The emerging role of HJURP as a therapeutic target in cancers

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ABSTRACT

Holliday junction recognition protein (HJURP) is a key molecular chaperone for centromere protein A (CENP-A), which is essential for chromosome separation during mitosis and cell cycle regulation. Recent studies have identified the essential role of HJURP in carcinogenesis. Abnormal upregulation of HJURP expression has been observed in various human cancers, such as non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), bladder cancer, and breast cancer, which is associated with poor pathological development and prognosis. *In vitro* and *in vivo* studies have shown that HJURP exerts oncogenic functions mainly by regulating the cell cycle, cellular senescence, and epithelial-mesenchymal transition (EMT). This review aims to evaluate the prognostic significance of HJURP in human cancers and summarize antitumor studies targeting HJURP. The effects and regulatory factors of HJURP in carcinogenesis have also been discussed to provide new insights into targeting HJURP as a promising strategy for cancer treatment.

Keyword: HJURP, prognosis, carcinogenesis, cell cycle

Abbreviation: protein kinase B, AKT; ataxia telangiectasia mutated, ATM; Bcl-2-associated X, Bax; B-cell lymphoma, Bcl; bladder urothelial carcinoma, BLCA; breast invasive carcinoma, BRCA; bromodomain-containing protein 4, BRD4; cholangiocarcinoma, CCA; centromere protein A, CENP-A; cervical squamous cell carcinoma and endocervical adenocarcinoma, CESC; colon adenocarcinoma, COAD; colorectal cancer, CRC; disease free survival, DFS; double-strand breaks, DSB; extracellular regulated protein kinases, ERK; exon splicing enhancer, ESE;

epithelial-mesenchymal transition, EMT; esophageal carcinoma, ESCA; forkhead box O3a, FOXO3a; glioblastoma multiforme, GBM; Gene Expression Profling Interactive Analysis, GEPIA; gene set enrichment analysis, GSEA; glycogen synthase kinase 3β, GSK3β; histone 3 lysine 4 dimethylation, H3K4me2; heme oxygenase-1, Hmox-1; head and neck squamous cell carcinoma, HNSC; c-Jun N-terminal kinase, JNK; kidney chromophobe, KICH; kidney renal clear cell carcinoma, KIRC; kidney renal papillary cell carcinoma, KIRP; kruppel like factor 11 KLF11; liver hepatocellular carcinoma, LIHC; lung adenocarcinoma, LUAD; lung squamous cell carcinoma, LUSC; murine double minute 2, MDM2; N-myc downstream regulated 1, NDRG1; non-small cell lung cancer, NSCLC; nuclear receptor-binding SET domain protein 2, NSD2; overall survival, OS; pancreatic adenocarcinoma, PAAD; poly-ADP-ribose polymerase, PARP; proliferating cell nuclear antigen, PCNA; pheochromocytoma and paraganglioma, PCPG; peroxisome proliferator-activated receptors γ, PPARγ; prostate adenocarcinoma, PRAD; renal cell carcinoma, RCC; rectum adenocarcinoma, READ; reactive oxygen species, ROS; sarcoma, SARC; sirtuin 1, SIRT1; skin cutaneous melanoma, SKCM; s-phase kinase associated protein 2, SKP2; superoxide dismutase, SOD; sphingosine kinase 1, SPHK1; stomach adenocarcinoma, STAD; signal transducer and activator of transcription 3, STAT3; Cancer Genome Atlas, TCGA; thyroid carcinoma, thymic epithelial tumor, TET; thyroid carcinoma, THCA; thymoma, THYM; tumor microenvironment, TME; tumor node metastasis, TNM; transcripts per million, TPM; uterine corpus endometrial carcinoma, UCEC; wingless-related integration site, Wnt; yes-associated protein 1, YAP1

1. INTRODUCTION

The proper segregation of chromosomes during cell mitosis is essential for maintaining chromosomal stability and preventing cancer development. The centromere and kinetochore are crucial structures involved in this process [1, 2]. Defects in proteins associated with the centromere and carcinogenesis can cause chromosomal instability and disrupt the cell cycle, ultimately leading to cell death [3]. One such protein is Holliday junction recognition protein (HJURP), which mediates the deposition of histone H3 variant- centromere protein A (CENP-A) at centromeres during the G1 phase of the cell cycle [4]. It was determined that the TLTY box located within the N-terminal domain of HJURP binds to the centromere targeting domain of CENP-A [5-7] and the interaction between these two proteins is critical for maintaining chromosomal stability and successful mitosis [8]. The essentiality of HJURP activation for the immortality of cancer cells was initially identified in the year 2007 [9, 10]. Furthermore, overexpression of HJURP has been observed in various tumor tissues and is associated with poor prognosis, making HJURP a potential prognostic biomarker of cancer [11-14]. Given these findings, HJURP could be a key target for cancer treatment. This review aims to summarize recent studies on the effects and mechanisms regulated by HJURP in human cancers, and to discuss the feasibility of HJURP as a promising target for antitumor treatment.

2. THE EXPRESSION OF HJURP IN CANCERS

Several studies in recent years have demonstrated that HJURP plays a significant role in the promotion and progression of cancer. The abnormal upregulation of HJURP has

been observed in various human cancers through public genomics databases and independent patient cohorts. Two pan-cancer analyses were conducted to investigate the relationship between HJURP and cancer [14, 15]. These studies found that HJURP expression is upregulated in most human cancers. Low levels of DNA methylation may lead to the overexpression of HJURP, and high mutation frequencies suggest that HJURP could act as an oncogene and may be involved in drug resistance mechanisms [14, 16, 17]. Additionally, overexpression of HJURP is responsible for poor prognosis and cancer progression. Bioinformatics databases were used to explore the molecular mechanisms involved in HJURP. It was found that HJURP mainly participates in cell cycle and p53 signaling pathways, which are supported by existing studies [10, 18]. The expression of HJURP increases during cell cycle progression, and G2 is the phase with the highest expression level, indicating the role of HJURP in cell cycle regulation [15]. Furthermore, HJURP has been investigated to mediate tumor immune evasion and interact with immune infiltration and T cell immune exclusion, promoting cancer progression and metastasis [15].

To provide insight into the expression pattern of HJURP and its correlation with cancer survival rates, two online tools including UALCAN Interactive web and Gene Expression Profiling Interactive Analysis (GEPIA) were used to analyze mRNA expression of HJURP, and Kaplan-Meier survival analysis was conducted using data from the Cancer Genome Atlas (TCGA) database [19, 20]. Our analysis revealed that HJURP mRNA levels were significantly higher in 19 types of tumor tissue compared to normal tissue (Figure 1). Moreover, the high level of HJURP was associated with

shorter overall survival (OS) and disease-free survival (DFS) in patients with ACC, KIRK, and other cancers (Figure 2). We also observed a strong positive correlation between HJURP expression and the pathological stage of patients with ACC, breast invasive carcinoma (BRCA), kidney chromophobe (KICH), and other cancers (Figure 3). These results suggest that HJURP has the potential to serve as a biomarker for prognosis and monitoring of disease progression in cancer patients. However, the expression of HJURP and its prognostic implications can vary among different cancer types. For instance, in thymoma (THYM) and colon adenocarcinoma (COAD), high expression of HJURP is strongly linked to better prognosis, indicating a potential tumor-suppressive role. Therefore, the relationship between HJURP and tumor occurrence and development is complex and may depend on the specific type of cancer. It's important to note that these findings are based solely on data analysis and may be subject to bias due to small sample sizes. Therefore, further research is necessary to fully understand the precise function of HJURP in different types of cancer.

3. FUNCTIONS AND REGULATION OF HJURP IN CANCERS

3.1 CANCER OF RESPIRATORY SYSTEM

Lung cancer is one of the leading causes of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases and its incidence increasing globally [21]. The significance of HJURP has been analyzed in both lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), where it was found to be highly expressed in tumor tissues and associated with a poor

prognosis [22, 23]. Gene set enrichment analysis (GSEA) revealed that HJURP-related genes were mainly enriched in the G1 pathway, ataxia telangiectasia mutated (ATM) pathway, cell cycle pathway, and extracellular regulated protein kinases (ERK) pathway in LUSC, while being associated with basal transcription factors, cell cycle, homologous recombination, non-small cell lung cancer, oocyte meiosis, p53 signaling pathway, pathways in cancer, RNA degradation, and spliceosome in LUAD [22, 23]. Furthermore, HJURP was found to be remarkably associated with 28 types of tumor-infiltrating lymphocytes, particularly activated CD4 cells in patients with LUAD [22]. The active role of immune infiltration in cancer growth and development highlighted the potential carcinogenicity of HJURP [24].

HJURP has been shown to play an oncogenic role in non-small cell lung cancer (NSCLC) cells, and its biological functions have been investigated [9]. During mitotic cell cycle, HJURP localized to the nucleolus in the G1 phase and interacted with hMSH5, NBS1, and MRE11 in subnuclear foci during the S phase. It then relocated to the nucleolus in the late G2 phase and finally localized to prenucleolar bodies during telophase. Further studies have demonstrated that HJURP was a downstream target in the ATM signaling pathway and was involved in DNA double-strand break (DSB) repair via the homologous recombination pathway. Knocking down HJURP significantly inhibited cell viability in U2OS cells by inducing cell cycle arrest at the G2/M phase. HJURP also protected cancer cells from genomic instability and senescence by deregulating recombination in the rDNA region.

NSCLC is known to have a high rate of metastasis at late stages, leading to a high

mortality rate. Clinical data have shown that high HJURP expression was associated with distant metastases and advanced tumor node metastasis (TNM) stage in NSCLC [25]. *In vitro* experiments have demonstrated that silencing HJURP induced apoptosis and inhibited proliferation, migration, and invasion of NSCLC cells by suppressing the epithelial-mesenchymal transition (EMT) and wingless-related integration site (Wnt)/β-catenin signaling pathway.

3.2 CANCER OF DIGESTIVE SYSTEM

3.2.1 Oral cancer

Oral cancer ranks as the sixth most prevalent form of malignancy globally, with dietary habits being a significant contributing risk factor [26]. Research has shown that HJURP was highly expressed in most oral cancer tissues, which is associated with a reduced overall survival rate [27]. Depleting HJURP has been shown to inhibit oral cancer cell growth by inducing cell cycle arrest and senescence, with the involvement of CENP-A. In oral squamous cell carcinoma (OSCC), the most commonly mutated gene is p53, and a general mutation in HJURP was observed concurrently [28]. Additionally, HJURP has been found to be upregulated in p53-null human cancers, including breast, melanoma, and pancreatic cancer [18]. The loss of p53 led to increased levels of HJURP and CENP-A, promoting cell growth and the cell cycle via the DREAM-CDE/CHR pathway. Depleting HJURP can activate p53 inversely, leading to cell cycle arrest at the G1 and G2/M phases. In the absence of p53, HJURP deletion led to the rapid loss of CENP-A from the centrosome, causing centromere dysfunction, aneuploidy, and p53-independent apoptosis. These results

indicated that targeting HJURP holds great promise in cancer therapy, particularly in p53-deficient cancers.

3.2.2 Hepatocellular carcinoma (HCC)

Polymorphisms in genes at the molecular level can alter the amino acids encoded by codons and affect gene function, which can lead to the development of cancer [29]. Specifically, a significant association has been found between the rs3771333 polymorphism in the HJURP gene and susceptibility to HBV-related HCC [30, 31]. The rs3771333 polymorphism is a non-synonymous single nucleotide polymorphism (SNP) located in exon 8 of the HJURP gene. This polymorphism results in a change from GAA to GAC in the codon encoding the 568th amino acid residue, leading to the substitution of glutamic acid with aspartic acid. According to computer predictions, the non-synonymous SNP rs3771333 does not appear to affect protein structure, but is expected to alter the binding of the exon splicing enhancer (ESE) SF2/ASF or the number of ESE binding sites [31]. The presence of the rs3771333 A/C or C/C genotypes was found to be associated with a higher risk of HBV-related HCC compared to the A/A genotype among Chinese, which expressed lower mRNA and protein levels of HJURP in EBV-transformed blood lymphocytes. Given the impact of HJURP on DSB repair and the potential acceleration of HCC onset and progression caused by impaired DSB repair, reducing the expression of HJURP could potentially contribute to the predisposition to HCC [32]. In addition to the Oncomine database, analysis of HCC tissues and cells has shown high expression levels of HJURP, which were correlated with poor patient survival rates and several pathological factors,

including patient age, microvascular invasion, tumor size, and stage [33, 34]. Furthermore, HJURP was strongly correlated with tumor number and differentiation and has been found to play a crucial role in the immunosuppressive tumor microenvironment (TME) [35, 36]. The pro-proliferative effect of HJURP on HCC has been demonstrated both *in vitro* and *in vivo* [33]. Mechanistic studies have investigated the role of p21 in HJURP-induced cell cycle transition, revealing that HJURP induced p21 ubiquitination and facilitated its translocation from the nucleus to the cytoplasm via mitogen-activated protein kinase (MAPK)/ERK1/2 and protein kinase B (AKT)/glycogen synthase kinase 3β (GSK3β) signaling pathways. Furthermore, HJURP upregulated sphingosine kinase 1 (SPHK1) and promoted EMT, thereby enhancing cell migration and invasion *in vitro* and promoting tumor metastasis to the lungs *in vivo* [34].

3.2.3 Pancreatic cancer

Pancreatic cancer is a highly aggressive and malignant form of digestive system cancer, often associated with a poor prognosis [37]. Research has shown that the expression of HJURP was significantly higher in pancreatic cancer cells and tissues compared to adjacent normal tissues, and that high expression of HJURP can predict a lower survival rate [38]. Furthermore, studies have demonstrated that HJURP promoted pancreatic cancer cell viability, sphere formation, migration, and invasion *in vitro*, as well as tumorigenesis and metastasis *in vivo*. The mechanism behind these effects was related to the ability of HJURP to promote the binding of histone 3 lysine 4 dimethylation (H3K4me2) at the promoter region of murine double minute 2

(MDM2), which resulted in the degradation of p53 and the blockage of downstream signaling pathways.

3.2.4 Cholangiocarcinoma (CCA)

The ectopic expression of HJURP and its prognostic significance in various subtypes of CCA, including intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) CCA were investigated [13]. The results showed that HJURP was highly expressed in all subtypes of CCA and served as an independent prognostic biomarker in both iCCA and pCCA, but not in dCCA. Additionally, the study found that the correlation between HJURP expression and clinicopathological factors varied between different subtypes of CCA, with iCCA showing the most significant correlation between HJURP and advanced tumor infiltration (T stage) [13]. Given that the efficacy of targeted therapy for CCA is currently limited, the identification of HJURP not only provides valuable prognostic information but also offers a novel target for the treatment of CCA [39].

3.2.5 Colorectal cancer (CRC)

CRC is a highly prevalent malignant digestive cancer that is responsible for a large number of cancer-related deaths worldwide [40]. Although the expression of the HJURP protein was higher in CRC tissues compared to normal tissues, there was no significant association between HJURP expression and clinicopathological factors such as tumor stage and metastasis [41]. In comparison to other types of cancer, the prognosis relevance of HJURP in CRC is not as significant, which may be due to the small sample size of studies. However, based on Kaplan-Meier analysis, the high

expression of HJURP has been found to be correlated with shorter survival rates in CRC patients. *In vitro* studies have demonstrated that HJURP promoted cell anchorage-independent growth, migration, and invasion in CRC cell lines. Further research is required to elucidate the molecular mechanisms underlying these carcinogenic effects.

3.2.6 Gastric cancer

Gastric cancer is a prevalent and deadly tumor, ranking as the third leading cause of cancer-related deaths worldwide. The most common pathological type of gastric cancer is stomach adenocarcinoma (STAD), which arises from gastric mucosal glands and accounts for approximately 95% of gastric cancer cases [42]. Recent studies have found that HJURP expression was significantly higher in gastric cancer tissues compared to normal tissues, and this expression was correlated with lymphatic metastasis, TNM stage, and the presence of cancer thrombus [43]. Moreover, microarray and bioinformatic analyses have shown that HJURP was upregulated in STAD and associated with TNM stage and a longer survival rate in patients without distant metastasis. These findings suggested that HJURP could be a valuable early prognostic marker for gastric adenocarcinoma.[44, 45].

3.3 CANCER OF REPRODUCTIVE SYSTEM

3.3.1 Breast cancer

Breast cancer and ovarian cancer are the most common malignant cancers in women, and both have common risk factors and gene expressions [46]. According to the Gene Expression Omnibus (GEO) database, the expression of HJURP in breast cancer cell

lines is higher than in normal breast cells, particularly in invasive ductal carcinomas (IDC) [11]. HJURP was strongly associated with shorter survival time and pathological factors of breast cancer, including estrogen-receptor (ER) negative, progesterone-receptor (PR) negative, advanced Scarff-Bloom-Richardson (SBR) grade, young age, and Ki67 proliferation indices. Additionally, HJURP was a better independent prognosis marker for patients with ER-positive luminal A breast carcinoma than the currently used proliferation marker Ki67 [47]. Furthermore, the expression levels of HJURP and YAP1 were significantly higher in triple-negative breast cancer, which is the most aggressive subtype with poor prognosis and limited therapeutic targets, and jointly associated with poor recurrence-free survival [48]. HJURP inhibited YAP1 ubiquitination and regulated the yes-associated protein 1 (YAP1)/ N-myc downstream regulated 1 (NDRG1) pathway to promote cell proliferation and decrease response to chemotherapy. Therefore, HJURP may be a candidate prognosis biomarker for breast cancer and a therapeutic target against drug resistant, especially fortriple-negative breast cancer [49]. Interestingly, although patients with a low level of HJURP generally have longer survival times, clinical data and *in vitro* experiments suggest that HJURP can enhance the sensitivity to radiotherapy and effectively prolong survival time after radiotherapy in breast cancer, possibly due to its role in DSB repair [11].

3.3.2 Ovarian cancer

Ovarian cancer is a highly aggressive and one of the most lethal gynecological tumors, with serous ovarian carcinoma being the most common subtype of recurrent ovarian

cancer [50]. HJURP, mainly expressed in the nucleus of serous ovarian cancer cells, was elevated in advanced serous ovarian cancer tissue samples. This increase in HJURP was significantly associated with lower overall survival rate, lymph node metastasis, and clinicopathological parameters indicative of malignant progression [50, 51]. The molecular mechanism of HJURP in the progression of ovarian cancer has been elucidated. HJURP targeted CENP-A and regulated EMT to facilitate the metastatic capacity of ovarian cancer cells. Silencing HJURP inhibited cell proliferation *in vitro* and *in vivo* by inducing apoptosis and cell cycle arrest through regulating proteins related to the cell cycle [51, 52]. GO analysis has identified that differential genes in ovarian cancer were enriched in the regulation of the cell cycle [51, 52]. WEE1 and MYC were found to be positively correlated with HJURP according to the GEPIA database and experiments. Silencing HJURP enhanced the sensitivity to cisplatin and a Wee1 inhibitor AZD1775 alone or in combination in ovarian cancer cells by inducing apoptosis partly through the MYC/WEE1 pathway and inhibiting DNA damage repair. These results suggested the promising role of HJURP interference in anticancer treatment against chemoresistance.

3.3.3 Prostate cancer

Chen et al. initially reported on the high expression of HJURP in prostate cancer, which has been found to be associated with several key indicators, including elevated levels of prostate cancer-specific antigen, a high Gleason score, advanced pathological stage, metastasis, and biochemical recurrence-free survival [53]. Subsequent clinical data from hospitals have also identified the prognostic value of

HJURP in prostate cancer [54]. *In vitro* and *in vivo* experiments have confirmed the pro-proliferation effect of HJURP in prostate cancer by inducing cell cycle transition. Further investigations aimed to clarify the molecular mechanisms underlying these effects revealed that HJURP activated CDKN1A ubiquitin-dependent proteasome degradation through the GSK3β/JNK signaling pathway.

3.4 CANCER OF URINARY SYSTEM

3.4.1 Bladder cancer

Bladder cancer is a prevalent malignant cancer of the urinary system that involves several biological processes, mainly including the cell cycle pathway and chromatin regulation [55]. Previous study has identified that HJURP was markedly upregulated in bladder cancer tissues. Furthermore, knockdown of HJURP was shown to inhibit bladder cancer cell proliferation [56]. Subsequent mechanistic studies revealed that silencing HJURP could induce the generation of reactive oxygen species (ROS), apoptosis, and cell cycle arrest at G0/G1 phase through the peroxisome proliferator-activated receptors γ (PPARγ)-sirtuin 1 (SIRT1) pathway. High expression of HJURP was discovered in bladder urothelial carcinoma (BLCA), the most common type of bladder cancer, and was found to be a poor prognostic indicator [57]. Spearman analysis showed that HJURP was upregulated with genes related to the c-Jun N-terminal kinase (JNK)/signal transducer and activator of transcription 3 (STAT3) pathway, cell proliferation, and cell cycle. Further studies verified that HJURP activated the JNK/STAT3 signaling pathway to regulate cell proliferation, cell cycle, and apoptosis *in vitro*.

3.4.2 Renal cancer

Renal cancer is a malignant tumor of the urinary system, second to bladder cancer in terms of incidence and mortality, mostly renal cell carcinoma (RCC) [58, 59]. Unlike other cancers, HJURP was downregulated in RCC tissues and cell lines. The overexpression of HJURP reduced the viability and colony formation of RCC cell lines and induced apoptosis, cell cycle arrest at G0/G1 phase, and oxidative stress through the PPARγ/SIRT1 signaling pathway [60]. In contrast, kidney renal clear cell carcinoma (KIRC) is the most common subtype of RCC, and HJURP was identified as a hub gene positively associated with the metastasis, progression, and worse prognosis of KIRC [61, 62]. Furthermore, correlation analysis showed that HJURP was closely related to immune infiltration and senescence processes, implying its critical role in the TME, which requires further investigation [62, 63].

3.5 CANCER OF CENTRAL NERVOUS SYSTEM

Astrocytoma is the most common type of cancer in the central nervous system, and glioblastoma is its most malignant subtype [64]. HJURP was overexpressed in patients with astrocytoma and glioblastoma of different grades, which was closely associated with poor prognosis and tumor aggressiveness [65, 66]. Consistent with previous findings, knocking down of HJURP inhibited the viability and migration of glioblastoma cells by inducing cell cycle arrest, premature senescence, and apoptosis, without affecting non-tumor cells [65, 67, 68]. Additionally, silencing HJURP increased the sensitivity of glioblastoma cells to irradiation, leading to higher rates of apoptosis and cell death. Molecular studies have shown that in addition to its

interaction with CENP-A, HJURP was positively regulated by Kruppel-like factor 11 (KLF11) enhancing the proliferation and migration of glioblastoma cells [67, 68]. Therefore, targeting HJURP could be a potential adjunct therapy for the treatment of glioblastoma.

3.6 CANCER OF ENDOCRINE SYSTEM

Anaplastic thyroid cancer is a highly aggressive and deadly subtype of thyroid cancer that currently has limited therapeutic effect. Effective targeted therapy is urgently needed to improve outcomes for patients [69]. Recent research has identified HJURP as a potential therapeutic target, was upregulated in anaplastic thyroid cancer. However, further investigation is needed to verify its efficacy as a treatment option [70].

3.7 OTHER CANCERS

3.7.1 Multiple myeloma

Multiple myeloma is a type of blood cancer that is currently considered incurable. However, there is promising research on targeted drugs that could potentially overcome drug resistance and improve patient prognosis [71]. In t(4;14)-positive multiple myeloma, HJURP has been identified as a super-enhancer (SE)-associated gene that was frequently overexpressed and linked to cancer progression and poor patient outcomes [72]. Further research has revealed that the transcription of HJURP was regulated by the nuclear receptor-binding SET domain protein 2 (NSD2)/bromodomain-containing protein 4 (BRD4) complex, which activated SE activity upstream of the gene. Notably, knocking down HJURP has been shown to

inhibit cell growth by inducing apoptosis, suggesting that SE-driven HJURP could be a potential therapeutic target for t(4;14)-positive multiple myeloma. These findings offer hope for improving treatment options for patients with this type of blood cancer.

3.7.2 Thymic epithelial tumor (TET)

Recent research has shed light on the relationship between HJURP and TETs [73]. HJURP expression was primarily confined to the nucleus, although cytoplasmic localization was more commonly observed in B3- and C-type TETs than in other TET subtypes, and was positively associated with advanced Masaoka-Koga stage. In contrast, nuclear HJURP expression does not exhibit such correlations, suggesting that the subcellular localization of HJURP may have distinct functional implications.

4. SUMMARY AND PERSPECTIVES

Pan-cancer analysis has revealed that HJURP is frequently overexpressed in a significant number of human cancers, and is closely associated with poor prognosis and disease progression. Recent studies have further confirmed that HJURP overexpression promotes cell proliferation, metastasis, and drug resistance, which may be attributed to its involvement in repairing DNA damage to maintain the genomic stability of cancer cells. Correspondingly, silencing HJURP can induce apoptosis, cell cycle arrest, and senescence, leading to antitumor effects. In addition, inhibiting HJURP expression can increase the sensitivity of breast and ovarian cancers to chemotherapy and glioblastoma to radiotherapy [48, 51, 67]. On the other hand, in breast cancer patients, HJURP overexpression may help prolong survival after radiotherapy, but only to a limited extent compared to patients with lower

expression levels of HJURP [11]. However, the *in vivo* efficacy of HJURP as an antitumor target has only been tested in HCC, pancreatic, prostate, and ovarian cancers, and should be validated in other cancer types.

Furthermore, the oncogenic properties of HJURP and its underlying regulatory mechanisms were elucidated. Studies have shown that HJURP is involved in multiple pathways that are related to cell cycle, drug resistance, cell proliferation, DSB repair, apoptosis, oxidative stress and EMT in different human cancers (Table 1, Figure 4). However, variations in regulatory mechanisms of the identical pathway can occur across different cancer types such as the PPARγ/SIRT1 signaling pathway in RCC and bladder cancer. Among a number of downstream targets, it's worth noting that the interaction between HJURP and CENP-A plays a critical role in cell cycle arrest and cell death. Phosphorylation of HJURP is required for its centromeric recruitment and loading of $CenH3^{CENP-A}$ at centromeres by binding to DNA during the regulation of the cell cycle [44]. HJURP, identified as the CENP-A chaperone, contains a cyclin A binding site that can regulate specific inhibitory phosphorylation to maintain cell-cycle control of CENP-A assembly [10]. Knockdown of HJURP impairs CENP-A deposition and maintenance at centromeres in cell mitosis, which leads to abnormal chromosome instability and separation defects and could subsequently induce senescence and death of cancer cells [8, 74, 75]. HJURP depletion also represses CENP-A levels that can induce cellular senescence through the p53-dependent pathway [76]. The suppression of HJURP could be exploited to induce senescence, and its combination with senolytic agents is now considered a promising

anticancer therapy [77]. However, despite its association with diverse immune signaling pathways and regulation of multiple immune cell infiltrations, the precise functions of HJURP on immune regulation remain elusive and need further exploration.

The biological functions of HJURP vary depending on the type of cancer and subcellular location. HJURP overexpression is generally associated with poor clinical outcomes and promotes tumorigenesis in most cancers, while contrary roles of HJURP have been observed according to database analysis in some cancers and it has been confirmed to act as a cancer suppressor in RCC, albeit with differences among RCC subtypes [60, 62]. Likewise, downregulation of HJURP expression caused by HJURP polymorphism may lead to susceptibility to HCC [29]. These findings suggest that HJURP may play a dual role in cancer and more evidence is needed to support this hypothesis.

The localization of HJURP expression has been a topic of disagreement among various studies, with different cancer cell types displaying varying molecular functions. For example, in U2OS cells, serous ovarian cancer cells, and t(4;14)-positive multiple myeloma cells, HJURP has been observed to localize in the nucleus [8, 9, 12, 72]. HJURP has been further found to co-localize with ER and microtubules in U2OS cells [15]. However, in various cancer cells, including HCC, prostate cancer, and breast cancer, HJURP is mainly expressed in the cytoplasm [34, 48, 53, 54]. In CRC, HJURP has been located in the cytoplasm and/or cell membrane [41], while in gliomas, HJURP immunoreactivity has been observed in both the

nucleus and cytoplasm, increasing with the grade of gliomas [64]. HJURP nuclear expression was more positive in epithelial and lymphoid cells, while cytoplasmic HJURP was positive in B3- and C- type TETs and associated with nuclear and cytoplasmic CENP-A [73]. The observed variations in the localization of HJURP imply its involvement in diverse functions, since HJURP is functionally associated with CENP-A, which leads to poor prognosis in human cancers when expressed in the nucleus, but a better prognosis in a small subgroup of patients with TETs when expressed in the cytoplasm [73, 78]. Further investigation is needed to advance our understanding of HJURP's complex mechanisms in cancer.

In conclusion, our study highlights the critical role of HJURP in cancer progression and suggests that HJURP may serve as a potential biomarker for predicting patient outcomes and as a novel therapeutic target. Therefore, regulating HJURP levels or identifying HJURP inhibitors may be promising strategies for cancer treatment.

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Competing interest

The authors declare that they have no competing interests.

Figure legends

Figure 1 The expression of HJURP in human tumor and normal tissues. The expression of HJURP is higher in tumor tissues than in normal tissues for the following types of cancer: BLCA, BRCA, CESC, CCA, COAD, ESCA, GBM, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PCPG, PRAD, READ, STAD, and UCEC.

Figure 2 The relationship between the expression of HJURP and clinical prognosis. The Kaplan-Meier method was used to analyze OS and DFS based on HJURP gene expression.

Figure 3 The relationship between the expression of HJURP and pathological stage of tumor. Violin plots of HJURP were used based on the patient's pathological stage.

Figure 4 The oncogenic regulation of HJURP and its downstream substrates.