Original Article
Human coilin interacting nuclear ATPase protein in cancer: uncovering new insights into pathogenesis and therapy

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Abstract: A deeper understanding of tumor pathogenesis has revolutionized cancer treatment strategies. The discovery of human coilin interacting nuclear ATPase protein (hCINAP) and increasing experimental research over the past 15 years have provided us with new insights into the diagnoses, prognoses, and therapeutic approaches of cancer. In the current review, hCINAP's effect on tumor growth, cell viability, invasion, metastasis, and drug resistance is summarized. In addition, an overview is given of the underlying mechanisms involved, including regulation of signaling pathways, ribosome biogenesis, metabolism, as well as DNA damage repair. Finally, hCINAP-based therapeutic approaches are examined, with the goal of improving efficacy of cancer treatments. This review can, therefore, serve as a reference for further hCINAP-related research and clinical trials, and we advocate those approaches to be initiated without delay.

Keywords: hCINAP, cancer, pathogenesis, function, mechanism, therapy

Introduction

Human coilin interacting nuclear ATPase protein (hCINAP) was first identified as an isoform of adenylate kinases (AKs) (ATP: AMP phosphotransferases, EC 2.7.4.3) in 2005 [1]. Based on enzymatic analyses, researchers identified the adrenal gland protein AD-004, which was highly homologous with other AKs, especially AK5, as a sixth AK isoform. AKs belong to the nucleoside monophosphate kinase family, which catalyze reversible phosphate transfers between nucleoside triphosphates and monophosphates and participate in nucleic acid synthesis [2]. For example, AKs induce the transfer of the γ-phosphate group from adenosine triphosphate (ATP) and dATP to adenosine monophosphate, thus releasing two molecules of adenosine diphosphate [3]. Thus, AKs play an important role in cellular metabolism and energy release through phospho-transfer networks.

AKs are also known to modulate disease through their participation in diverse cellular processes [3]. In the past three years, the biological functions of AK family members, as well as their association to disease, have been extensively elucidated. AK1 has been reported to regulate a range of cellular and physical activities in a variety of organisms, including the Jingyuan Chicken, *Schistosoma japonicum* schistosomula, and humans [4-6]. Variants of AK2 in the human genome lead to reticular dysgenesis, hematopoietic defects, and mitochondrial dysfunction [7-10]. In addition, AK2 was identified as a candidate biomarker for cancer prognosis as well as for late normal tissue radiotoxicity [11, 12]. Similarly, AK3 [13], AK4 [14-17], and AK5 [18] have also been demonstrated to be involved in tumorigenesis and cancer progression. The roles of the AK enzymes are summarized in **Table 1** and can be divided into two categories: those that have an oncogenic effect, including AK2, AK4, and AK5, and those

Table 1. The role of other AK family members in human cancers

Adenylate kinase	Types of cancers involved	Expression	Function
AK1	Lung adenocarcinoma	↑	Correlated with good prognosis
AK2	Lung adenocarcinoma	↑	Proliferation↑ Migration↑ Invasion↑ Autophagy↑ Apoptosis↓
AK3	Breast cancer	↓	Correlated with good prognosis
AK4	Lung cancer	↑	Cisplatin-sensitizing↓
	Breast cancer	↑	Proliferation↑ Invasion↑ Growth↑ Metastasis↑
	Bladder cancer	↑	Proliferation↑ Growth↑ Metastasis
	Lung adenocarcinoma	↑	Metastasis↑
	Esophageal cancer	↓	Radioresistance↓
	Osteosarcoma	↓	Multi-chemoresistance↓
AK5	Gastric cancer	↑	Apoptosis↓ Autophagy↑ Proliferation↑

AK, adenylate kinase.

Table 2. Expression and function of hCINAP in human cancers

Cancer types	hCINAP expression	Function	Reference
AML	↓	DR↑	[25]
Breast cancer	↑	--	[27]
Osteosarcoma	↑	Tumor growth↑ DR↑	[27]
Colorectal cancer	↑	Cell motility↑ DR↑	[26]
Colon cancer	↑	--	[27]

AML, acute myeloid leukemia; DR, drug resistance; hCINAP, human coilin interacting nuclear ATPase protein.

that have an antitumor effect, including AK1 and AK3. Also of note, being the downstream target of microRNAs, AK4 was also confirmed to be downregulated in cancer tissues, and AK4 silencing promoted radio-resistance and multi-chemoresistance of cancer cells, which indicated that the role of AK4 in cancer was controversial [19, 20].

Unlike the other AKs, AK6 has a unique sequence, crystal structure, nuclear localization, and enzymatic characteristics. The human AK6 gene is located on chromosome 12p11, is 1,119 base pairs in length, and has four exons and three introns [1]. The AK6 protein contains three functional domains, including a core domain for ATP binding, a nucleoside monophosphate (NMP)-binding domain, and a lid domain. The NMP-binding domain and the lid domain move during enzymatic cycles [1]. Located in the nucleus, with a wider range of phosphate donors compared to other AKs, including cytidine triphosphate and uridine triphosphate, AK6 has a unique functional position and, therefore, potential for clinical appli-

cation [1]. AK6 orthologs have been identified in a broad range of organisms, including *Caenorhabditis elegans*, *Drosophila melanogaster,* and *Arabidopsis thaliana* [21-23]. The *C. elegans*-derived AD-004-like protein (ADLP) shares approximately 40% homology in its sequence with human AK6, and the depletion of ADLP causes worm growth inhibition [21]. *Arabidopsis* AK6 was identified as a key growth factor for plant stem, indicating the importance of AK6 in diverse species [23].

Due to its high ATPase activity and tight interaction with coilin, which is a marker protein of Cajal bodies, AK6 was renamed as hCINAP and further examined [24]. The hCINAP gene transcript has two 5'-terminal exons that are shared with TAFIID32; however, these two proteins do not share amino acid sequences [24]. Although the function of hCINAP in human diseases has not been adequately explored, a multitude of recent articles have provided emerging evidence that it is a promising candidate in cancer treatment, describing hCINAP's oncogenic role [25-27]. Here, we review the regulatory role of hCINAP in tumor progression as well as the mechanisms involved. In addition, its potential clinical value is discussed, which may provide new insights into the precise diagnosis, prognosis, and therapy of cancer.

Regulation of tumor progression

hCINAP has been identified as an oncogenic factor and is aberrantly expressed in some human cancers. It exerts its cancer-promoting effects via regulating tumor growth, cell viability, invasion, metastasis, and chemosensitivity

(**Table 2**). In this section, we will focus on the oncogenic abilities of hCINAP.

Tumor growth and cell viability

Rapid tumor growth is caused by abnormal cell proliferation and the inhibition of apoptosis. In a recent study, hCINAP depletion was a specific rate-limiting factor during tumor growth [27]. In this study, the effect of hCINAP knockdown on insulin-dependent protein synthesis and tumor growth was evaluated. The results revealed that following hCINAP depletion, uptake of ^{35}S-methionine was not increased by insulin treatment, in contrast to the control group, which exhibited increased ^{35}S-methionine uptake. hCINAP knockdown significantly inhibited tumor growth, and this result was consistent with the MTT assay data. In addition, it was confirmed by fluorescence-activated cell sorting analysis (FACS) that hCINAP knockdown stimulated cell cycle arrest at the G1 phase, thus promoting cancer cell apoptosis while decreasing proliferation and inhibiting tumor growth.

Research studies involving apoptosis, necrosis, or drug discovery often rely on monitoring cell viability [28]. To investigate whether hCINAP influenced cell viability, researchers used FACS analysis to determine the effect of hCINAP knockdown on cell cycle progression in HeLa cells [29]. Interestingly, the number of cells in sub-G1 phase was increased, however the number of G0/G1 phase cells was not increased, indicating that hCINAP depletion did not immediately induce cell cycle arrest. Further, the activity of caspase 3, a predominant executioner caspase that carries out the demolition phase of apoptosis, increased more than two-fold after hCINAP depletion, resulting in a lowered cell survival rate. These results illustrate that hCINAP can play an essential role in cell viability. Therefore, it would be beneficial to pursue such studies on various cancer tissues.

Cell motility

Cell motility is a fundamental cellular activity that contributes to cancer cell invasion and metastasis. Cell motility enables cancer cells to travel from their primary colony to form new colonies in other tissues and organs via the blood and/or lymph vessels. Metastasis remains the primary threat for cancer-induced mortality [30]. hCINAP expression was found to be significantly higher in colorectal cancer tissues than in adjacent normal tissues [26]. In this study, wound-healing and transwell migration assays were conducted to evaluate hCINAP's ability to enhance cell motility. hCINAP depletion by short hairpin RNAs markedly impeded cancer cell invasion and migration, and hCINAP overexpression had the opposite effect. Similar results were also observed in colorectal cancer stem cells, where the overexpression of hCINAP enhanced the formation of tumorspheres [26].

Drug resistance (DR)

DR refers to the resistance that patients develop to available drug therapies. It remains an unresolved problem for the treatment of advanced cancer, despite great progress in cancer biology and therapies [31]. Therefore, investigating the mechanisms of DR is essential for improving cancer therapeutic strategies. hCINAP was reported to be the mediator of DR in acute myeloid leukemia (AML) [25]. Using a patient-derived xenograft AML mice model, researchers found that hCINAP knockdown resulted in increased cell apoptosis and decreased proliferation as well as higher chemosensitivity than that of the control group. Notably, after chemotherapy, the expression of hCINAP was increased in AML patients. AML cells developed DR as hCINAP was positively involved in maintaining genome integrity.

Related mechanisms

Downstream signaling pathways

Activation of numerous cellular signaling pathways closely correlate with tumor pathogenesis. Two signaling pathways have been shown to be targeted by hCINAP, including the p53 and NF-κB pathways (**Figure 1**).

p53 pathway

The *p53* gene is a well-known tumor-suppressor gene that controls tumor development by encoding a transcription factor, which is activated by physiological stress, such as genotoxic damage, oncogene activation, chemical insult, and ribosomal stress [32]. A recent study demonstrated that hCINAP induced p53 pathway inhibition via complex mechanisms
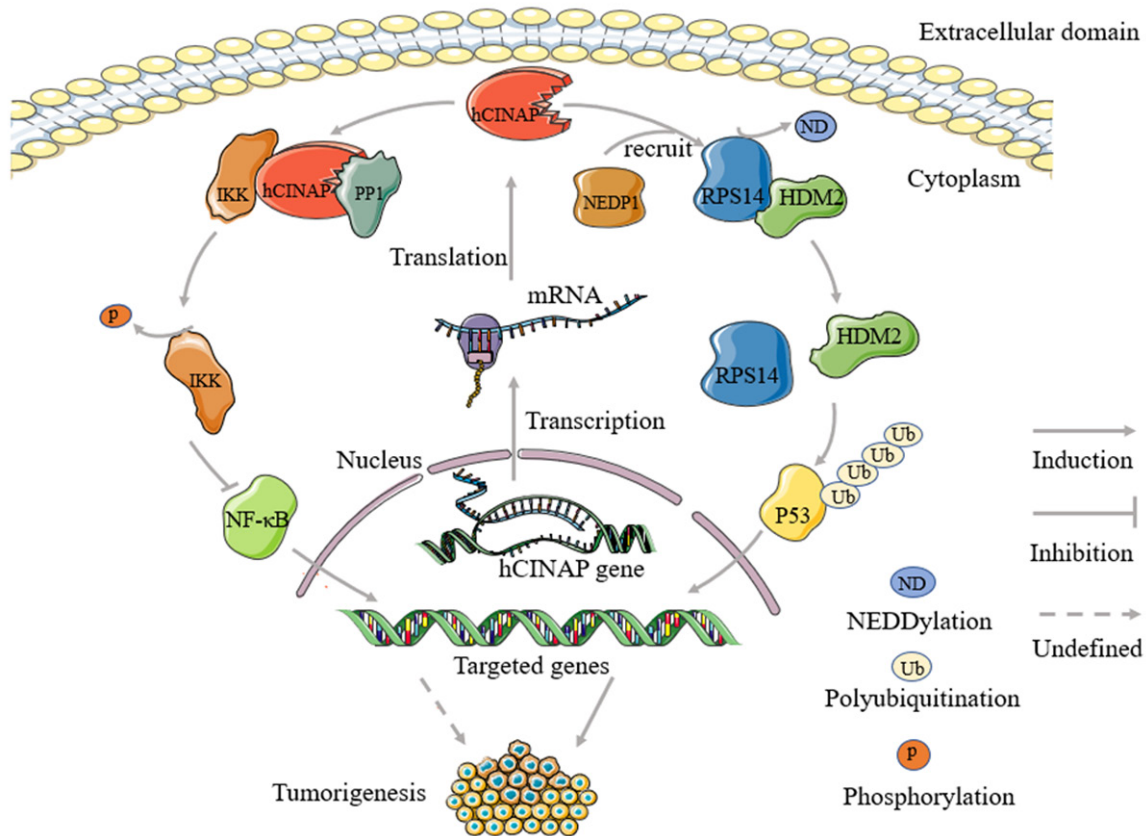
Figure 1. hCINAP promotes tumorigenesis via regulation of the p53 and NF-κB signaling pathways.

[33]. hCINAP negatively regulated the stability and correct subcellular localization of the ribosomal protein S14 (RPS14), thus recruiting neural precursor cell expressed developmentally downregulated 8 (NEDD8)-specific protease 1, inhibiting the NEDDylation of RPS14. The incorrect localization and instability of RPS14 caused the release of human double-minute 2, a principal cellular antagonist of p53, and stimulated p53 polyubiquitination and degradation, ultimately exerting an oncogenic effect.

NF-κB pathway

The NF-κB pathway, which normally remains inactive, plays a critical role in maintaining the immune system response to various cytokines and stimuli. Hyperactivity of NF-κB results in a variety of inflammation-associated diseases including cancer [34]. hCINAP was found to negatively regulate the activation of the NF-κB pathway by inhibiting the phosphorylation of the IκB kinase (IKK) complex, the key modifier of NF-κB activation [35]. hCINAP was recruited

and directly bound to the catalytic subunits of protein phosphatase 1, thus inducing IKK dephosphorylation. These results suggest a positive role for hCINAP in maintaining immune system homeostasis, which appears to contrast its oncogenic function. Therefore, further investigations are needed to explain this seemingly contradictory observation.

DNA damage repair

As a deleterious type of DNA damage, double strand breaks (DSBs) need to be properly repaired to maintain genome integrity and enable cell survival. DSBs can result in tumorigenesis or apoptosis if improperly repaired or left unrepaired [36, 37]. Two key pathways are involved in DSB repair, including classical non-homologous end-joining and homologous recombination (HR). Known to participate in DSB repair in AML, hCINAP promoted tumorigenesis and negatively correlated with poor prognosis in AML patients (**Figure 2**) [25]. When DSB occurs, BRCA1 is recruited to the damaged sites
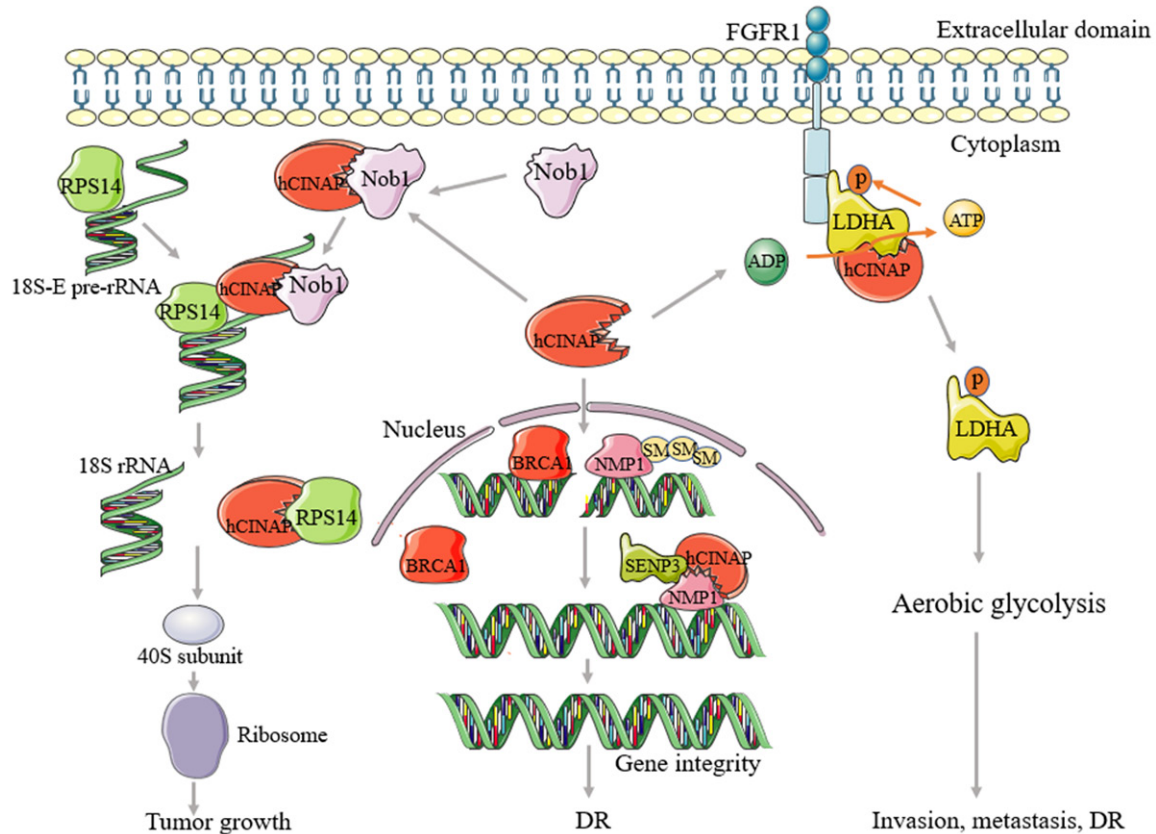
Figure 2. hCINAP induces tumor growth, invasion, metastasis, and DR via regulation of DNA damage repair, ribosome biogenesis, and metabolism. SM: SUMOylation, P: Phosphorylation.

and the repair process is activated by nucleophosmin 1 (NPM1) SUMOylation, which recruits DNA repair proteins and increases HR repair efficiency. To ensure genome integrity, hCINAP limited repair mediated by NMP1 SUMOylation via facilitating the interaction between NMP1 and SUMO1/sentrin/SMT3-specific peptidase 3. These results provide a possible explanation for the observation that hCINAP was downregulated in AML samples and induced resistance of cancer cells to chemotherapy by enhancing genome stability. In addition, patients with lower hCINAP expression had better prognosis. DR was also observed in osteosarcoma and colorectal cancer tissues [26, 27].

Regulation of ribosome biogenesis

Aberrant ribosome biogenesis, which is induced by signaling proteins, oncoproteins, and tumor suppressors, has long been considered to confer competitive advantages to cancer cells [38]. The overexpression of hCINAP in cancer tissues is known to stimulate ribosome

assembly and protein synthesis, thus promoting cancer malignancy (**Figure 2**) [27]. As an ATPase, hCINAP is required for the processing of 18S rRNA as it mediates the cleavage of 18S-E pre-rRNA via binding to endonuclease Nob1. However, by binding to the C-terminal RNA-binding element of RPS14, hCINAP functions as a chaperone to ensure the transfer of RPS14 to the assembly site and the assembly of the 40S subunit. Therefore, hCINAP is strongly associated with alterations in the ribosomal machinery that increase susceptibility to cancer.

Regulation of metabolism

Aerobic glycolysis, also known as the Warburg effect, occurs when cancer cells switch their energy source from mitochondrial oxidative phosphorylation to glycolysis despite sufficient oxygen supply. In this way, cancer cells maintain viability and build new biomass for tumor progression [39]. It was reported that hCINAP acted as a positive glycolysis regulator in co-

lorectal cancer stem cells that were dependent on hCINAP's AK activity (**Figure 2**) [26]. Through its binding to the C-terminal domain of lactate dehydrogenase A (LDHA), which is an essential metabolic enzyme in glycolysis, hCINAP enhanced the activity of LDHA. hCINAP's facilitation of LDHA phosphorylation, catalyzed by Fibroblastic Growth Factor Receptor-1 at tyrosine 10, resulted in aberrant aerobic glycolysis and conferred metabolic advantage to the cancer stem cells through enhanced proliferation, invasion, and metastasis.

Future clinical applications

Although great progress has been made in traditional surgery, chemotherapy, and radiotherapy, current cancer treatments are still facing huge challenges. Because of undesired side effects and increasing cancer-induced deaths, new insights into cancer therapy are urgently needed. Targeted therapy is gradually being considered as a breakthrough and mainstream approach against cancer. Therefore, identifying biomarkers for early prediction of cancer progression and immunotherapy is essential for developing precision medicine and personalized treatment. Based on the above discussion, hCINAP is promising candidate to be investigated as a novel therapeutic target for cancer.

hCINAP as a biomarker for diagnosis

Advanced stage diagnosis of cancer may result in DR, frequent tumor relapse, and low survival rate of cancer patients. It is extensively acknowledged that designing diagnostic biomarkers for early stage diagnosis of cancer to ensure timely treatment and improve therapeutic efficacy is necessary. hCINAP has been reported to have abnormal expression in not only solid cancer tissues, but also hematologic malignancies, and is an important mediator of tumor progression. One study revealed that hCINAP was significantly upregulated in 83.87% of samples derived from breast cancer tissues and 82.22% of colorectal adenocarcinoma-derived samples [27]. Consequently, it is feasible to utilize hCINAP as a diagnostic biomarker for cancer. Combining hCINAP with traditional diagnostic biomarkers, such as CA153 and carcinoembryonic antigen, may improve diagnostic efficiency.

hCINAP as a biomarker for prognosis

Prognostic information, which is independent of clinical/pathological parameters, is critical for therapy planning and life expectancy of patients. There is emerging evidence that hCINAP can be used as a prognostic biomarker in cancer. For example, the 5-year overall survival of 90 patients with colorectal adenocarcinoma indicated that patients with high levels of hCINAP showed poor prognosis [27]. In AML, hCINAP expression negatively correlated with the survival rate of patients, suggesting its potential application as a prognostic biomarker [25].

hCINAP as a therapeutic target

Genes, proteins, and signaling pathways involved in tumorigenesis have long been considered as suitable therapeutic targets [40]. As an oncogenic factor, hCINAP is an ideal candidate. Targeted hCINAP depletion is known to improve chemosensitivity of cancer cells, limit rapid cell growth and viability, promote apoptosis, and inhibit cell motility [25-27, 29]. Importantly, more extensive investigations are needed to confirm the clinical value of hCINAP.

Conclusion

hCINAP, also known as AK6, is unique among the AK family of proteins for differences in substrate preference, intrinsic ATPase activity, and cellular localization. Emerging evidence indicates that hCINAP functions as an oncogenic factor by inducing tumorigenesis and a malignant phenotype. The underlying mechanisms of these effects are gradually being elucidated. However, over the past 15 years, studies that focused on investigating the crucial role of hCINAP in oncogenesis have been limited. Therefore, numerous questions remain to be investigated, including the altered expression of hCINAP in a wide range of cancers types, hCINAP regulation of epithelial-mesenchymal transition, angiogenesis, and/or cancer stem cell features, hCINAP involvement in a broader regulatory network and cross-talk with mRNAs, noncoding RNAs, and proteins, and the clinical effectiveness of targeting hCINAP. Overall, further research related to hCINAP has great potential and is urgently required to harness the potential of hCINAP in the diagnosis, prognosis, and treatment of cancer.

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Disclosure of conflict of interest

None.

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