accumulation of genetic mutations, such as chromosomal translocations or aneuploidy, which lead to structural rearrangements in genes or imbalances in gene dosage (48). Cancer cells derived from solid tumors exhibit chromosomal instability and aneuploidy linked with aggressive tumor behavior and adverse prognosis (48, 49). The situation is similar in liver cancer, where HCC cells carry abnormal chromosomes with various genetic rearrangements such as translocations, deletions, and gene amplifications (50). Increased chromosomal instability induced by irregularities in mitotic control mechanisms leads to aneuploidy, which is much more common compared to other oncogenic or tumor suppressor mutations in cancer (51). It has been reported that the changes in chromosomes are observed in about 90% of solid tumors (52), and the chromosome loss or gain can lead to the development of treatment resistance in cancer cells (https://www.cancer.gov/). The formation of aneuploidy can result in the simultaneous occurrence of multiple genetic changes necessary for both tumor initiation and progression (53, 54). The mutations in the mitotic control genes and overexpression of these gene products are frequently observed in CIN-related cancers. The irregular activity, particularly high expression of mitotic control genes such as *CENP-A/E*, is known to lead to chromosomal aberrations, aneuploidy, and rearrangements in HCC cells (50).

CENP-A, one of the first identified components of the kinetochore in humans, which has an important role in mitotic regulation, is a centromere-specific protein of 17 kDa encoded by the *CENPA* gene. It regulates the kinetochore formation and establishes centromere identity through epigenetic mechanisms during mitosis and meiosis. It is also necessary for the localization of all other centromere and kinetochore components (53). The mutations in or knockouts of CENP-A, which have a primary role in mitotic division and normal chromosome segregation, cause chromosome missegregation (53).

The evidence so far indicates that CENP-A and other centromeric proteins are commonly overexpressed in cancers, and that this protein excess is linked with the formation of aneuploidy, a characteristic of tumour cells (15). High levels of CENP-A have been noted in various cancers, including colorectal (53), hepatocellular (15), lung (55, 56), prostate (57), ovarian (58), and breast cancers (59). In human hepatocellular carcinoma, CENP-A mRNA expression is substantially higher in immortalized HepG2 cell lines compared to SMMC-7721 cells, and overexpression of CENP-A is also observed in primary tumor tissues. CENP-A levels correlate with histological grade progression in patients, and a significant relationship has been observed between CENP-A and P53 protein levels. Furthermore, siRNA-mediated inhibition of overexpressed CENP-A in HepG2 cells has reversed cancerous properties (15, 60). Data obtained from bioinformatic analyses revealed that CENP-A overexpression is associated with poor prognostic features such as poor survival, late-stage tumor and tumor size, and vascular invasion in HCC (61). It has been suggested that CENP-A functions as a transcriptional regulator with Yin Yang 1 (YY1) in the pathogenesis of HCC and stimulates HCC. YY1, which is composed of a transcriptional activation domain, transcriptional repression domain, spacer domain and DNA-binding domain, binds to CENP-A via a zinc finger region. The fact that YY1 is a part of the GL-Kruppel family of zinc finger DNA binding proteins that can differentially regulate gene expression as a transcriptional activator and repressor, and the demonstration of its interaction with CENP-A, reveals the function of CENP-A as a transcriptional regulator in the pathogenesis of HCC. It has also been suggested that lactylation of CENP-A ubiquitylation on lysine 124 (K124) facilitates HCC tumor progression by stimulating the transcriptional activation of CENP-A (62). Data have been provided that CENP-A may suppress cell ferroptosis and enhance tumor progression in HCC by inducing the transcription of stathmin1 (STMN1), a cytoplasmic phosphorylated protein that regulates the cell cytoskeleton in HCC pathogenesis. (63). It has also been reported that the COOH-terminal deletion of hepatitis B virus X protein (HBx), which is linked with hepatocellular carcinoma, is positively correlated with CENP-A expression, may indirectly increase CENP-A expression and may be effective on tumour progression in HCC (64).

## 4. CENP-A Chaperone Holliday Junction Recognition Protein (HJURP) and Hepatocellular Carcinoma

In mammalian cells, the dynamics of CENP-A are closely linked with cell cycle progression. HJURP is recognized as the chaperone for CENP-A, based on structural differences in H3 variants that particularly recognize CENP-A (65). HJURP is crucial for the accumulation of CENP-A at human centromeres during the late mitosis/early G1 phase of the cell cycle in a CDK-dependent manner (32). It facilitates the incorporation of CENP-C at the centromere, aiding in the assembly of functional kinetochores, which mediate cell division and chromosome segregation (66).

While HJURP is known to regulate the cell cycle, its regulatory mechanism is considered more complex than merely managing cell cycle progression. Various proteins that affect HJURP function, as well as downstream proteins regulated by HJURP, have been reported to interact with HJURP. The most prominent molecule regulated by HJURP is the histone H3 variant CENP-A. The collaboration between CENP-A and its chaperone HJURP is crucial for normal cell cycle progression, whereas ectopic activation of HJURP is associated with chromosomal instability and immortality in

cancer cells (66).

In *Saccharomyces cerevisiae*, overexpressions of Scm3p and HJURP have been linked to chromosomal loss phenotypes. The studies involving GFP-tagged HJURP in transfected human HeLa cancer cell lines have observed increased HJURP expression leading to nuclei with micronuclei or delayed chromosomes compared to controls. These findings indicate that improper regulation of HJURP results in defects in kinetochore function and chromosomal instability in human cells (67).

Cancer cells exhibit high levels of CIN, characterized by frequent chromosomal segregation errors leading to aneuploidy (48). This relationship has been validated in studies on solid tumors, confirming the high expression of HJURP in cancer cells. Research by Tatsuya Kato and colleagues identified HJURP as a newly overexpressed gene in non-small cell lung cancer (NSCLC) in comparison with normal lung tissues through cDNA microarray analysis (68). HJURP is similarly overexpressed in various cancers, as seen with other histone chaperones. A 2020 study on colorectal cancer found that HJURP acts as an oncogene and may serve as a potential prognostic biomarker and therapeutic target. Inhibition of HJURP with siRNA suppressed cancer cell proliferation, migration, invasion, and tumor formation (69). In liver cancer, HJURP expression is significantly increased compared to healthy tissues and could be a biomarker of poor prognosis (66). Overexpression and mislocalization of HJURP have also been noted in lung cancer cell lines (68). It has been proposed that HJURP expression levels are linked with radiation therapy response, making it a prognostic factor for disease-free and general survival and a predictive biomarker for radiation sensitivity (40). The effect of HJURP on cancer mechanisms has started to emerge in recent years, though studies are still limited. The expression levels of HJURP protein in various cancer cells and their association with tumor behavior are summarized in **Table 1**. For all cancers examined, high levels of HJURP have shown a strong association with poor prognosis. Additionally, HJURP may contribute to restoring DNA double-strand breaks, potentially increasing resistance to genotoxic agents (70).

**Table 1.** Expression levels of HJURP protein in various cancer and tumor behavior

| Cancer Type | Expression Level | Association with Tumor Behavior | Related Pathway | Reference |
|---|---|---|---|---|
| Liver | High Expression | High HJURP expression is associated with poor prognosis. | p21 ubiquitination via MAPK/ERK1/2 and AKT/GSK3β pathways | (66, 75) |
| Breast | High Expression | HJURP mRNA level is a prognostic factor for disease-free and overall survival in breast cancer patients and a predictive biomarker for radiosensitivity. | - | (33, 40) |
| Pancreas | High Expression | Patients with high HJURP levels have significantly worse survival rates compared to those with low HJURP levels. | Regulation of MDM2 expression via H3K4me2 dimethylation. | (32) |
| Colorectal | High and Low Expression | High HJURP expression significantly reduces cancer-specific survival rates compared to low HJURP expression. | - | (69) |
| Bladder | High Expression | The prognostic relationship is not specified. | Regulation of ROS metabolism and cell cycle via PPARγ-SIRT1 feedback loop | (77) |
| Lung | High Expression | HJURP expression is associated with the progression and metastasis of NSCLC. | Activation of the Wnt/β-catenin pathway | (78) |
| Glioma | High Expression | HJURP levels are related to patient prognosis. | - | (79, 80) |
| Ovarian | High and Low Expression | High HJURP expression levels are significantly associated with lymph node metastases and lower overall survival. | - | (81) |
| Prostate | High Expression | HJURP levels may be associated with patient prognosis. | - | (82) |
| Renal Cell Carcinoma | Low Expression | HJURP expression may be associated with poor prognosis in RCC patients. | Regulation of cell apoptosis via PPARγ/SIRT1 | (83) |

Determining HJURP expression levels is important not only for classifying high-risk patients but also for selecting suitable candidates for radiotherapy. To date, little is known about the function of HJURP expression in human cancer, and there is still no specific HJURP inhibitor or treatment that can block its role in cancer cells. The high correlation of HJURP with cancer highlights the potential of HJURP inhibitors for future therapeutic applications (81).

Although the relationship between HJURP and cancer mechanism has been revealed, there are a limited number of research investigating its potential oncogenic role in the emergence of HCC (summarized in **Table 2**). In hepatocellular carcinoma tissues from 164 liver cancer patients, higher HJURP expression was observed, particularly in tumor tissues larger than 5 cm. This underscores HJURP's role in supporting HCC cell proliferation and also shows that patients with elevated HJURP expression have poorer survival rates contrasted to those with low expression (66). In HBV-related HCC patients, the non-synonymous SNP in exon 8 of the HJURP gene (rs3771333) was significantly linked with the

onset of HCC. Individuals carrying the rs3771333 C allele (A/C or C/C genotypes) have a higher risk of HCC development contrasted to those with the A/A genotype (73). Genome integrity is regulated through the collaboration of cell cycle checkpoints and DNA repair systems. Disruptions in the genes responsible for regulating genome integrity contribute to genomic instability, premature aging, and cancer susceptibility (84). The hepatocarcinogenesis process, like other carcinogenesis processes, is quite complex and includes heterogeneous mechanisms involving abnormalities in multiple signaling pathways. However, similar to many other carcinogenic processes, deregulation of the cell cycle is commonly observed in liver cancers (85, 86). The cell cycle is closely controlled by cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors (CKIs), and the retinoblastoma protein family (pRb) (87). Key regulators of the cell cycle include cyclin-dependent kinase inhibitors (CDKIs) such as p21, p27, and p16, which are known as tumor suppressors (88). p21 is known to suppress tumors by inducing cell cycle arrest in response to various stimuli. It has also been shown to act as a major effector in many tumor suppressor pathways, causing anti-proliferative effects independently of the p53 tumor suppressor mechanism. However, recent research suggests that under certain conditions, p21 can induce cellular proliferation and exhibit oncogenic effects. These data suggest that p21 is dysregulated in human cancers but can act as either a tumor suppressor or an oncogene depending on cellular conditions (89). HJURP inhibition has been described to induce cell cycle arrest in the G0/G1 phase in HCC cells without inducing apoptosis, indicating that HJURP could be an important regulator in the cell cycle. Chen et al. are showing that HJURP suppresses p21 expression in HCC cells and alters p21 stability through MAPK/ERK1/2 and AKT/GSK3β signaling pathways. It is known that SKP2, CDT2, LRR1, and CDC20 E3 ligases are responsible for p21 degradation. The research has shown that HJURP is significantly associated with SKP2, but not with LRR, CDT2, or CDC20, and that HJURP supports ubiquitination-mediated p21 degradation (75).

**Table 2.** The role of HJURP protein in hepatocellular carcinoma and its relationship with prognosis

| Cancer Type | Expression Level | Association with Tumor Behavior | Related Pathway | Reference |
|---|---|---|---|---|
| Hepatocellular carcinoma | High Expression | Hypomethylation-induced overexpression of the HJURP promoter is inversely associated with survival; a potential prognostic biomarker and therapeutic target | DNA hypomethylation. | (71) |
| Hepatocellular carcinoma | High Expression | HJURP is significantly associated with the immunosuppressive tumor microenvironment, T cells, dendritic cells and B cells in hepatocellular carcinoma and has potential in determining prognosis. | Immune system related pathway | (72) |
| Hepatocellular carcinoma | Single nucleotide polymorphism | A non-synonymous SNP rs3771333 in exon 8 of the HJURP gene is significantly associated with the onset of hepatocellular carcinoma. | Single nucleotide polymorphism | (73) |
| Hepatocellular carcinoma | High Expression | HJURP and ASF1A histone chaperones are more effective in determining the prognosis of HCC patients with the two-gene model, rather than alone. | - | (74) |
| Hepatocellular carcinoma | High Expression | HJURP deregulated p21 via MAPK/ERK1/2 and AKT/GSK3β signaling pathways and induced ubiquitin-mediated degradation of p21; Induced HCC cancer cell proliferation and associated with poor prognosis. | p21 ubiquitination via MAPK/ERK1/2 and AKT/GSK3β pathways | (75) |
| Hepatocellular carcinoma | High Expression | HJURP expression is a prognostic marker for HCC, and its high expression stimulates the proliferation of HCC cancer cells. | - | (66) |
| Hepatocellular carcinoma | High Expression | High expression of HJURP upregulates Sphingosine kinase 1, stimulates epithelial-mesenchymal transition, increases migration and invasion of cancer cells, and reduces survival. | Sphingosine kinase1 (SPHK1) upregulation | (76) |

Epithelial-to-mesenchymal transition (EMT), which plays a essential role in cancer cell invasion, metastasis, or therapy resistance, is characterized by the loss of epithelial cell junctions and apical-basal polarity, rearrangement of the cytoskeleton, changes in cell shape, and activation of genes associated with a mesenchymal phenotype, along with downregulation of epithelial gene expression profiles. As a result, cell mobility increases, and a more invasive phenotype is exhibited (90-92). EMT is generally controlled by the transcription factors SNAIL, zinc-finger E-box-binding (ZEB), and basic helix–loop–helix (bHLH), which suppress epithelial-specific genes such as E-cadherin and cytokeratin and upregulate genes that lead to a mesenchymal phenotype. Expression changes at the gene level prevent the formation of epithelial cell-cell junctions and result in loss of epithelial function. In addition, the degradation of epithelial cell junctions is also supported by the increased expression of mesenchymal proteins such as fibroblast-specific protein (FSP-1) as well as EMT-transcription factors such as SNA1, SNA2 (92, 93). HJURP's role in the epithelial-mesenchymal

transition in hepatocellular carcinoma has been revealed. It has been shown that HJURP facilitates EMT, supporting HCC migration and invasion and that HJURP degradation inhibits HCC cell migration and invasion by upregulating E-cadherin and downregulating N-cadherin and Vimentin. In addition, HJURP overexpression in Huh7 cells has been linked with reduced E-cadherin and increased Vimentin expression. Microarray analysis in Huh7 cells identified 20 EMT-related genes among 164 differentially expressed genes, with sphingosine kinase 1 (*SPHK1*) changing in association with HJURP regulation. KEGG pathway analysis supported that HJURP regulates sphingosine metabolite processes. HJURP degradation led to increased SPHK1 expression and reversed EMT marker expression in HCC cells, reducing invasion capabilities (76). SPHK1, as a regulator of sphingolipid metabolism, contributes to HCC development. SPHK1 converts sphingosine, which induces tumor suppression via apoptosis, into sphingosine-1-phosphate (S1P), which promotes cell proliferation and survival. Increased protein and mRNA levels of SPHK1 in HCC tissues induce S1P expression and support metastasis in HCC cells. Inhibition of SPHK1 with an inhibitor or siRNA suppresses cell migration and invasion in human liver cancer cells (94, 95). Liu et al. reported that SPHK1 supports EMT by inducing autophagy and stimulating the lysosomal degradation of the epithelial marker CDH1 in hepatocellular carcinoma cell lines. The effect of SPHK1 on the EMT process has also been shown in non-small cell lung cancer and colorectal cancer cells (96, 97).

In recent years, the CENP-A chaperone HJURP has gained increasing importance in cancer mechanisms and its association with prognosis. Several research have shown that high expression of HJURP in hepatocellular cancers is linked with poor prognosis and lower survival rates. However, there is very little research exploring the mechanisms that mediate the significant increase in HJURP expression in hepatocellular carcinoma. The study showed that HJURP promoter region methylation levels are lower in cancer tissues compared to adjacent normal tissues. The study suggested that the overexpression of HJURP in HCC is associated with hypomethylation of HJURP. The same study performed cell cycle and apoptosis analyses to determine the underlying mechanism of HJURP's negative impact on HCC prognosis and found that HJURP inhibition led to G0/G1 phase arrest in HuH7 and SK-HEP-1 cells. In addition, the apoptotic cell rates were significantly increased in hepatocyte-derived carcinoma cell line (HuH7) and human liver adenocarcinoma cell line (SK-HEP-1) lacking HJURP. In HepG2 cells with induced ectopic expression of HJURP, G0/G1 phase arrest and apoptotic cell rates were significantly reduced. Based on these data, it is thought that HJURP supports cancer cell proliferation by inhibiting G0/G1 arrest and apoptosis in HCC cells (71).

Hepatocellular carcinoma is commonly linked with the inactivation of the tumor suppressor p53, significant chromosomal instability, and factors causing chronic hepatocyte death (98). Chromosomal abnormalities and genomic instability are particularly common in HBV and HCV-related HCCs (99). In the molecular pathogenesis of HCC, different genetic mechanisms such as somatic mutations in the p53 tumor suppressor gene and activation of the WNT signaling pathway are known to be significant (100-103).

High levels of CENP-A and HJURP are linked with poor prognosis in human cancers, making both factors prominent as prognostic and predictive biomarkers in recent years. The tumor suppressor p53 is known to induce an antiproliferative response in the cell when various cellular stress factors that stimulate oncogenic signaling are involved. In addition, its importance in chromatin organization is now known. Gain-of-function p53 mutations can upregulate key chromatin regulators such as MLL1 and MLL2 through epigenetic mechanisms in cells. Additionally, p53 can induce cell cycle arrest in response to nucleosome depletion, leading to extended S phase and eventual cell death in p53-deficient cancer cells. Therefore, p53 is a significant sensor of altered chromatin environments, and loss-of-function or gain-of-function mutations in p53 often cause chromatin changes that affect tumor development. Research has shown that CENP-A and HJURP gene expression is specifically upregulated in p53-deficient human cancers. Researchers have proposed that HJURP and CENP-A genes may be suppressed by intact p53 in normally proliferating cells. Mutant or deficient p53 is therefore thought to play a key role in promoting HJURP and CENP-A expression and regulating chromatin changes in cancer cells (104).

Centromeric factors have emerged as significant elements in cancer biology, serving as both prognostic markers and potential therapeutic targets. Studies focusing on pharmacological targeting of histone chaperone complexes have reported that targeting FACT, a histone chaperone that promotes chromatin reclamation during transcription, with drug-like small molecules may yield significant results in cancer treatment. These data demonstrate the importance of identifying histone chaperones as important target proteins involved in cancer mechanisms and targeting them for treatment in cancers such as HCC, where successful survival rates are still not achieved (105).

## 5. Conclusion

This summarized information suggests that HJURP is linked to tumor development and metastasis in many solid malignancies, including hepatocellular carcinoma. Determining its expression could significantly contribute to molecular diagnosis in clinic, and developing anti-cancer drugs targeting this protein may offer a novel therapeutic approach.

## Conflict of interest

All authors declared no conflict of interest.

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**Authors' contributions**

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