Roles of kinesin superfamily proteins in colorectal cancer carcinogenesis (Review)

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Abstract. Colorectal cancer (CRC), a commonly occurring carcinoma, now ranks the second in terms of cancer-associated deaths around the world. Among the numerous factors that contribute to CRC tumor progression, a class of motor proteins known as the kinesins has been found to play a vital role. Kinesins are responsible for the intracellular trafficking of functional proteins, organelles and biomacromolecules along microtubules. Dysregulation of kinesins has been revealed to influence the cell cycle to cause abnormal cell growth and affect cell adhesion to promote epithelial-mesenchymal transition in breast, bladder, ovarian and prostate cancer. Studies on the function of kinesins in CRC have also been performed, although, to the best of our knowledge, little is known about the underlying mechanisms of kinesins in CRC progression. The present review outlines the roles played by different kinesins in CRC carcinogenesis, mainly discussing the most studied subfamilies (kinesin 3-6, 8, 10, 11 and 13), This review aims to illustrate the functions of kinesins in CRC cell growth, cancer metastasis and chemoresistance to provide insights regarding kinesins as potential targets for determining CRC prognosis and selecting therapy.

Contents

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1. Introduction

Colorectal cancer (CRC) is one of the most frequently occurring carcinomas, ranking third in terms of cancer incidence and second terms of in cancer-related mortality worldwide in 2020 (1). Globally, ~0.9 million CRC-associated deaths are reported annually (2). The incidence of this disease has increased over the past decades in a number of developing countries, possibly owing to changes in lifestyle and aging populations. Tumorigenesis is a complicated biological process regulated by various factors, and requires timely and accurate transport of functional molecules to their targets by motor proteins. Kinesins, a group of motor proteins, act as transporters along microtubules (MTs) (3) and have vital roles in various physiological processes, such as protein sorting and chromosome dynamics. Defects in kinesin function can lead to dysregulated distribution of various proteins and organelles within cells, and have been implicated in numerous diseases, including left-right asymmetry, Alzheimer's disease and amyotrophic lateral sclerosis (4-6). Studies have also revealed a correlation between kinesins and CRC. For example, elevated expression of kinesins positively influences several clinical features, such as lymph node metastasis (7-11) and tumor status (7,9,10,12-14), and is relevant to the overall survival rate of patients with CRC (7,9-13,15). The dysregulation of kinesins affects cell proliferation, tumor formation and metastasis in CRC (7-18). Given the importance of kinesins, the present review aims to illustrate their roles in the prognosis of CRC and the potential underlying regulatory mechanisms involved in CRC carcinogenesis, to provide new targets for the clinical therapy of the disease.

2. Kinesins

Classification and structure. The kinesin superfamily in humans comprises 45 members classified into 14 families, Kinesin-1 to Kinesin-14, according to their structural differences (19). Kinesin family members (KIFs) vary in shape, but share three distinct domains, the head, stalk and tail, which

perform different functions during cargo transportation. The head, which is an orbicular domain, is conserved among different KIF members; this domain binds to the MT and regulates movement through two binding sites: One binds the MT and is characterized by a Rossman fold, while the other binds to ATP (20). There are three elements within the ATP-binding site, Switch-I, Switch-II and the P-loop, which are responsible for the hydrolysis of ATP and contribute to the conformational changes of the MT-binding domain (21). The location of the head correlates with the direction of kinesin movement along the MTs. The head domain of Kinesin-1 to Kinesin-12 family members is found in the NH_2-terminal region and moves to the plus ends of MTs; these are called the N-kinesins, whereas Kinesin-14A/B family members are C-kinesins and contain the motor domain at the COOH-terminus and the head for the minus end of the MTs. Kinesin-13 family members are M-kinesins, with the head domain situated in the center of the molecule structure, and these are involved in depolymerizing MTs (9).

In contrast to the conserved head domain, the amino acid sequences in the stalk and tail domains are highly variable (22). Most often, KIFs dimerize with each other to form homo- or heterodimers through the stalk domain, and the dimerization status is determined by the length of this domain. KIFs can also function as monomers. KIFs bind with cargo for its selective transport through the highly variable tail domain and may be accompanied by light chain and/or associated proteins (Fig. 1).

Two mechanisms have been suggested to describe the movements of kinesins: The 'hand-over-hand' and 'inchworm' models (23). In the 'hand-over-hand' model, the front head alternates with the rear one on the MTs to forge ahead, and every step consumes two molecules of ATP. In the 'inchworm' model, by contrast, the relative positions of the two heads are maintained, enabling movements of 8 nm for the anterior head (Fig. 2).

Biological activity of kinesins and relevance to diseases. KIFs are responsible for the transport of cellular organelles, functional proteins packed in vesicles and macromolecules such as chromosomes to the required destinations; thus, they are vital for protein sorting and appropriate positioning of various biological molecules (24). Owing to these functions, KIFs are involved in numerous diseases. Kinesin-1 has been reported to interact with key molecules such as adenomatous polyposis coli protein participating in the Wnt signaling pathway (25) and GluN2B, which regulates N-methyl-D-aspartate receptor activity (26). Thus, dysregulated Kinesin-1 potentially causes neurological diseases (27). Selective knockout of *KIF5B* in pancreatic β cells and adipocytes affects insulin and adipokine secretion, which leads to metabolic disorders (28,29). For organelle transport, KIF5B is found to regulate mitochondrial localization and activity (30), and contributes to pathological hypertrophic responses in cardiomyocytes (31). Moreover, during the cell cycle, kinesins are responsible for the formation of the spindle apparatus and the alignment and detachment of chromosomes (32). Modulations in KIF activity could influence the cell cycle and alter the apoptosis level of cells. The dysregulation of kinesins has also been reported to affect cell multiplication and migration, with effects on the carcinogenesis of various cancer types, including breast and lung cancer (33,34).

3. Kinesins in CRC

CRC occurs when epithelial cells in the colon and rectum gain the ability for abnormal growth. To date, the expression of 10 KIFs has been reported to be increased in CRC tissue and has been associated with patient prognosis and CRC metastasis (Table I). KIFs interact with intracellular molecules to influence the activity of CRC cells, with effects on proliferation, migration, invasion and the immune reaction (Fig. 3).

Kinesin-3. The Kinesin-3 family is distinguished from conventional kinesins by a peculiar neck region containing a β-sheet and a helix (35), and by the incorporation of a forkhead-associated domain in the tail region. Kinesin-3 motors are essential for organelle transport and cytokinesis, which suggest potential roles of kinesin-3 family members in modulating the cell cycle (36).

KIF14, a member of the Kinesin-3 family, serves as a mitotic kinesin and is encoded by a gene situated on chromosome 1q32.1 (37). In CRC, Wang *et al* (17) found that elevated KIF14 levels contributed to cell proliferation. Flow cytometry results showed that high KIF14 expression could cause G_0/G_1 arrest, indicating a role in the modulation of the cell cycle. Additional experiments confirmed that high KIF14 expression increased the phosphorylation of protein kinase B (also known as Akt), thereby advancing the cell cycle to promote tumorigenesis. This study also demonstrated that microRNA such as miR-200c might directly bind to the 1402- to 1409-bp locus of KIF14; thus, miR-200c could negatively regulate KIF14 function to inhibit overgrowth of cells at the post-transcriptional level.

Kinesin-4. Kinesin-4 motors participate in the transportation of organelles and in chromosome dynamics, and are vital to the regulation of cycle phase transitions during mitosis (38). In vertebrates, the Kinesin-4 family has five members (KIF4, KIF7, KIF21, KIF27 and NcKIF21A) and KIF4A plays a significant role in the cell cycle (32,38).

KIF4A forms part of the chromosome condensation and separation machinery (38), and the disordered function of KIF4A affects cell division and chromosome integrity. Hou *et al* (9) described the marked upregulation of KIF4A and its association with the poor survival rate of patients with CRC. Using Transwell assays, high expression of KIF4A increased the migration of CRC cells and their invasion abilities. Given the role of KIF4A in mitosis, cell cycle analysis was performed. The study showed an accumulation of cells in the G_0/G_1 phase when KIF4A expression was decreased. Subsequent assays confirmed that KIF4A could accelerate the multiplication of cancer cells by negatively modulating the promoter of the p21 gene (39). p21 is downstream of p53 and serves as a tumor suppressor regulating G_0/G_1 arrest. Matsumoto *et al* (8) showed that KIF4A also affected the lymph node metastasis of CRC cells. However, KIF4A was not involved in tumor status, venous invasion or liver metastasis, and did not influence the overall survival rate.

Kinesin-5. Homotetrameric kinesin-5 motors have vital roles in the cell cycle via regulation of spindle formation (40). Thus,

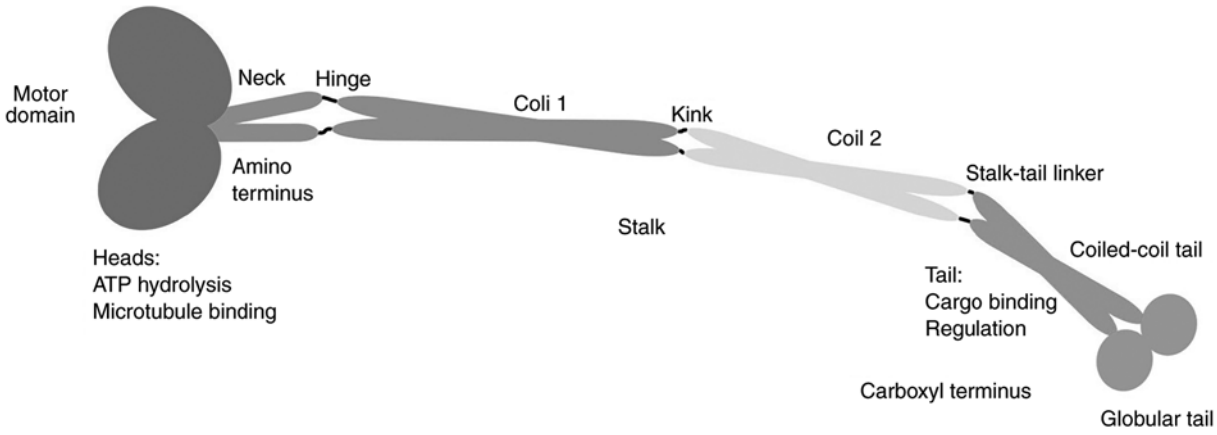

Figure 1. Outline for the kinesin dimer structure, showing its domains and the neck.

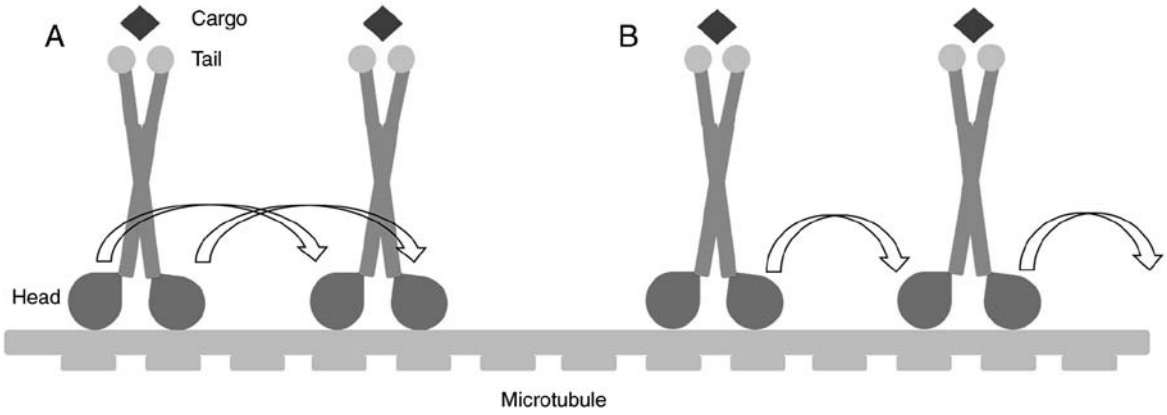

Figure 2. Kinesin proteins convey cargo along microtubules via mechanical force powered by ATP hydrolysis and walk in an (A) 'inchworm' or (B) 'hand-over-hand' manner. The arc-shaped arrows represent the direction that the heads of the kinesins move in.

Kinesin-5 family members are essential for cell growth and multiplication (41).

Cancer stem cells (CSCs) are involved in the initiation of carcinoma cell growth and tumorigenesis (42). Imai *et al* (43) detected a significantly upregulated level of KIF11 in gastric cancer (GC) and showed that KIF11 was correlated with the activity of CSCs in GC. A subsequent study used spheroid colony formation assays to measure how KIF11 expression affected the stemness of CRC cells (16). In CRC cells, the KIF11 defect markedly decreased the number and dimension of spheres, indicating an important role of KIF11. However, phenotypic studies indicated that there were no correlations between KIF11 and clinicopathological characteristics.

Kinesin-6. Categorized as an N-type kinesin, Kinesin-6 family members have a conventional structure and are involved in cytokinesis and spindle arrangement (44). This family comprises three proteins, KIF20A, KIF20B and KIF23, two of which have been reported to correlate with CRC progression (12,15).

KIF20A is localized in the Golgi apparatus and is responsible for the converse conveyance of Golgi membranes. Upregulation of KIF20A has been observed in some malignant carcinomas (45). With regard to CRC, Xiong *et al* (15) demonstrated that KIF20A was upregulated in CRC cells and promoted tumor growth *in vivo*. From data extracted by the Gene Expression Omnibus database (http://www.ncbi.nlm.nih.gov/geo/) and The Cancer Genome Atlas (TCGA; https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga), it was found that elevated expression of KIF20A was associated with the poor survival rate of patients with CRC. Furthermore, deficient KIF20A expression could increase the apoptosis of cancer cells after treatment with fluorouracil and oxaliplatin. By contrast, the overexpression of KIF20A via transfection was associated with the downregulation of apoptosis-related proteins, which provided evidence that KIF20A affected the chemoresistance of CRC cells. Notably, this study also showed that increased KIF20A expression contributed to the increased phosphorylation of JAK2 and STAT3. Interference with the JAK2/STAT3 pathway markedly prohibited CRC cell proliferation and reversed the decrease in apoptosis of CRC cells stimulated by the dysregulation of KIF20A. Thus, KIF20A was proposed to promote CRC carcinogenesis by activating the JAK2/STAT3 signaling pathway.

Lin *et al* (12) found that silencing KIF20B decreased the migration and invasion abilities of cancer cells, and had effects on the expression of the epithelial-mesenchymal transition (EMT)-associated transcription factors Snail and Twist. Subsequent experiments showed that the decrease

Table I. Roles of various KIFs in colorectal cancer.

Family name	Kinesin	Kinesin type	Subcellular localization	Reported roles in CRC	Supposed mechanisms	(Refs.)
Kinesin-3	KIF14	N-3	Spindle, nucleus, cytoplasm, midbody	Overexpressed in CRC tissue. Upregulation is associated with CRC tumorigenesis.	Activates Akt and expedites the cell cycle, which is negatively correlated with miR-200c.	(17)
Kinesin-4	KIF4A	N-5	Spindle, nucleus matrix, midbody, chromosome	Overexpressed in CRC tissue. High expression leads to poor survival in human patients with CRC and increased migration and invasion in CRC.	Negatively modulates the promoter of p21 gene, which is downstream of the p53 gene and serves as a tumor suppressor regulating G_0/G_1 arrest.	(8,9)
Kinesin-5	KIF11	N-2	Spindle pole, cytoplasm	Regulates cancer cell stemness.	N/A	(16)
Kinesin-6	KIF20A	N-6	Spindle, Golgi apparatus	Overexpressed in CRC tissue. Elevated expression associated with poor survival, increased cell proliferation and resistance to chemotherapy in CRC.	N/A	(15)
	KIF20B	N-6	Nucleus, nucleolus, nucleoplasm, centrosome, spindle, spindle pole, midbody, axon, growth cone	Overexpressed in CRC tissue. Associated with cancer metastasis and patient prognosis.	Promotes the EMT mediated by Gli1 and influences the formation of cell protrusions. Activates the JAK/STAT3 pathway.	(12)
Kinesin-8	KIF18A	N-8	Centrosome, nucleus, ruffle, cytoplasm	Overexpressed in CRC tissue. Increased KIF18A expression is correlated with elevated proliferation, migration and invasion of CRC cells. Loss of KIF18A increases apoptosis.	Promotes CRC progression and influences apoptosis by regulating Akt signaling.	(10,51)
Kinesin-10	KIF22	N-8	Nucleus, cytoskeleton	Overexpressed in colon cancer tissue. Elevated expression associated with tumor grade and clinical stage. Suppression of KIF22 could repress cancer cell proliferation and xenograft tumor growth.	N/A	(14)
Kinesin-11	KIF26B	N-11	Cytoskeleton, cytoplasm	Overexpressed in CRC tissue. High expression associated with tumor size, AJCC stage, T stage, N stage and differentiation histology. An independent prognostic factor of overall survival for patients with CRC.	N/A	(13)

Table I. Continued.

Family name	Kinesin	Kinesin type	Subcellular localization	Reported roles in CRC	Supposed mechanisms	(Refs.)
Kinesin-13	KIF2A	M	Centrosome, spindle, pole, spindle, cytoplasm	Overexpressed in CRC tissue. High expression associated with TNM stage and tumor status, and indicates a poor prognosis in patients with CRC.	N/A	(7)
	KIF2C/ MCAK	M	Nucleus, cytoskeleton, centromere, kinetochore	Overexpressed in CRC tissue. Elevated expression associated with lymph node metastasis, venous invasion, peritoneal dissemination, Dukes' classification and the poor survival of patients with CRC.	Induces spontaneous CD4(+) T-cell responses of the Th1-type. Aurora B phosphorylates MCAK and regulates its catalytic ability, which influences the cell cycle.	(11,18,62,65)

KIFs, kinesin family members; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; miR, microRNA.

in glioma-associated oncogene 1 (Gli1) expression was associated with impaired KIF20B expression, while the overexpression of Gli1 could relieve the loss of migration ability of CRC cells resulting from the silencing of KIF20B. Gli1 can activate EMT, thereby promoting cancer metastasis (46). Thus, KIF20B was speculated to stimulate Gli1-mediated EMT. The latter experiments performed by Lin *et al* (12) also revealed the significance of KIF20B in the formation of cell pseudopod protrusions and actin cytoskeleton dynamics. An evaluation of clinical data found that KIF20B was associated with tumor status and metastasis, and its high expression was correlated with the poor overall survival rate of patients with CRC.

Kinesin-8. Kinesin-8 is indispensable for appropriate allocation of chromosomes in several animal species (47,48). Members of the Kinesin-8 family can modify spindle activity and participate in the segregation of chromosomes (49).

A member of the Kinesin-8 family, KIF18A, serves as an MT depolymerase and plays an important role in chromosome agglutination (50). Nagahara *et al* (10) showed that increased KIF18A expression notably increased the proliferation, migration and invasion abilities of CRC cells. Zhu *et al* (51) confirmed that overexpression of KIF18A could accelerate tumor growth in chronic colitis. By contrast, silencing the gene encoding KIF18A increased the apoptosis of tumor cells, which was further confirmed by the observation of the elevated expression of caspase-3 (51). Immunohistochemical assays showed that the phosphorylation level of Akt was significantly decreased in *kif18a*$^{-/-}$ dysplasia compared with that in the wild-type (51). These data indicated that KIF18A promotes CRC progression and influences apoptosis by regulating Akt signaling.

Kinesin-10. The Kinesin-10 subfamily in humans has a single member termed KIF22, which is also known as Kinesin-like 4 (KNSL4)/Kinesin-like DNA binding protein. KIF22 is a chromokinesin that participates in regulating chromosome dynamics during mitosis (52). KIF22 has two nuclear localization sequences (53) and possesses a helix-hairpin-helix DNA-binding motif feature, which contributes to its activity as a transcription factor and the regulation of gene expression (54). The expression of KIF22 has been reported to be upregulated in CRC, and is correlated with tumor stages, rather than with lymph node metastasis or tumor differentiation (14). In addition, interference with KIF22 expression by short hairpin RNA inhibited cell proliferation *in vitro* and xenograft tumor growth in *in vivo* models (14). Since it has been reported that KIF22 modulates the expression of CDC25C, a gene involved in the regulation of CDK1 activity and control of mitosis (55), it is quite possible that KIF22 promotes CRC cell proliferation by regulating CDC25C/CDK1 activity.

Kinesin-11. Characterized by the presence of a divergent catalytic core, Kinesin-11 proteins are distinct from other kinesins and play a role in signal transduction pathways (56).

KIF26B, encoded by a gene situated on the chromosome region lq44 (57), is located downstream of the zinc finger protein Stall1. Wang *et al* (13) identified a marked upregulation of KIF26B in CRC cells and reported that the expression of KIF26B was associated with tumor size, tumor status and

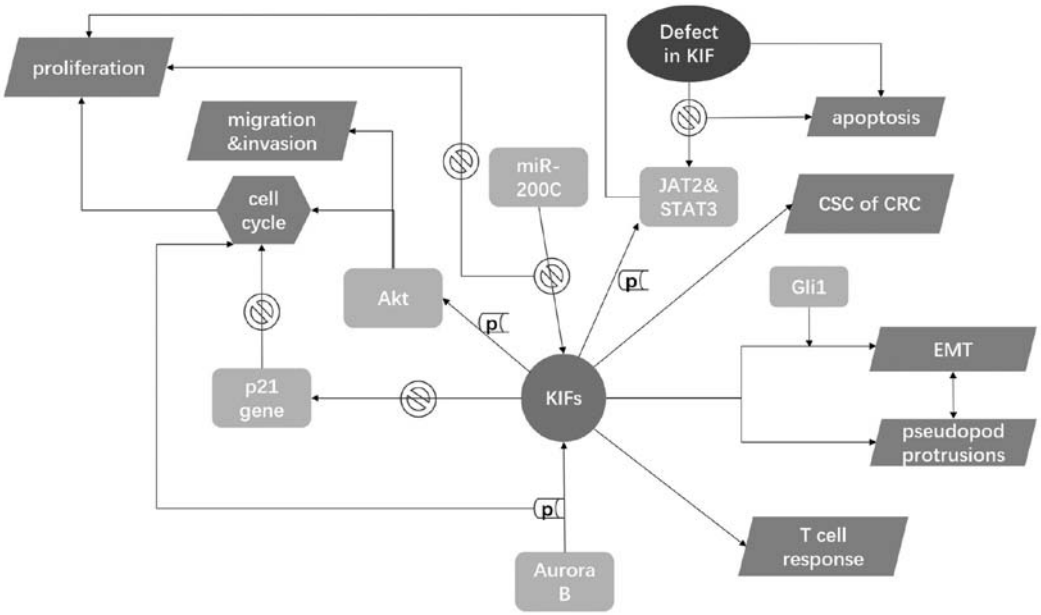

Figure 3. Roles of KIFs in the regulation of CRC tumorigenesis. KIFs participate in diverse biological processes as microtubule-dependent transporters. Aurora B phosphorylates MCAK to regulate its catalytic ability and thus affects CRC cell growth by modulating the cell cycle, whereas miR-200C binds to KIF14 to inhibit its promotion of cell proliferation. Moreover, KIFs participate in various signaling pathways, some of which are relevant to the cycle phase transition in mitosis. Deficiency of KIFs increases apoptosis and affects the activity of CSCs. KIFs also are involved in evoking the T cell-mediated immune response, as well as accelerating EMT and the formation of EMT-related pseudopod protrusions. The one-way arrows represent a facilitation effect. The bidirectional arrows represent a link between two events. The stop signs represent a blocking effect. The box that contains a 'p' represents a phosphorylation effect. KIFs, kinesin family members; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; miR, microRNA; CSC, cancer stem cell.

histological differentiation. Survival analyses showed that a high expression level of KIF26B led to low overall survival rate and was a biomarker for a poor prognosis in patients with CRC. Further, defects in KIF26B expression induced a decrease in the expression of cyclin D1 and attenuated CRC cell proliferation.

Kinesin-13. Members of the Kinesin-13 family function as MT depolymerases, participating in the formation and separation of cilia, as well as the regulation of axon development and rehabilitation (58,59). The proteins of this family are M-type kinesins and include KIF2A, KIF2B, KIF2C/MCAK and KIF24 (35).

KIF2A functions as a MT depolymerase. In CRC, Fan *et al* (7) analyzed the expression of KIF2A in various tissue samples and observed its significant upregulation in cancer tissues compared with that in normal tissues. Furthermore, KIF2A was correlated with TNM stage and tumor status. Specifically, higher expression of KIF2A correlated with later TNM stages and higher levels of lymph node metastasis. However, no correlations were found between KIF2A expression and preoperative carcinoembryonic antigen level, histological type, tumor location or differentiation. Survival analyses also demonstrated the potential value of KIF2A in predicting a poor prognosis in patients with CRC.

MCAK, encoded by a gene on the chromosomal region 1p34.1 (60), catalyzes the disassembly of MTs from both ends by modulation of mitotic kinases (61). Ishikawa *et al* (11) found that the overexpression of MCAK mRNA expression could predict lymph node metastasis and could be used as an independent predictor of a poor prognosis in patients with CRC. Furthermore, Ritter *et al* (18) showed that Aurora B, a vital kinase involved in modulating mitosis, could induce the serine-192-mediated phosphorylation of MCAK to influence its catalytic ability and affect tumor metastasis. Interfering with MCAK phosphorylation led to interference with the transition from prometaphase to metaphase and induced abnormalities in chromosome dynamics. Bioinformatics analysis of a variety of single-nucleotide polymorphisms showed that an E403K mutation could also affect MCAK activity and is crucial for CRC progression (62).

NY-CO-58, which is identical to MCAK and KNSL6 (63), is classified as a tumor antigen and interacts with IgG antibodies in patients with CRC (64). Gnjatic *et al* (65) observed significant upregulation of NY-CO-58/MCAK expression in CRC samples. Notably, NY-CO-58/MCAK also seemed to influence tumor growth, based on the detection of Ki-67 expression, and could stimulate spontaneous T-cell responses consisting mainly of $CD4^+$ T cell-mediated immune reactions. Cytoplasmatic staining indicated that $CD4^+$ T cells stimulated by NY-CO-58/MCAK secreted Th1-type cytokines to evoke an immune response, under the regulation of T regulatory cells.

4. Summary and perspectives

As the main MT-dependent cellular transporters, kinesins have been studied for decades and have been shown to be involved in a number of diseases. Studies have shown that dysregulated kinesin expression and function could contribute to the tumorigenesis and metastasis of several cancer types, including breast, lung and colon cancer. In CRC, expression levels of KIF14, KIF18A, KIF20A, KIF4A, KIF20B and MCAK have been reported to be associated with tumor progression and prognosis via the regulation of cell survival, the cell cycle, EMT and MT dynamics (Figs. 4 and 5). KIF11,

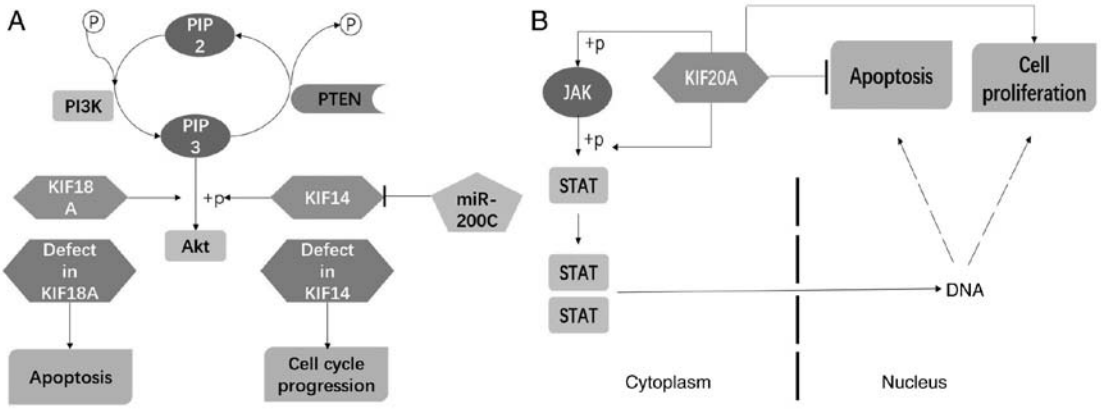

Figure 4. KIFs regulate CRC carcinogenesis via (A) Akt and (B) JAK2-STAT3 signaling pathways. The straight arrows represent a direction facilitation effect. The curved arrows represent a transformation from reactants to products. The dotted arrows represent an indirect facilitation effect. The circle that contains a 'p' represents a phosphate group. The combination of a horizontal line and a vertical line represents a repression effect. KIFs, kinesin family members; miR, microRNA.

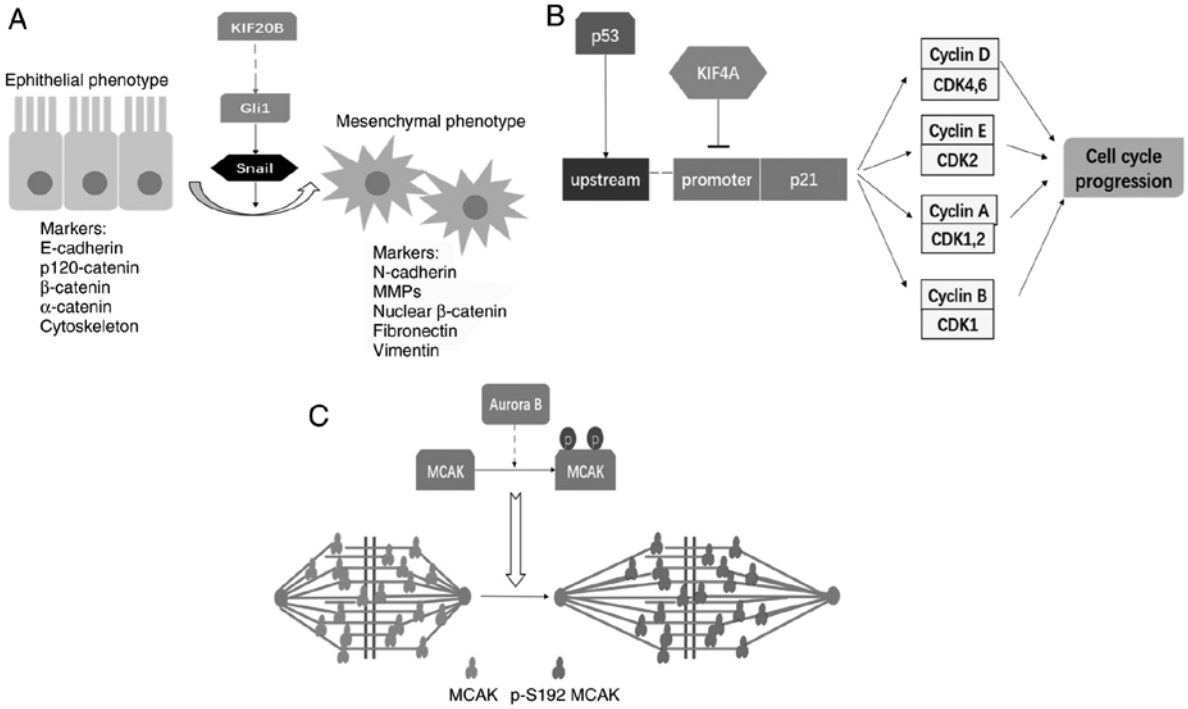

Figure 5. KIFs function to affect the CRC cell cycle, EMT and the MT dynamic. (A) KIF20B modulates Gli1-mediated EMT to affect CRC carcinogenesis (The red arrow shows the potential role of KIF20B in Gli1/Snail induction). (B) KIF4A negatively regulates the promoter of p21 to influence the cell cycle. (C) The phosphorylation of S192 in MCAK induced by Aurora B plays an essential role in the catalytic ability of MCAK to influence the MT dynamic [referred to by Zong *et al* (78) and Ritter *et al* (18)]. The arc-shaped arrows represent a transformation between two different cell phenotypes. The solid arrows in (A) and (B) represent a direct facilitation effect. The solid arrow in (C) represents a transformation. The dotted arrow represents an indirect facilitation effect. The combination of a horizontal line and a vertical line represents a repression effect. The broad arrow in (C) represents the contribution of the phosphorylation of MCAK to MT dynamics. KIFs, kinesin family members; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition.

KIF22, KIF26B and KIF2A also contribute to the development of CRC carcinogenesis; however, the underlying mechanisms remain to be identified.

Recent studies have revealed that kinesins regulate CRC cell survival via Akt and JAK2-STAT3 signaling pathways (Fig. 4). Akt serves as a key regulator of signal transduction in several classic pathways. In the PI3K-Akt pathway, PI3K modulates the phosphorylation of Akt via the induction of PIP3, stimulating a cascade able to activate downstream signal molecules such as NF-κB and p53 to control cell survival (66). Additional studies have shown that KIF14 and KIF18A regulate CRC cell proliferation and apoptosis by increased Akt signaling (Fig. 4A). With respect to the JAK2-STAT3 pathway, the activation of the expression of downstream genes such as p53, Bcl-2 and Cyclin D1 is involved in regulating cell growth and apoptosis (67). Xiong *et al* (15) found that KIF20A modulates the activity of JAK2 and STAT3 to affect CRC tumorigenesis and chemoresistance (Fig. 4B). These studies have provided insight into the KIF-associated signaling pathways that modulate tumor cell proliferation and survival, but further studies are still needed to verify the mechanisms involved.

Dysregulation of cell cycle-related factors can trigger disorders in the cell cycle and cause impairments in cell proliferation (68). p21 is a well-known cyclin-dependent kinases inhibitor (CDKI) that regulates the activities of the CDKs, including cyclin D/CDK4 or CDK6, cyclin E/CDK2, cyclin A/CDK1 (Cdc2) or CDK2, and cyclin B/CDK1, to modulate the cell cycle, serving as a tumor suppressor (69). Hou *et al* (9) found that the nuclear localization of KIF4A results in its direct binding on the p21 promoter and negative regulation of the expression of p21. Overexpression of KIF4A in CRC has been reported to downregulate p21 expression, which further enhances cell proliferation by promoting cell cycle progression, suggesting that KIF4A-targeted therapy could be effective in inhibiting CRC tumor growth (Fig. 5B).

Epithelial cells undergo EMT to gain migrative and invasive capacity, favoring the metastasis of cancer cells from the primary tumor site to other tissues or organs (Fig. 5A). Tumor metastasis is associated with the aggravation of cancer and a poor prognosis for patients. Lin *et al* (12) found that KIF20B in pseudopod protrusions promoted cell invasion and metastasis by regulating actin cytoskeleton dynamics, and that knockdown of KIF20B downregulated Gli1 expression and decreased the expression levels of EMT marker proteins. Thus, targeting KIF20B could be a promising treatment approach in cancer therapy (12).

MTs, as components of the cytoskeleton, play crucial roles in cellular transport and spindle dynamics. Furthermore, MCAK acts as a MT depolymerase to regulate the assembly of the mitotic apparatus and disassembly of the sister-chromosome to affect the cell cycle via MT dynamics (70). Overexpression of MCAK has been correlated with several cancer types (71). Ritter *et al* (18) showed that in CRC, serine 192 was the key site regulating MCAK catalytic ability induced by Aurora B (Fig. 5C). Thus, the regulation of phosphorylation at serine 192 might be a novel way to modulate the activity of MCAK for cancer therapy.

In addition to regulating cell survival, the cell cycle, EMT and MT dynamics, kinesins are also involved in regulating CRC chemoresistance. Fluorouracil and oxaliplatin are anticancer agents that have been used in clinical trials to treat CRC (72,73). Xiong *et al* (15) found that the overexpression of KIF20A could attenuate the increase in the BAX/BCL-2 ratio induced by fluorouracil and oxaliplatin to protect cancer cells against apoptosis. After knocking down KIF20A, CRC cells underwent increased apoptosis. The contribution of KIF20A to chemoresistance in CRC indicates that kinesins might play a vital role in the clinical therapy of CRC.

Given that a considerable number of kinesins have been found to promote tumorigenesis and growth in CRC, targeting this family of motor proteins seems a promising approach for cancer treatment. Several inhibitors against KIFs have already been tested for their efficacy in the treatment of cancer: Ispinesib, AZD4877, ARRY-520, SB-743921, ARQ 621, LY2523355, MK-0731, EMD534085 and 4SC-205 targeting Eg5; GSK923295 targeting CENPE (KIF10); peptide targeting MPP1 (KIF20B); AZ82 and SR31527 targeting KIFC1; and lidocaine and tetracaine targeting KIF5C (74,75). In CRC, studies have reported novel agents targeting KIF11 (also known as Eg5, a kinesin spindle protein), which can repress tumor progression. Zhang *et al* (76) identified SRI35566 as a new inhibitor that could interact directly with Eg5. More importantly, SRI35566 could prevent drug resistance, which is common among agents targeting monastrol-binding sites. K858 was shown by Nakai *et al* (77) to interfere with centrosome separation and cause cell cycle arrest, effectively eliminating cancer cells without damaging MT activity. Considering the crucial roles of KIFs in CRC, more studies are needed to explore the mechanisms by which kinesins influence tumor progression, to provide insight into using kinesins as biomarkers for prediction of CRC progression, and to identify therapeutic targets for efficient treatment of CRC in the future.

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Availability of data and materials

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Authors' contributions

DH performed the analysis and wrote the manuscript. HY contributed to the conception of the study. JDH contributed to the conception of the study and revised the manuscript. JPC contributed to the conception of the study. JC contributed to the conception of the study, manuscript preparation and revision. All authors have read and approved the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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