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Research Progress of CENPA and Cancer

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Abstract

Abnormal cell division leading to chromosomal instability is a hallmark of cancer development. Accurate chromosome classification Lysis plays an important role in cell division, and the centromere is the key to accurate chromosome separation. Centromeric protein A CENPA is a centromere-specific histone H3-like variant gene and is also the most studied in the centromere protein family. A wide range of factors are overexpressed in various cancers. Overexpression of CENPA may lead to centromere heterochromatin along chromosome arms. Diffusion leads to microtubule kinetochore anchoring defects, ultimately resulting in genomic instability. Therefore, exploring the relationship between CENPA overexpression and the relationship between cancer progression is of great significance for finding new targeted treatment methods.

Keywords

Centromere, Centromere Protein A, Cancer, Chromosomal Instability

1. Introduction

In organisms, the transmission of genetic material requires the correct separation of chromosomes during cell division, and the failure of this process can lead to chromosome instability (CIN). CIN is an important factor in the occurrence of cancer, and centromere is the key to ensuring correct chromosome segregation [1]. The currently discovered members of the centromere protein family include centromere proteins (CENPs) A, B, C, D, E, F, etc. [2]. Among them, CENPA is a histone H3 variant protein that plays an important role in chromosome separation, cell division, cell cycle regulation, and tumorigenesis [3], therefore, CENPA has gradually gained attention from scholars in the field of oncology during the occurrence and development of malignant tumors, and has become one of the new

research hotspots. This article reviews the role of CENPA in the occurrence and development of malignant tumors, its abnormal expression, and its relationship with prognosis. It explores the potential carcinogenic mechanisms of CENPA in various malignant tumors and its relationship with clinical and pathological indicators, aiming to further reveal CENPA as a potential biological target for malignant tumors and provide a theoretical basis.

2. Structure and Function of CENPA

2.1. Composition of Centromeres

Centromere is the complex structure of DNA protein, located in the heterochromatin region, and plays an important role in the division of sister chromatids in the metaphase of mitosis in eukaryotes. It includes three domains: central domain, kinetochore domain and paring domain. The cooperation of these three domains ensures that sister chromatids are divided into two by centromere and equally distributed to daughter cells [4]. Centromeric proteins are the protein components of the centromere, including two types: constitutive proteins and facultative proteins. The basic proteins mainly include CENP-A, CENP-B, CENP-C, and CENP-D, which run through the entire cell cycle. And facultative proteins include CENP-E CENPF, Kinesin, tubulin, cytoplasmic dynein, etc. [5], which only briefly function during a certain period of mitosis. Centromeric proteins are involved in the precise assembly and location of centromere in time and space, ensuring the correct separation and equal distribution of sister chromatids and maintaining the stability and fidelity of the genome.

2.2. Structural Characteristics of Centromere Protein A

Centromeric protein A (CENP-A) is one of the fundamental proteins, which was first described in patients with scleroderma [6]. Later, William Earnshaw and Naomi Rothfield isolated, purified, and identified these three types of centromere proteins, including CENP-A, CENP-B, and CENP-C [7]. CENPA, as one of the centromere protein families, is located at 2p24-p21. Its genomic DNA is 8534 bp in length, including 4 introns and 5 exons. The structural features of CENP-A include two main domains: the NH2 terminal domain and the COOH terminal domain containing 93 amino acids. Due to the 62% homology between the COOH terminal domain and nucleosome histone H3, which is one of the basic units of chromosomes, CENP-A is also known as a variant of H3 [8].

2.3. Function and Mechanism of Action of Centromere Protein A

The growth and development of cells cannot be separated from the process of mitosis, which is divided into interphase and division phase: DNA replication and related protein synthesis are completed in the interphase to prepare for subsequent mitosis. The splitting period includes the early, middle, late, and late stages. As the interphase gradually transitions to the pre-mitotic stage, chromatin short-

ens and thickens to form chromosomes, which gradually radiate from the centrosome into spindle filaments (also known as spindle filaments), which gradually transform into spindle bodies. After entering the middle stage, the centrioles are arranged on the equatorial plate. When cell mitosis enters the late stage from the mid-stage, the centromere splits into two and moves down to the two poles of the cell under the traction of the spindle fibers. In the final stage of mitosis, the spindle disappears and forms the cell wall. During the cell cycle, centromere protein A plays an important role.

2.3.1. Localization of Centromere Protein A on the Centromere

CENP-A is one of the centromere protein families and the only variant of histone H3, located in the centromere region. It is typically expressed conservatively during normal cell mitosis to ensure genomic stability. However, high expression of CENPA gene is found in many tumors. This high expression makes centromere mispositioning, and the corresponding sister chromatids appear separation defects. Chromosomes are clustered and unstable, resulting in aneuploidy [9]. Further research has found that FBW7 regulates the localization of CENPA gene to filaggrin, thereby affecting chromosome stability. As a tumor suppressor, Fbw7 belongs to the F-box protein family and is an important component of the SCF (Skp1-PUL1-F-box protein) E3 ubiquitin ligase complex. F-box protein can specifically bind to various proteins, including cyclin E1 [10] [11]. After FBW7 protein expression loss, activation of cyclin E1/CDK2 causes excessive phosphorylation of the Ser18 residue of CENPA gene, leading to disrupted centromere localization and promoting the occurrence of CIN and tumor progression [12]. Therefore, high expression of CENPA gene promotes centromere mislocalization, which is one of the reasons for tumor induction and is related to the occurrence and development of tumors.

2.3.2. Centromeric Protein A Mediates Cell Cycle

The normal progression of mitosis relies on the precise regulation of centromere proteins (including CENPA) during the mitotic period. The CENPA gene is not expressed during the S phase of mitosis, and only assembles and assembles into the filament during the M phase. Among them, HJURP is a chaperone protein of CENP-A [13], and the absence of HJURP can cause assembly defects of CENPA protein in the M phase [14]. Mis18 complex is an important group of proteins targeted by CENPA and its chaperone protein HJURP. It is a complex composed of three components (including MIS18α, MIS18-β and M18BP1). When Mis18 mutation occurs, it can inhibit CENPA's assembly and synthesis of filaggrin, resulting in chromosome centromere mislocation, sister chromosome misseparation, interphase micronucleus and other defects [15]. Abnormal expression of CENPA gene has been found to affect the progression of cell division cycle in various tumors. In lung cancer, knocking down the CENPA gene leads to a decrease in expression, resulting in an increase in the proportion of G0/G1 phase tumor cells and inhibition of cell mitosis [16]. In renal cancer cells, the CENPA gene can

regulate the cell cycle through the Wnt/β-Catenin signaling pathway. Overexpression of the CENPA gene activates the downstream target gene CCND1 of the Wnt/β-Catenin signaling pathway, accelerating the transition from G0/G1 phase to S phase and promoting the proliferation of renal cancer cells. In summary, abnormal expression of CENPA gene can regulate the cell cycle progression of mitotic cells.

3. Research Progress of CENPA Gene in Tumors

3.1. Research Progress of CENPA in Renal Cell Carcinoma

Renal cancer can be divided into clear cell carcinoma, chromaffin cell carcinoma, spindle cell carcinoma, collecting duct carcinoma, and eosinophilic cell carcinoma based on histological types. Smoking, obesity, environmental and occupational exposure are the main risk factors for kidney cancer [17]. Previous studies have found that abnormal expression of tumor suppressor genes such as PTEN, P53, RB1, and ERBB4 affects the occurrence and development of renal cancer tumors [18] [19]. Wang *et al.* [20] found in their study of clear cell renal cell carcinoma that compared with adjacent normal tissues, the expression level of CENPA in tumor tissues was significantly increased; Bioinformatics analysis in the TCGA database has preliminarily confirmed that the CENPA gene is an upregulated gene, overexpressed in renal cell carcinoma, and may serve as one of the candidate biomarkers for the diagnosis, treatment, and prognosis of renal cell carcinoma [21]. The CENPA gene promotes the occurrence, progression, and metastasis of renal cell carcinoma by regulating the Wnt/β-Catenin signaling pathway. Overactivation of the Wnt/β-catenin signaling pathway can cause abnormal cell proliferation and differentiation, leading to tumor formation [22]. It can be inferred that CENPA may be a potential therapeutic target for clear cell renal cell carcinoma. Li *et al.* [23] determined through immunohistochemistry that CENPA is significantly upregulated in papillary renal cell carcinoma tissue, and its upregulation is associated with pathological TNM staging and clinical staging. Meanwhile, survival analysis suggests that overexpression of CENPA is closely associated with poor prognosis, which may affect the prognosis of patients with papillary renal cell carcinoma by regulating the levels of B cells and CD8+ T cells. Therefore, the CENPA gene can regulate the cell cycle through the Wnt/β-Catenin signaling pathway, mediating the proliferation, invasion, and metastasis of tumor cells [20].

3.2. Research Progress of CENPA in Colorectal Cancer

Colorectal cancer is one of the common malignant tumors in the digestive tract. Its incidence rate ranks third in the global cancer, and its mortality rate ranks second [24]. Comprehensive treatment based on surgery is the main treatment for colorectal cancer. However, 50% of patients still relapse and migrate despite five years of standardized treatment [25]. With the development of medical technology and the improvement of socio-economic level, people are paying more and more attention to the occurrence and development of tumors. At present, screen-

ing for colorectal cancer mainly relies on tumor serum biomarker testing. However, due to the susceptibility of serological test results to specimen collection and storage, drug concentration, biological factors, and low specificity, it is difficult to use for early diagnosis of tumors. Patients with colorectal cancer are often in the advanced stage when seeking medical treatment, missing the optimal treatment time and resulting in poor treatment outcomes. Although surgery and adjuvant chemotherapy can improve the survival rate of colorectal cancer patients, their early metastasis rate and postoperative recurrence rate are high, and the overall survival of patients is still relatively short [26].

Tomonaga *et al.* first verified the overexpression of CENPA gene in colon cancer from an in vitro experiment, and found that after overexpression of CENPA gene, the centromere was mislocated in the non-chromatin region, and sister chromatid division was disordered [27]. Further research has found that sirtuins SIRT7 can regulate CENPA gene assembly and affect the occurrence and development of colorectal cancer. Sirtuins are a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase family and one of the only Sirtuins protein families located in the nucleolus. They regulate various biological processes by targeting histones, transcription factors, metabolic enzymes, and many protein substrates [28]. Therefore, Sirtuins can regulate cell growth and development, metabolic activity, and genome stability through multiple pathways. Under physiological conditions, SIRT7 can regulate the acetylation status of histones, ensuring the correct assembly of CENP-A with the pre nucleosome CENP-A: H4 complex, which is beneficial for the enrichment of centromere proteins in the G1/S phase of mitosis. *In vitro* cell experiments have shown that downregulating SIRT7 inhibits the assembly of CENP-A nucleosomes and the production of aneuploidy, while also activating the Wnt signaling pathway and upregulating the expression of colorectal cancer-related genes (including LRP5, Fzds, Apcdd1, and Wnts). This indicates that the abnormal expression of SIRT7 promotes chromosome misdivision and the production of aneuploidy, and may promote the occurrence and development of colorectal cancer by activating the Wnt signaling pathway [29]. The CENPA gene can also transcriptionally activate the expression of KPNA2 to regulate the energy metabolism and biological behavior of tumor cells in colon cancer patients. Compared with normal cells, tumor cells undergo significant changes in glucose metabolism: tumor cells accelerate their uptake of glucose, and the rate of glycolysis significantly increases. However, the products of glycolysis are not transferred to mitochondria for electron transfer and oxidative phosphorylation, but are directly used to produce lactate [30]. This change in energy metabolism can quickly supply energy for the growth and development of tumor cells, and can also consume glucose to provide energy in the hypoxic tumor microenvironment, which helps with the value-added metabolism of tumor cells. In this energy metabolism process, riboflavin alpha 2 (KPNA2) is a member of the nuclear mucin alpha (also known as input alpha) protein family [31], consisting of three structures: a short C-terminus, an N-terminal hydrophilic domain, and a

central region [32]. The N-terminus is the nuclear mucin beta 1 (KPNB1, also known as Importin beta 1) binding domain, which participates in the regulation of energy metabolism and the nuclear-cytoplasmic transport pathways of various tumor-associated proteins. Previous studies have found that overexpression of KPNA2 in various tumor tissues can increase glucose uptake by tumor cells and accelerate the glycolysis pathway. Overexpression of CENPA in colon cancer can activate the promoter region of KPNA2, accelerating energy uptake and glycolysis pathways, providing more energy sources for tumor cells, and providing an energy basis for the proliferation, invasion, and metastasis of colon cancer cells [32].

3.3. Research Progress of CENPA in Breast Cancer

Breast cancer is one of the most common malignant tumors in women, and its risk factors for inducing breast cancer include the continuous exposure of related factors such as early menarche, late menopause, infertility, old age and primipara, as well as obesity [33]. Rajput *et al.* conducted immunohistochemical analysis of 63 breast cancer tissues and 20 normal breast tissues for the first time, and found that CENPA gene was overexpressed in breast cancer. After follow-up of breast cancer patients, it was found that the three-year tumor free survival rate of patients with CENPA gene overexpression was worse than that of patients with low expression, indicating that CENPA gene overexpression was positively correlated with the malignancy of tumors, and negatively correlated with prognosis [34]. To explore the mechanism of CENPA gene in breast cancer, we found that CENPA gene can affect the response of breast cancer to chemotherapy drugs by regulating PI3K/Akt/mTOR pathway. The PI3K/Akt/mTOR pathway plays an important role in various tumors, regulating cell cycle progression, intracellular metabolism, angiogenesis, and tumor cell proliferation, invasion, metastasis, apoptosis, etc. [35]. When insulin or insulin-like growth factor binds to cell membrane receptors (such as G protein-coupled receptor GPCR or tyrosine kinase receptor), it can activate PI3K and transfer AKT (also known as protein kinase B, or PKB) to the cell membrane, thereby changing the conformation of AKT and phosphorylating target proteins in the cytoplasm and nucleus, stimulating the malignant biological potential of tumor cells [36]. Overexpression of CENPA gene in breast cancer can upregulate PI3K/Akt/mTOR pathway, regulate cell cycle and promote malignant biological behavior of tumor, while down regulation of CENPA gene can target PI3K/Akt/mTOR pathway to increase sensitivity of breast cancer to chemotherapy response [37]. In view of the increasingly in-depth research on PI3K/Akt/mTOR pathway by CENPA, in recent years, rapamycin analogues (including tirolimus and everolimus), inhibitors targeting PI3K/Akt/mTOR pathway, can inhibit the mTOR complex, increase the sensitivity of breast cancer to chemotherapy drugs, and further research is still needed in drug targeted treatment of breast cancer, in order to broaden the treatment methods for breast cancer patients, improve the prognosis of patients with advanced breast cancer, and improve the quality of life of

patients. The MBNL1-AS1/ZFP36/CENPA axis also plays an important role in the genesis and development of breast cancer. LncRNAs are a class of non-coding RNAs (NcRNAs). Although most NcRNAs do not encode proteins, studies have found that most NcRNAs can interact with other regulators and proteins to regulate biological behaviors such as tumor cell proliferation, invasion, and metastasis, and also play an important role in the cell cycle [38]. MBNL1-AS1 is a kind of negative regulated LncRNAs in breast cancer, which combines with RNA binding protein (RBP) to regulate the expression of downstream target genes: MBNL1-AS1 shows low expression in breast cancer. After overexpression of MBNL1-AS1 in breast cancer cell line MDA-MB-231, it can downregulate the expression of CENPA and inhibit the proliferation, invasion and metastasis of breast cancer cells. And during the mitotic cycle, the ratio of S and G2/M phase cells decreases, while the ratio of G0/G1 phase cells increases. In addition, in estrogen-positive (ER positive) breast cancer patients, CENPA is also an important prognostic marker. The higher the expression of CNEPA gene, the lower the 5-year distant recurrence-free survival rate (DRFS) of breast cancer patients. However, in ER-negative breast cancer patients, the expression of CENPA is higher than that in ER-positive breast cancer patients, but it is not an independent prognostic factor. One explanation is that FOXM1 is upregulated through ER signaling pathway in ER-positive breast cancer. FOXM1 itself, as an independent prognostic factor, increases the expression of CENPA [39]. Therefore, CENPA gene is overexpressed in breast cancer and regulates the biological behavior of breast cancer cells through a variety of signal pathways. All evidence indicates that CENPA gene is an important marker in the development of breast cancer.

3.4. Research Progress of CENPA in Ovarian Cancer

Ovarian cancer is also one of the most common malignant tumors in women, with approximately 313,000 new cases and 207,000 deaths worldwide each year [40]. Early symptoms are not obvious in patients, and by the time they are diagnosed, they often have already metastasized, resulting in poor treatment outcomes. Finding early diagnostic and prognostic markers is of great significance for improving the survival rate of ovarian cancer patients [41]. HJURP is crucial for the correct deposition of CENPA, playing an important role in DNA repair and proper chromosome segregation. Overexpression of HJURP is associated with poor prognosis in various cancers [42] and has been used as a prognostic biomarker for cancers such as ovarian cancer [43] and prostate cancer [44]. Zhang *et al.* [45] found that low expression of HJURP causes mitochondrial damage through the CENPA pathway, leading to apoptosis of ovarian cancer cells; HUJRP directly targets CENPA and promotes ovarian cancer progression through CENPN. This provides new clues for the diagnosis and treatment of ovarian cancer.

MYBproto oncogene like 2 (MYBL2) is a transcription factor that plays an important role in regulating cell cycle, survival, and differentiation in medulloblastoma. Currently, high expression of MYBL2 has been detected in various cancers,

indicating its ability to drive cancer occurrence and/or progression. Han *et al.* [46] found in their study of ovarian cancer that CENPA levels decreased with knockdown of MYBL2 in SKOVE cell lines, indicating a positive correlation between MYBL2 and CENPA expression. MYBL2 can directly regulate the expression of CENPA by binding to its promoter region, thereby promoting the proliferation of ovarian cancer cells. The proliferative role of MYBL2/CENPA signaling pathway in ovarian cancer cell lines suggests that it may be a potential therapeutic target for ovarian cancer.

3.5. Research Progress of CENPA in Lung Cancer

Lung cancer is one of the common malignant tumors, and in recent years, lung adenocarcinoma has become the most common type of tumor, followed by squamous cell carcinoma and large cell carcinoma [47]. As one of the main components of centromere protein, centromere A (CENPA) plays an important role in regulating the cell cycle and ensuring the correct separation of chromosomes. It has also been extensively and deeply studied in lung cancer. Wu *et al.* collected lung cancer tissues and adjacent tissues from 20 lung cancer patients for RT qPCR and Western blotting experiments, and preliminarily confirmed that the expression of CENPA gene in lung adenocarcinoma was significantly higher than that in adjacent tissues. Subsequently, immunohistochemical analysis of 309 lung cancer patient tumor tissue samples revealed that the differential expression of CENPA gene was related to the staging, grading, pleural infiltration, Ki-67 expression, and P53 mutation of lung cancer. It is speculated that CENPA gene may serve as an important molecular marker of lung cancer, and its abnormal expression may regulate the occurrence and development of lung adenocarcinoma. In addition, the P53 gene, as a tumor suppressor gene, can regulate cellular stress response, and induce cell cycle arrest, aging, and apoptosis [48] [49]. The expression of CENPA gene is significantly correlated with P53 mutation, indicating that the P53 pathway may be involved in the regulation of CENPA gene on mitosis [50]. Early studies found that after knockout of CENPA gene in mouse embryonic cells, its proliferation ability decreased and apoptosis increased [51], suggesting that CENPA gene may also regulate the biological behavior of lung cancer cells in lung cancer. Downregulation of CENPA gene expression in cell experiments can inhibit the proliferation, invasion, and metastasis ability of lung cancer A549 and PC-9 cell lines, and increase apoptosis. Further research has found that knocking down the CENP-A gene can upregulate the expression of negative regulatory factors (including p21, p27, and CHK2). The proportion of lung cancer cells staying in the G0/G1 phase increases, while the proportion staying in the S and G2/M phases decreases, indicating that the mitotic process is inhibited after knocking down the CENPA gene [16]. These pieces of evidence fully demonstrate that the CENPA gene can affect the mitotic process of tumor cells by regulating cell cycle-related regulatory factors. In addition, the regulatory mechanism of CENPA gene on lung cancer stem cells has also been studied. Tumor stem cells have stem-like characteristics, in-

cluding self-renewal, abnormal differentiation, and proliferative potential [52], which play an indispensable role in the occurrence, development, drug resistance, and recurrence of tumors. Using bioinformatics analysis, key genes related to lung cancer (including CCNB1, CCNA2, TTK, CENPA, PRC1, NEK2) were screened and subsequently explored. It was found that the CENPA gene was overexpressed in lung cancer cells and significantly correlated with prognosis. Knocking down the CENPA gene in lung cancer A549 cell line inhibited the proliferation ability of tumor cells, and the expression of regulatory molecular markers related to tumor stem cells (CD44, EpCAM, SOX2, C-MYC) was also downregulated [53]. With the deepening of research on CENPA gene in lung cancer, CENPA gene may become an important molecular target for regulating lung cancer, which broadens the direction for the diagnosis and treatment of lung cancer.

3.6. Research Progress of CENPA in Liver Cancer

Hepatocellular carcinoma (HCC) has risen to become the fourth-largest malignant tumor worldwide due to its high invasiveness [54]. Fatty liver, alcoholic liver, and hepatitis virus infection are the three main risk factors for hepatocellular carcinoma [55]. Despite extensive research on liver cancer, the understanding of its etiology and pathogenesis is still insufficient, and the treatment efficacy for advanced liver cancer patients is limited [56]. Therefore, it is particularly important to search for new therapeutic targets for liver cancer patients. Previous studies have shown that CENPA is abnormally overexpressed in HCC tissues, and knocking down CENPA can block the G1 phase and reduce the proliferation ability of HCC cells [57]. Therefore, overexpression of CENPA may promote the progression of HCC. Li *et al.* [58] found that overexpression of CENPA is associated with advanced histological grading, serum HBsAg positivity, high Ki-67 expression levels, and p53 positivity. Zhang *et al.* [59] found that upregulation of CNEPAmRNA is negatively correlated with overall survival and disease-free survival in HCC. There are literature reports on the potential mechanism of CENPA gene in the occurrence and development of liver cancer. In the mammalian cell mitotic cycle, the G1 and S phases of mitosis are co-regulated by cyclin-dependent kinase (CDK) [60]. P21waf1, as one of the CDK inhibitors, plays a key role in regulating the G1 and S phases of mitosis [61]. Skp2 is an important regulatory factor of the NUCKS1-Skp2-p21/p27 axis. Upregulation of Skp2 expression reduces the expression of p21 and p27, accelerates the G1/S transition of the mitotic cycle, accelerates cell division speed, and enhances proliferation ability. On the contrary, the process of mitosis is inhibited [62]. Knocking down the CENPA gene in liver cancer cells increases the expression of Chk2 and P21waf1, while the expression of Skp2, RAD51, and CCNG1 decreases. Tumor cells are trapped in the G1 phase, and cell proliferation ability decreases, thereby regulating the biological behavior of liver cancer HepG2 cell line, reducing its proliferation ability and increasing cell apoptosis. After overexpression of the CENPA gene, the expression of Skp2, RAD51, and CCNG1 increased, while the expression of Chk2 and P21waf1 decreased, promoting the pro-

liferation of liver cancer cells [58]. These pieces of evidence indicate that the CENPA gene regulates the process of mitosis by mediating the expression of cell cycle-related regulatory factors. HJURP is a molecular partner of CENP-A, with a short and conserved N-terminal domain, also known as CBD (CENP-A binding domain). It forms the HJURP-CENP-A/H4 complex with CENP-A and participates in the deposition and enrichment of CENPA genes during the G1 phase of mitosis [63]. Research has shown that the use of RT qPCR experiments and immunohistochemistry methods has revealed overexpression of HJURP in liver cancer tissues. HJURP is also overexpressed in liver cancer HuH-7 and SK-HEP-1 cell lines. Knocking out HJURP reduces the proliferation, invasion, and metastasis ability of liver cancer cells, increases apoptosis, and inhibits the mitotic process of liver cancer cells [64]. In addition, previous literature has also reported a decrease in CENPA gene expression after knocking down HJURP. Therefore, the abnormal expression of HJURP is also involved in the regulation of mammalian mitosis by CENPA gene.

3.7. Research Progress of CENPA in Osteosarcoma

Osteosarcoma is a common malignant bone tumor, commonly affecting children and adolescents [65]. Its causes are related to age, gender, race, genetics, and other factors [66]. Due to its high invasiveness, despite extensive research on the causes and mechanisms of osteosarcoma, its prognosis is still poor, with a five-year survival rate of less than 70% [67]. Bioinformatics analysis of the CENPA gene revealed that it is an important molecular marker for osteosarcoma, and its overexpression may regulate osteosarcoma cells through the PI3K Akt signaling pathway [68]. Further application of RT qPCR and Western blotting experiments confirmed that the CENPA gene is significantly overexpressed in osteosarcoma tissues. Immunohistochemical staining of 123 osteosarcoma specimens revealed a significant correlation between CENPA expression and osteosarcoma tumor size, neoadjuvant chemotherapy efficacy, local recurrence/lung metastasis, Ki-67 positivity rate, and P53 mutation. These research results suggest that the expression of CENPA gene may be involved in the occurrence and development of osteosarcoma, and the median overall survival and recurrence-free survival of patients with high CENPA expression in osteosarcoma are significantly lower than those with low CENPA gene expression. Therefore, it can be inferred that the CENPA gene can serve as an important molecular target for the occurrence and development of osteosarcoma. In addition, the FOXM1 gene affects the occurrence and development of osteosarcoma by regulating the expression of downstream target gene CENPA. The Forkhead Box (Fox) transcription factor family is composed of over 50 mammalian proteins [69], and the Forkhead Box M1 (FOXM1) gene is a key gene for G1/S phase transition, playing a crucial role in regulating the process of mitosis. After knocking down FOXM1 in the osteosarcoma U2OS cell line, the expression of the mitotic regulatory gene CENPA, which targets FOXM1, also decreased, the number of S phase cells decreased, the number of G2/M phase cells increased, and

more osteosarcoma cells stagnated in the S phase [70].

4. Summary and Prospect

An important characteristic of cancer is uncontrolled cell division. As a key regulator of the normal process of mitosis, the centromere protein A gene (CENPA) can ensure the correct separation of sister chromatids and their uniform distribution in daughter cells, thus ensuring the stability of the genome. However, in most solid tumors (including ovarian cancer, kidney cancer, rectal cancer, breast cancer, lung cancer, liver cancer, etc.), the high expression of centromere protein A gene (CENPA) has been found, and it participates in the biological process of malignant tumors through a variety of signal pathways. However, CENPA has not yet entered the clinical stage as a therapeutic and diagnostic target for malignant tumors. This research progress helps to promote CENPA as a cancer target and provides more options for clinical decision-making.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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