Roles and regulatory mechanisms of KIN17 in cancers (Review)

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Abstract. KIN17, which is known as a DNA and RNA binding protein, is highly expressed in numerous types of human cancers and was discovered to participate in several vital cell behaviors, including DNA replication, damage repair, regulation of cell cycle and RNA processing. Furthermore, KIN17 is associated with cancer cell proliferation, migration, invasion and cell cycle regulation by regulating pathways including the p38 MAPK, NF-κB-Snail and TGF-β/Smad2 signaling pathways. In addition, knockdown of KIN17 was found to enhance the sensitivity of tumor cells to chemotherapeutic agents. Immunohistochemical analysis revealed that there were significant differences in the expression of KIN17 between cancer tissues and adjacent tissues. Both the Kaplan-Meier survival analysis and multivariate Cox regression analysis indicated that KIN17 is aberrantly high expressed in various tumor tissues and is also associated with poor prognosis in patients with various tumor types. Taken together, KIN17 has key roles in tumorigenesis and cancer development. Investigating the relationship between KIN17 and neoplasms will provide a vital theoretical basis for KIN17 to serve as a diagnostic and prognostic biomarker for cancer patients and as a potential target for cancer therapy.

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Contents

1. Introduction

KIN17 was initially discovered due to the cross reaction with antibodies against the RecA protein of *Escherichia coli*. In addition, KIN17 is a highly conserved gene across evolution. Previous studies have indicated that KIN17 is involved in global genome repair, DNA replication, transcription and regulation of the cell cycle as part of a multi-protein complex. The above biological processes have important roles in tumorigenesis, cancer development and chemoresistance in tumor cells. Indeed, KIN17 is abundantly expressed in a variety of tumors, including breast, thyroid, colorectal, liver, cervical, lung and ovarian cancer. It is worth mentioning that KIN17 has vital impacts on tumor genesis and development. The present review was the first, to the best of our knowledge, to systematically summarize and clarify the relevance between KIN17 and tumor development from different aspects (Table I), including the structure, function, expression level and regulatory mechanisms of KIN17, so as to explore the potential of KIN17 as a tumor diagnostic and prognostic biomarker and as a potential therapeutic target. The present study aimed to summarize the influence of KIN17 on tumor development and the possibility of KIN17 as a tumor diagnostic and prognostic biomarker and as a potential therapeutic target.

2. KIN17, a DNA and RNA binding protein

Structure of KIN17. KIN17 gene is highly conserved across evolution (1). It is mainly composed of three parts, including a zinc finger (ZF) domain (27-50 nt) (2,3), a nuclear location signal (240-257 nt) and a motif named Kyprides-Onzonis-Woese (KOW; 335-373 nt), which mediates

protein and RNA interaction (Fig. 1) (4), and these three motifs determine that KIN17 are 45 kDa nuclear proteins and highly conserved across evolution. There is a domain with homology to the RecA protein from *Escherichia coli* (162-201 nt; Fig. 1) (5-7), which is how KIN17 was initially discovered, i.e. because of its cross-reaction with *Escherichia coli* RecA protein antibody (8). Based on the phylogenetic analysis, the mean identity of the ZF domain and the winged helix (WH) domain (51-160 nt) (Fig. 1) of KIN17 was respectively 90.37 and 65.36%, which means that the two domains are highly conserved, whereas this conservative phenomenon in the KOW motif was only found in the higher eukaryote, speculating that the KOW motif appeared late in evolution. >50% of the secondary structure of KIN17 consists of random coil and β-turns, while the components of α-helices and β-strands make up for <50% of the structure of KIN17 (9).

Function of KIN17. KIN17 preferentially binds to the curved DNA found at the illegitimate recombination positions in the chromosomes of eukaryotic cells (10,11), inferencing that KIN17 has key roles in global genome repair. In addition to binding with the curved DNA and in regulating the association with chromatin, KIN17 also has roles in RNA binding via the tandem SH3 domain (12). Based on the above findings, KIN17 is known as a DNA and RNA binding protein.

The DNA damage increased after ultra-violet C radiation or ionizing radiation, resulting in an increase in the expression level of KIN17. In fact, KIN17 gathered in the nucleus forming lesions in cells (Fig. 2) (13); therefore, KIN17 also participates in the general response to genotoxic stress (14-17), but this depends on the genome integrity in the DNA repair mechanism; particularly the existence of XPA and XPC is of great importance for the increase of KIN17 after exposure to ultra-violet C radiation or ionizing radiation (14). In several studies, KIN17 was co-mentioned with DNA damage repair-associated proteins (18-22), and even forms complexes with DNA damage repair-associated proteins. In addition, KIN17 is able to efficiently repair DNA double strand breaks (DSBs) caused by ionizing radiation or activation-induced cytidine deaminase (AID). Of note, low expression levels of KIN17 lead to an increase in the frequency of deletions in the mutation of AID. Furthermore, low expression of KIN17 influences multiple repair pathways of DSBs, particularly homologous recombination and non-homologous end joining (23).

In the detection and analysis of proteomics, KIN17 was found to exist in the spliceosome, inferring that it is of great importance in the regulation of transcription (Fig. 2) (4). Besides this, KIN17 was observed to accumulate with replication protein A, forming intranuclear foci following γ-irradiation, using electron microscopy (8). In addition, low expression of KIN17 was also associated with a long S phase in the cell cycle due to the increased sensitivity following γ-irradiation and decreased DNA synthesis rate (24). Another study reported that a physical interaction between human KIN17 and simian virus 40 (SV40) large T antigen led to DNA synthesis inhibition both *in vitro* and *in vivo* (25). KIN17 has also been found to be part of a multi-protein complex participating in DNA replication and regulation of the cell cycle (26-28). New interactions between KIN17 and other proteins have also been found, particularly proteins related to RNA processing, such as certain proteins associated with pre-mRNA splicing and ribosome biogenesis (Fig. 3) (29).

In addition, it was reported that KIN17 was methylated on lysine 135 and transferred from the nucleus to the cytoplasm after overexpression of methyltransferase 22, which means that lysine 135 of KIN17 has key roles in regulating methylation and chromatin association (Figs. 2 and 3) (30). It appears that KIN17 is closely related to the involvement of methyltransferase in methylation (31-36), and histone methylation is an epigenetic modification (37-41), which refers to the process of transferring methyl to the N-terminal arginine or lysine residues of H3 and H4 histones under the catalysis of histone methyltransferase (42-46). Methylation at different sites and different degrees of methylation lead to different effects. Histone methylation is related to the activation, extension or inhibition of gene expression, which has an important role in the occurrence and development of cancer (47-55). Of note, it was reported that the WH domain of human KIN17 may mediate protein-protein interactions between KIN17 and a series of methyltransferases (56).

To sum up, KIN17 has been discovered to participate in several vital cell behaviors, including DNA replication, damage repair, regulation of the cell cycle, epigenetic modification, ribosome biogenesis and RNA processing, including pre-mRNA splicing.

Distribution of KIN17. Under normal circumstances, KIN17 is mainly expressed in cardiac, testicular and skeletal muscle, while exhibiting lower expression in other organs (5). Of note, the DNA damage increased after ultra-violet C radiation or ionizing radiation, resulting in an increase in the expression level of KIN17; in fact, KIN17 gathered in the nucleus forming lesions in cells (13). Furthermore, one study on colorectal cancer revealed that KIN17 is mainly expressed in the nucleus in para-carcinoma tissues, whereas it is expressed both in the nucleus and cytoplasm in the tumor tissues (57). In another study, the components of nuclear and chromatin-related proteins were analyzed, the expression pattern of KIN17 was detected in all components and an increase in the concentration of chromatin-related components of clones with low metastatic potential was observed (58).

3. Roles of KIN17 in cancer cells

Expression of KIN17 in tumors and its relationship with survival and prognosis. Immunohistochemical analysis of clinical specimens from patients with colorectal cancer revealed that tumor tissues exhibited higher expression levels of KIN17 than para-carcinoma tissues. In addition, patients in the T1 and T2 groups exhibited high expression levels of KIN17 compared with patients in the T3 and T4 groups. Furthermore, compared with patients without lymph node metastasis, patients with lymph node metastasis exhibited high expression levels of KIN17. Finally, patients with distant metastasis exhibited higher expression levels of KIN17 than patients without distant metastasis. The TNM staging system is based on the primary tumor, lymph node metastasis and distant metastasis; therefore, the above immunohistochemical results indicate that KIN17 expression is associated with tumor genesis and development (57).

Table I. Effects of KIN17 in cancers.

Cancer type	KIN17 expression	Function	Pathway	(Refs.)
Luminal-A breast cancer	High	High expression promotes migration and invasion	-	(60)
Triple-negative breast cancer	High	Knockdown of KIN17 promotes apoptosis of MDA-MB-231 cells	Mitochondrial pathway of apoptosis	(66)
Thyroid cancer	High	High expression promotes proliferation, migration and invasion	p38 MAPK signaling pathway	(68)
Colorectal cancer	High	High expression associated with poor prognosis	-	(57)
Hepatocellular carcinoma	High	i) High expression promotes proliferation; ii) High expression associated with poor prognosis; iii) Knockdown of KIN17 inhibits migration and invasion, on the contrary, overexpression of KIN17 promotes migration and invasion	TGF-β/Smad2 signaling pathway	(65,69)
Cervical cancer	High	i) High expression associated with poor prognosis; ii) Knockdown of KIN17 inhibits proliferation, migration and invasion, but promotes apoptosis	NF-κB-Snail pathway	(61,62,67,73)
Ovarian cancer	High	i) High expression associated with poor prognosis; ii) KIN17 knockdown sensitized SKOV3 cells to cisplatin and inhibited the proliferation ability and migration ability of epithelial ovarian cancer cells	-	(64)
Non-small cell lung cancer	High	i) High expression associated with poor prognosis; ii) Knockdown of KIN17 inhibits migration and invasion	MEK/ERK signaling pathway	(63)

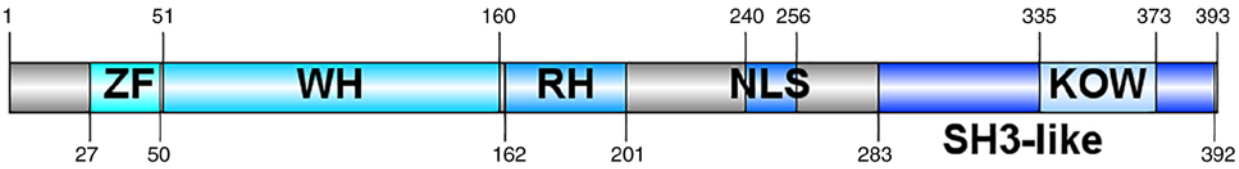

Figure 1. Structure of KIN17. It includes two SH3-like in tandem and the KOW motif. ZF, zinc finger; WH, winged helix; RH, domain with homology to the RecA protein from *Escherichia coli*; NLS, nuclear location signal; KOW, Kyprides-Onzonis-Woese.

Univariate analysis and Kaplan-Meier survival analysis suggested that KIN17 may serve as a prognostic biomarker for colorectal cancer. In addition to univariate analysis and Kaplan-Meier survival analysis, multivariate Cox regression analysis also indicated that KIN17 was an independent prognostic factor in colorectal cancer (57).

Similarly, the immunohistochemical analysis of clinical breast tumor specimens also demonstrated that the expression of KIN17 was significantly increased in breast cancer tissues and related to the expression levels of Ki-67 and progesterone receptor, the mutation status of p53 and the tumor stage (59).

Survival analysis of clinical data from The Cancer Genome Atlas (TCGA) database revealed that high expression of KIN17 was associated with a low overall survival rate in patients with breast cancer, particularly the subtype of luminal-A among the 4 subtypes. Furthermore, besides overall survival, high expression of KIN17 was also found to be associated with poor relapse-free survival, distant metastasis-free survival and post-progression survival, indicating that the high expression of KIN17 has important roles in disease progression and prognosis (60).

In addition to colorectal cancer and breast cancer, the immunohistochemical analysis of clinical cervical tumor specimens also indicated that the expression level of KIN17 in invasive cervical cancer and cervical intraepithelial neoplasia (CIN) or carcinoma *in situ* was higher than that in normal cervical tissues, indicating that KIN17 may serve as a biomarker for progression to cervical carcinoma. Furthermore, it was found that the expression level of KIN17 was associated with the expression of Ki-67, the degree of differentiation and the status regarding lymph node metastasis (61).

Of note, a recent study found that the expression level of KIN17 was positively associated with the severity of cervical lesions, indicating that KIN17 is a novel protein biomarker for high-grade CIN (62). High-grade CIN is considered to be the precursor of cervical carcinoma, which further suggests that

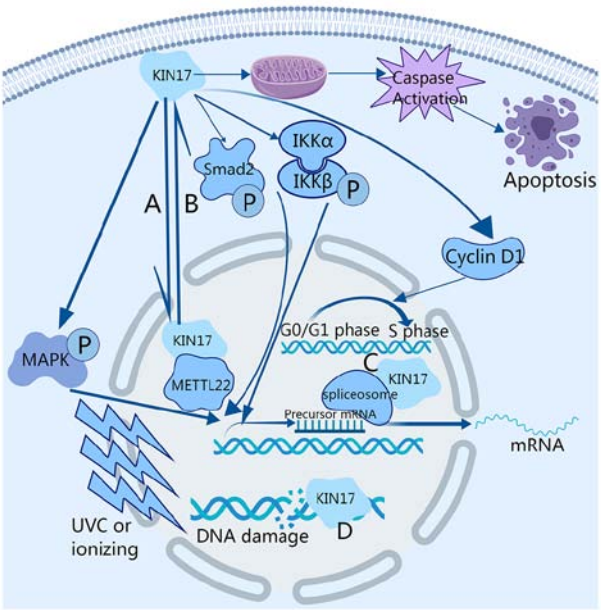

Figure 2. Function of KIN17. (A) KIN17 may be transferred from the cytoplasm to the nucleus. (B) KIN17 is methylated on lysine 135 by METTL22 and then migrates from the chromatin to the cytoplasmic fraction. (C) KIN17 participates in RNA binding and may interact with spliceosome, which means that KIN17 may affect the expression of downstream products and ultimately affect the proliferation, migration and invasion of cancer cells. (D) KIN17 is able to participate in damaged DNA binding and has vital roles in the DNA damage response. METTL22, methyltransferase 22, Kin17 lysine; UV, ultraviolet; P, phosphate; IKK, inhibitor of NF-κB.

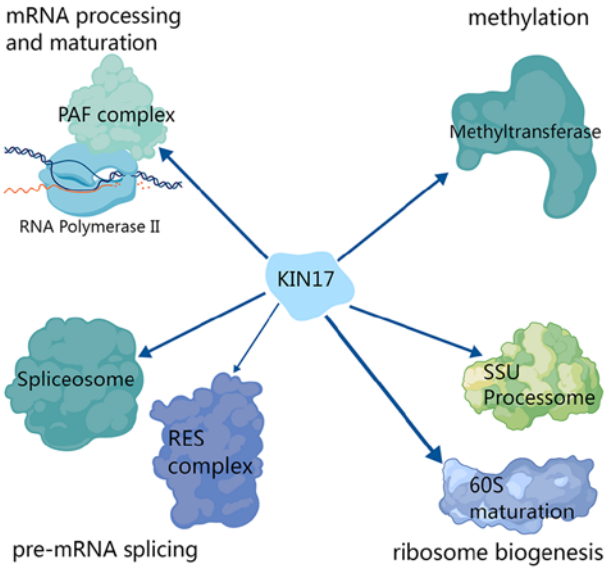

Figure 3. Protein complex of high-confidence interactions with KIN17. SSU processome, small-subunit processome; RES complex, retention and splicing complex; PAF complex, polymerase associated factor 1 complex.

KIN17 may be used as a predictive biomarker for cervical cancer.

Elevated KIN17 mRNA and protein expression was detected in non-small cell lung cancer (NSCLC). Furthermore, it was found that the expression of KIN17 was relevant to the grading of tumors and the status of lymph node metastasis, which are both indicators related to poor survival prognosis (63).

Analysis of clinical data from patients with ovarian tumor in the TCGA database indicated that KIN17 expression was significantly increased in ovarian serous adenocarcinoma tissues compared with normal ovary tissues ($P<0.05$). It was found that the DNA expression level of KIN17 in ovarian serous adenocarcinoma was also higher than that in normal ovarian tissues. Furthermore, the transcription level of KIN17 in ovarian serous adenocarcinoma was also higher than that in borderline epithelial stromal tumor of the ovary. However, the mRNA expression of KIN17 exhibited no difference between normal ovary tissues and other epithelial ovarian cancer (EOC) tissues. Using the Kaplan-Meier method and a log-rank test, the results indicated that, similar to colorectal cancer, KIN17 may also serve as a prognostic biomarker in EOC. In addition to univariate analysis and Kaplan-Meier survival analysis, multivariate Cox regression analysis suggested that KIN17 and the tumor stage were independent prognostic factors in EOC. However, there was no association between the localization (cytoplasm or nucleus) of KIN17 and the overall survival (64).

A recent study related to KIN17 demonstrated that the expression level of KIN17 in hepatocellular carcinoma (HCC) tissues was higher than that in para-carcinoma tissues, as proved by multiple analytic methods, including Bioinformatics, western blot analyses and immunohistochemistry (65). In addition, the expression levels of KIN17 in portal vein tumor thrombus tissues and intrahepatic metastasis tissues were higher than those in the primary tumor tissues, suggesting that KIN17 is related to metastasis in HCC. Furthermore, Kaplan-Meier survival analysis, univariate analysis and multivariate Cox regression analysis indicated that KIN17 is significantly relevant to the survival rates and prognosis.

The above immunohistochemical analysis and survival analysis results reveal that KIN17 is abundantly expressed in neoplasms and closely associated with clinical features and prognosis of neoplasms.

Roles of KIN17 in tumor cell apoptosis induction. A study on triple-negative breast cancer revealed that knockdown of KIN17 promoted the apoptosis rates of MDA-MB-231 cells. Furthermore, not only the caspase activity (Fig. 2), but also the expression levels of cleaved poly ADP ribose polymerase (PARP) in the KIN17-knockdown group were both higher than those in the mock and negative control groups (66).

In addition to triple-negative breast cancer, Annexin V-APC staining performed in cervical cancer demonstrated that the apoptosis rates of HeLa cells in the KIN17 knockdown group were also higher than those in the negative control group (61,67).

These results suggest that KIN17 has key roles in induction of cell apoptosis and a PARP-related mechanism may be attributed to it.

Roles of KIN17 in regulation of tumor cell proliferation. A study on thyroid cancer revealed that in the colony-formation assay, the number of colonies in the KIN17-knockdown group was lower than that in the KIN17-overexpression group (68). Furthermore, cell-cycle analysis by flow cytometry suggested that the cell number in G1 phase in the KIN17-knockdown

group was higher than that in the negative control group, while the cell number in S phase and G2 phase in the KIN17-knockdown group was lower than that in the negative control group. On the contrary, the cell number in G1 phase in the KIN17-overexpression group was lower than that in the negative control group, while the cell number in S phase and G2 phase in the KIN17-overexpression group was greater than that in the negative control group. Western blot analysis demonstrated that the expression levels of phosphorylated (p)-p38, cyclin D1 and p27 were downregulated following the knockdown of KIN17 in 8505C cells and SW579 cells, while the expression levels of p-p38, cyclin D1 and p27 were upregulated following the overexpression of KIN17 in 8505C cells and SW579 cells. These results demonstrated that KIN17 is able to promote the proliferation of thyroid cancer cells (Fig. 2) (68).

In addition to the effects of KIN17 *in vitro*, *in vivo* xenograft assays also proved that the tumor weight in the KIN17 knockdown group was markedly lower than that in the control group. Correspondingly, the abundance of Ki-67-positive cells in the KIN17 knockdown group was lower than that in the control group. In addition, the level of p-p38 in KIN17 knockdown group was lower than that in the control group. In conclusion, these findings indicate that knockdown of KIN17 may repress the progression of thyroid cancer *in vivo* (68).

Overexpression of KIN17 also promoted the growth of hepatoma cells *in vitro* and *in vivo*. The number of colonies in the KIN17-overexpression group was significantly increased compared with that in the negative control group in both HepG2 cells and SMMC-7721 cells, indicating that overexpression of KIN17 promoted the cell proliferation ability in both HepG2 cells and SMMC-7721 cells. Further study indicated that the expression of cyclin D1 and p27 in the KIN17-overexpression group was markedly higher than that in the negative control group in both HepG2 cells and SMMC-7721 cells. Taken together, KIN17 may be relevant to the cell proliferation activity in hepatocellular carcinoma (69).

Ki-67 is regarded as a cell proliferation marker (70). In one study, the expression of KIN17 and Ki-67 in breast cancer tissues was detected by a double-labeled immunofluorescence assay (59). The analysis revealed that KIN17 and Ki-67 were both mainly located in the nucleus and they were co-positive in MDA-MB-231 cells, indicating that KIN17 and Ki-67 were co-expressed in the nucleus. Co-expression of KIN17 and Ki-67 in both tumor tissues and cells suggested that KIN17 may be associated with cellular proliferation. Western blot analysis revealed that overexpression of KIN17 increased the expression of ERK1/2 autophosphorylation and cyclin D1 in MCF-10A and BT474 cells, whereas knockdown of KIN17 decreased the expression level of ERK1/2 autophosphorylation and cyclin D1 in MCF-10A and BT474 cells. This revealed that KIN17 may be relevant to the cell proliferation activity in breast cancer.

Epidermal growth factor (EGF) has been reported as a major growth factor associated with cell proliferation and tumorigenesis in breast cancer (71,72). The expression level of KIN17 was significantly increased following the stimulation of EGF in MDA-MB-231, BT474 and MCF-10A cells. It was also found that the effect of EGF on stimulating cell proliferation was weakened following knockdown of KIN17, which means that KIN17 is a prerequisite for EGF to stimulate cell proliferation (59).

Overall, these data indicate that KIN17 participates in cancer cell proliferation by regulating the expression levels of cell cycle-related proteins.

Roles of KIN17 in the regulation of tumor cell migration and invasion. In thyroid cancer, the cell migratory ability was markedly suppressed following knockdown of KIN17, while the cell migratory ability was markedly enhanced following overexpression of KIN17 in 8505C and SW579 cells, as indicated by a wound-healing assay. The Transwell assay results indicated that the cell invasion ability was inhibited following knockdown of KIN17, while the cell invasion ability was promoted following overexpression of KIN17. Furthermore, silencing of KIN17 upregulated the expression of epithelial to mesenchymal transition (EMT)-associated E-cadherin, while overexpression of KIN17 downregulated the expression of EMT-associated E-cadherin in 8505C and SW579 cells. On the contrary, silencing of KIN17 downregulated the expression of EMT-associated N-cadherin, while overexpression of KIN17 upregulated the expression of EMT-associated N-cadherin in 8505C and SW579 cells. These findings suggest that KIN17 promoted cell migration and invasion in thyroid cancer (68).

In cervical cancer, the migration rates in the KIN17-knockdown group were lower than those in the negative control group in both HeLa cells and SiHa cells in the wound-healing assay and Transwell assay without Matrigel. Furthermore, the number of invasive cells was also downregulated in both HeLa cells and SiHa cells following knockdown of KIN17 (73).

The migration and invasion ability were suppressed in the NSCLC cell line A549 following the knockdown of KIN17. In addition, the expression levels of MMP-7, EGF receptor and MYC were downregulated following the knockdown of KIN17, as proved by reverse transcription-quantitative PCR and western blot analysis (63).

A latest study related to KIN17 demonstrated that the migration and invasion ability were inhibited following the knockdown of KIN17 in Huh7 cells and HepG2 cells both *in vitro* and *in vivo*, while the migration and invasion ability were enhanced following overexpression of KIN17 in MHCC-97L cells and HepG2 cells both *in vitro* and *in vivo* (65).

Taken together, the expression of KIN17 has a vital impact on the migration and invasion ability of tumor cells.

Roles of KIN17 in chemoresistance. A study on ovarian cancer revealed that the mRNA expression of KIN17 in cisplatin-resistant ES-2 cells was higher than that in cisplatin-sensitive cells (OVCAR-3, FU-OV-1 and OA W42 cells) and moderately sensitive cells (SKOV3 cells). KIN17 knockdown sensitized SKOV3 cells to cisplatin and inhibited the proliferation and migration ability of EOC cells in ovarian cancer (64).

The DNA damage detected in breast cancer cells treated with adriamycin (ADM) was greater than that in breast cancer cells without ADM induction. Of note, the DNA damage detected in BT474 cells was greater compared with that in MCF-10A cells. In addition to DNA damage, the expression level of KIN17 was upregulated following induction with ADM. The DNA damage was enhanced in the MCF-10A cells and BT474 cells following knockdown of KIN17. However, the DNA damage in BT474 cells was greater compared with that

in MCF-10A cells following knockdown of KIN17. In addition, the sensitivity to ADM in BT474 cells was increased following knockdown of KIN17, while the sensitivity to ADM treatment in MCF-10A cells exhibited no significant change following knockdown of KIN17 (59).

Similarly, in addition to breast cancer cells, KIN17 knockdown significantly enhanced the inhibitory effects of Doxorubicin on the cell viability and proliferation in the thyroid cancer cell lines 8505C and SW579. Silencing of KIN17 also promoted the suppressive effects of Doxorubicin on the protein levels of p-p38, cyclin D1 and p27 in 8505C cells and SW579 cells. The inhibitory effects of Doxorubicin on the cell migration and invasion abilities of 8505C cells and SW579 cells were enhanced by knockdown of KIN17 proved by a Transwell assay. Silencing of KIN17 also promoted the downregulation effect of Doxorubicin on the expression of N-cadherin and the upregulation effect of Doxorubicin on the expression level of E-cadherin. These findings indicate that the sensitivity to the treatment of Doxorubicin in thyroid cancer cells was enhanced by knockdown of KIN17 (68). The above study highlights the changes in chemosensitivity of tumor cells following knockdown of KIN17, indicating that KIN17 may have a key role in chemoresistance and is expected to alleviate chemoresistance in tumor cells to a certain extent.

4. Regulatory mechanism of KIN17 in tumor cells

The metastasis of luminal-A breast cancer was promoted by EMT signaling activated by KIN17. The expression levels of β-catenin, Vimentin and claudin-1 in the KIN17-knockdown group were lower than those in the mock and negative control groups, while the expression levels of β-catenin, Vimentin and claudin-1 in the KIN17-overexpression group were higher than those in the mock and negative control groups (60).

KIN17 facilitates thyroid cancer cell migration and invasion by activating the p38 MAPK signaling pathway (Fig. 2). P79350, a p38 agonist, reversed the suppressive effects of knockdown of KIN17 on the colony-forming, migratory and invasive ability of 8505C and SW579 cells. In addition, P79350 also reversed the effect of knockdown of KIN17 to increase the G1-phase population and to decrease the S- and G2/M-phase populations in 8505C and SW579 cells. Furthermore, western blot analysis revealed that P79350 rescued the downregulation effect of knockdown of KIN17 on the protein levels of p-p38, cyclin D1, p27 and N-cadherin in 8505C and SW579 cells. These findings suggest that the inhibitory effects of knockdown of KIN17 on the cell proliferation, migration and invasion of thyroid cancer cells were abolished by P79539 and activation of the MAPK signaling pathway (68).

KIN17 knockdown suppressed the migration and invasion of cervical cancer cells through the NF-κB-Snail pathway (Fig. 2). Knockdown of KIN17 repressed the phosphorylation level of certain molecules related to the NF-κB pathway and downregulated the expression level of Snail in HeLa and SiHa cells. In addition, migration and invasion were inhibited in cervical cancer cells following knockdown of KIN17, indicating that KIN17 may promote cell migration and invasion in cervical cancer cells by activating the NF-κB-Snail pathway (73).

A study about KIN17 demonstrated that recombinant human TGF-β1 reversed the suppressive effects of knockdown of KIN17 on HCC cell migration and invasion (65). In addition, TGF-β1 also reversed the promotion effects of knockdown of KIN17 on the expression levels of epithelial-related proteins and the suppressive effects of knockdown of KIN17 on the expression levels of mesenchymal-related proteins. On the contrary, Y2109761, a selective TGF-β receptor type I/II dual inhibitor, reversed the promotion effects of overexpression of KIN17 on the cell migration and invasion ability. In addition, Y2109761 also reversed the suppressive effects of overexpression of KIN17 on the expression levels of epithelial-related proteins and the promotion effects of overexpression of KIN17 on the expression levels of mesenchymal-related proteins. In conclusion, these findings revealed that KIN17 may impact cell migration and invasion in HCC cells through stimulating the TGF-β/Smad2 signaling pathway (Fig. 2).

In conclusion, KIN17 facilitates cell proliferation, migration and invasion in cancers by activating various processes, including EMT, the p38-MAPK signaling pathway, NF-κB-Snail pathway and the TGF-β/Smad2 signaling pathway.

5. Application prospect and limitation

As mentioned above, immunohistochemical analysis of clinical specimens confirmed that the expression level of KIN17 in tumor tissues is higher than that in para-carcinoma tissues, and the expression level of KIN17 is related to TNM stage. In addition, survival analysis also indicated that high expression of KIN17 in various tumor types is related to poor prognosis. Therefore, it is worth mentioning that KIN17 is expected to be a novel target and diagnostic marker and serve as a novel prognostic biomarker in neoplasms.

It was verified *in vivo* and *in vitro* that KIN17 has impacts on the genesis and development of various tumors in numerous aspects, such as apoptosis, proliferation, migration and invasion. Knockdown of KIN17 may inhibit the proliferation, migration and invasion of tumor cells. Because of this, it may be speculated that using small-molecule inhibitors to reduce the expression of KIN17 may effectively inhibit the proliferation and metastasis of tumor cells in the clinic, thereby inhibiting the development of tumors and improving the survival rate of patients. However, to the best of our knowledge, to date, no further in-depth clinical experiments have been performed and their findings applied in clinical practice. Therefore, it may be proposed that KIN17 may serve as a potential therapeutic target, but further in-depth research is required to verify this.

In addition, KIN17 is a highly conserved gene across evolution and is expressed in almost all types of cells, which indicates its limitation as a therapeutic target in tumor therapy because of its non-specific properties; its interference may have detrimental effects, such as destroying the balance of the organism, reducing the overall responsiveness of the organism and bringing about unknown side effects.

However, the prospect of KIN17 as a tumor diagnostic and prognostic biomarker and as a potential therapeutic target in neoplasms is clinically significant and promising.

6. Conclusion and prospect

KIN17 is highly expressed in a variety of tumor types and is closely related to the clinical and pathological features of

patients, which indicates that KIN17 is expected to be a novel target and serve as a novel diagnostic and prognostic biomarker in neoplasms. In addition, knockdown of KIN17 may inhibit cell proliferation and metastasis in various tumor types. As mentioned above, although more in-depth clinical experiments are required to verify its clinical therapeutic effects, cell and molecular experiments *in vitro* and xenograft assays *in vivo* proved that KIN17 may be a potential therapeutic target.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

TZ and QH conceived the study. XH, ZD and QL prepared the original draft. XL reviewed and edited the original draft. XH conducted the literature search. QH was responsible for the visualization. TZ and QH, acquired the funding and were the supervisor and project administrator. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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