Review

Role of motor proteins in human cancers

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A B S T R A C T

Motor proteins include several protein families (Kinesin, Dynein and Myosin) responsible for intracellular transport, intercellular communication, among other functions. In cancer cells, motor proteins along with microtubules (MT) and other tubulin and actin structures, are crucial for cell proliferation and invasion. The cBioPortal platform for Cancer Genomics database was queried for solid cancers in a combined cohort of 9204 patients with complete cancer genomics data. To assess the importance of motor proteins in cancer, copy number alterations (CNAs) and survival rates were analyzed in the combined dataset. Kinesin, Dynein, and Myosin families showed CNAs in 47%, 49%, and 57% of patients, respectively, in at least one of their members. Survival analysis showed that CNAs in Kinesin and Dynein, families' genes in the same patients were significantly correlated to decreased overall survival. These results added more evidence to previous literature highlighting the importance of motor proteins as a target in cancer therapy. Kinesin inhibitors could act by several mechanisms such as inhibiting spindle assembly or centrosome separation during mitosis, leading to cell cycle arrest and eventually apoptosis. Dynein inhibitors modulate Dynein's activity and MT binding, inhibiting cell proliferation and invasion. Myosin inhibitors act by stabilizing MT, inducing cell cycle arrest and inhibiting invasiveness. Increasing the specificity of motor proteins targeting drugs could improve cancer therapy and patient survival.

1. Classification and functions of motor proteins

Motor proteins are a general term that includes several families of proteins responsible for intracellular transport, intercellular communication, among many other functions. Three superfamilies of motor proteins are responsible for directional movements along microtubules (MT) or actin filaments in an energy-requiring process (Kruppa and Buss, 2021). Motor proteins carry and transport several types of cargo within the cell integrating with other proteins to allow for intercellular communication. Tunneling nanotubes (TNTs), which are thin membranous channels, play a crucial role in intercellular communication. They are basically formed of F-actin with a width 50–1000 nm and a length from a few to 100 μm (Wiger et al., 2014). TNTs allow the rapid exchange of cellular cargos between connected, non-adjacent cells. Through this process, cellular organelles, proteins, microRNAs, vesicles, molecules, ions and even pathogens could be transported. Thus, TNTs are involved in many physiological and pathological processes such as signal transduction, immune response, cell differentiation, and apoptosis (Roehlecke and Schmidt, 2020).

Kinesin and Dynein move on MT towards the plus end (exposing the β-tubulin subunits) and the minus end (exposing the α-tubulin subunit), respectively. On the other hand, Myosin...
motors move on actin filaments forming a dynamic network between cellular membrane compartments and cytoskeleton (Kruppa and Buss, 2021). Myosin and Kinesin had a common ancestor protein related to GTPases, whereas Dynein is an AAA ATPase (Sweeney and Holzbaur, 2018).

Kinesin superfamily proteins (KIFs) consist of many proteins that have some structure similarity. They all share two heavy chains (motor domain) and two light chains (cargo binding domain). Motor domain has a highly conserved ATP-binding and MT-binding sequences (Okada and Hirokawa, 2000). Cargo carried by KIFs may include vesicles, organelles or macromolecules. Kinesins are also involved in mitosis through aiding in assembly of spindle MTs, spindle-chromosome attachment, and centrosome separation (Skold et al., 2005). Mutations in KIFs could cause mitotic arrest and apoptosis (Hallen et al., 2008).

On the other hand, Dyneins could be classified into two classes, axonemal and cytoplasmic. Axonemal dynein could be found in cilia and flagella. Alterations in Dynein axonemal heavy chain (DNAH) genes have been initially detected in patients with cilia dysfunction diseases such as sperm immobility (Ben Khelifa et al., 2014) and primary ciliary dyskinesia (Li et al., 2016).

Cytoplasmic dynein is a large protein complex consisting of heavy chain (DYNCH1), intermediate chain (DYNCH1L1), light intermediate chain (DYNLIC), and light chain (DYNLC) that moves along MTs to their minus end (Neubauer et al., 2018). Cytoplasmic dynein transports several types of cargo such as mRNA, vesicles, growth factors, and transcription factors. Also, they play an important role in mitotic spindle localization (Reck-peterson et al., 2018).

Myosin superfamily is actin-dependent molecular motor proteins that interact with microfilaments, converting energy from ATP hydrolysis to mechanical stress (Krendel and Mooseker, 2005). More than 18 distinct classes of myosins were discovered (Li and Yang, 2016).

2. Role in cancer pathogenesis

Motor proteins play important roles in many human diseases via multiple pathways including disrupted mitochondrial dynamics. For example, in cancer cells, mitochondrial positioning is crucial for providing energy for invasion in a MT-dependent manner (da Silva et al., 2014). Localization of mitochondria in the leading edge of the cell correlates with faster and directional cell movement, helping invasion and early metastasis. Some Kinesins such as Kinesin-1 were reported to be involved in re-localization of mitochondria to the leading edge of the cell. Hence, depletion of Kinesin-1 suppresses mitochondrial re-localization slowing tumour cell migration and reducing invasion (Desai et al., 2013).

Kinesins were reported to be overexpressed or under-expressed in many cancers, suggesting that different members have different functions. For instance, KIF2, KIF14 were found to be overexpressed in breast cancer and some retinoblastomas, suggesting an oncogenic role (Stevens et al., 2011). On the other hand, KIF14 acts as a tumour suppressor and metastasis inhibitor in lung adenocarcinoma (Hung et al., 2013). KIF20A is overexpressed in pancreatic cancer while KIF10 is under-expressed in hepatocellular carcinoma (Taniuchi et al., 2005; Liu et al., 2009). KIF3 and KIF4 could be playing a tumour suppressor role in gastric cancer (Haruki et al., 2010; Gao et al., 2011). However, some KIF family members, including KIF3, KIF4 and KIF22, have conflicting roles in tumorigenesis (Stevens et al., 2011; Hung et al., 2013). Inhibition of some Kinesins was reported to reduce cancer cell motility. KIF20A inhibition was reported to reduce motility of bladder cancer cells (Mandal et al., 2019).

Also, silencing of KIF21B was found to suppress the proliferation of several cell lines, increase apoptosis, and inhibit NSCLC tumor growth in vivo, suggesting a sort of proliferation promoting effect of KIF21B (Sun et al., 2020). Another member of Kinesins, KIF26B, was observed to play an important role in cell invasion in breast cancer through driving epithelial-mesenchymal transition (EMT) (Yang et al., 2019).

One possible mechanism by which Kinesins play a crucial role in tumorigenesis could be through their effect on MT. Some Kinesins proteins such as KIF4, KIF8, and KIF13 were reported to actively regulate MT dynamics (Walczak et al., 2013). The role of MT was reported in many cancers in humans and animal models. Thin membrane tubes were observed in animal model of malignant brain tumors in vivo. The observed membrane tubes, termed tumor microtubes (TMs), are longer and wider than TNTs observed in vitro (Osswald et al., 2015). Effective intercellular communication and signaling through both TNTs and TMs may play an important role in the cancer pathogenesis, tumor survival and progression particularly in solid tumors. Also, they could affect treatment response (Roehlke and Schmidt, 2020).

Regarding Dynein superfamily, several nonsynonymous single nucleotide variations and indels were reported in some members such as DNAH2, DNAH5 and DNAH10 in some types of renal cell carcinomas (Arai et al., 2015). Also, DNAH5 could play an important role in the development of colorectal cancer (Xiao et al., 2015). DNAH8 has been associated with metastasis and poor prognosis of prostate cancer (Wang et al., 2016). DNAH9 was reported to show a high mutation rate in breast cancer (Gruel et al., 2014). There are several reports of the role of cytoplasmic dynein in cancer. For example, cytoplasmic Dynein was reported to promote tumor progression in colorectal and cervical cancer (Martini et al., 2018). Such reports could suggest that cytoplasmic Dynein could be an important drug target in cancer treatment.

Overexpression of myosin has been reported in various cancers, including ovarian cancer (Yoshida et al., 2004), breast cancer (Betapudi et al., 2011), colorectal cancer (González et al., 2012), prostate cancer (Ruppender et al., 2015), among many others. Hence, Myosins have been a target of several cancer therapy studies.

3. Analysis of clinical data

3.1. Methods

Virtual combined study on 9204 patients / 9276 samples in 19 studies with solid tumors (including brain (Glioma), lung, breast, colorectal, HCC, ………) were created using public datasets on cbioPortal (RRID SCR: 014,555 (Cerami et al., 2012; Gao et al., 2013) platform. The selected studies provide multidimensional cancer genomics data. Queried data include disease-specific survival, normalized gene expression values, mutation status, and copy number alterations (CNAs) of genes, along with demographic and clinical data. Studies containing hematological malignancies were excluded. CNAs was performed using Genomic Identification of Significant Targets in Cancer (GISTIC) algorithm in cbioPortal.

The study included 4811 females and 4199 males of different ethnicities (white: 6456; African: 847; Asian: 515; American Indian or Alaska native: 26; native Hawaiian or other pacific islanders).

3.2. Transcriptomic analyses

The generation and normalization of gene expression values (represented as z-score) are described in the cohorts’ respective publications. Wilcoxon rank-sum test and Kruskal-Wallis test were used to test for differences between two or more than two groups, respectively. Significance in survival analyses was determined by
log-rank tests. P-value was corrected for multiple comparisons using Bonferroni correction, values < 0.05 were considered significant.

### 3.2.1. Kinesins

For the Kinesin family, 4362 cases (47 %) have an alteration in at least one of the 46 members. The highest CNAs frequency in Kinesin family members was recorded for KIF2C and KIF26B for which the frequency of alteration was 9 % and 6 % respectively. Most of CNAs for both genes were gain (a low-level gain (few additional copies, often broad) or copy number deviation from the normal state will be reflected as increment of the read count) (Fig. 1, A, B, respectively). Both KIF13B and KIF21B have CNAs frequency of 5 %, for KIF13B was mostly gain, whereas for KIF21B CNAs showed shallow deletion (shallow loss, possibly a heterozygous deletion) (Fig. 1, C, D, respectively).

A: KIF2C mRNA expression versus its CNAs; B: KIF26B mRNA expression versus its CNAs; C: KIF13B mRNA expression versus its CNAs; D: KIF21B mRNA expression versus its CNAs. The lower panel shows the color scheme used for CNAs types.

Previously, KIFC1 was reported to be highly expressed in several types of cancer including ovarian cancer (Pawar et al., 2014), breast cancer (Pannu et al., 2015), bladder cancer (Alekseev et al., 2014), lung cancer (Grinberg-Rashi et al., 2009), and others (Chan, 2011). However, the exact mechanism of KIFC1 overexpression remains unclear (Pannu et al., 2015).

One mechanism could be through some hormones. For example, E2 (estrogen-17beta-estradiol) has been shown to cause overexpression of some Kinesins including KIF4A, KIF15, KIF20A, and KIF23 in experimental context (Zou et al., 2014). Both KIF26B mRNA and protein were upregulated in breast cancer. Also, high expression of KIF26B in breast cancer was significantly associated with larger tumor size, higher histological grade, lymph node involvement, metastasis, and short survival (Sun et al., 2013). In addition, high KIF26B expression positively correlated with ER (estrogen receptor) status in breast cancer (Uchiyama et al., 2010).

Also, KIF21B overexpression was found to be correlated with poor disease-free survival in prostate cancer (Arai et al., 2019), non-small lung cancer (Sun et al., 2020) and hepatocellular carcinoma (Zhao et al., 2020).

### 3.2.2. Dynains

Regarding the Dynein family, 4509 cases (49 %) have an alteration in at least one of the 38 members. For DNAH5 the CNAs frequency was 9 %, mostly gain and other few mutations. The CNAs in DYNL1T2B were amplifications (high-level amplification i.e.: more copies, often focal) with frequency 8 % (Fig. 2 A, B respectively). DNAH7, DNAH8, DNAH9, DNAH11, DNAH17 and DYNHC2H1 all have a frequency of 5 %, mostly with gain alterations (Fig. 2 C, D respectively).

A: DNAH5 mRNA expression versus its CNAs; B: DNAHT2B mRNA expression versus its CNAs; C: DNAH9 mRNA expression versus its CNAs; D: DNAH11 mRNA expression versus its CNAs. The lower panel shows the color scheme used for CNAs types.

Previously, DNAH5 was reported to have an increased number of nonsynonymous single- nucleotide mutations and indels in some types of renal cell carcinomas (Arai et al., 2015). It could also play an important role in the development, prognosis and treatment response of colorectal cancer (Xiao et al., 2015). DNAH8 has been reported to be associated with metastasis and poor prognosis in prostate cancer (Wang et al., 2016). DNAH9 has a substantially increased mutation rate in breast cancer (Gruel et al., 2014).

DNAH17 was also reported to be significantly associated with poor survival in many cancers, including HCC (Zhang et al., 2015). DNAH17 overexpression in cancer tissue could be explained by both gene amplification and hypomethylation (Xiaoxiao et al., 2019).

### 3.2.3. Myosins

For the Myosin family, 5210 cases (57 %) have CNAs in at least one of the 66 members. PPP1R16A, MYOM2 and MYO10 have CNAs frequency of 9 %, 7 % and 6 % respectively, observed CNAs were mostly gain, (Fig. 3).

A: PPP1R16A mRNA expression versus its CNAs; B: MYOM2 mRNA expression versus its CNAs; C: MYO10 mRNA expression versus its CNAs; D: the color scheme used for CNAs types.

Similarly, MYO10 was shown to be upregulated in many human cancers including leukemia (Ross et al., 2003), breast cancer melanoma, (Cao et al., 2014), and lung cancer (Sun et al., 2015). MYO10 overexpression was observed to be correlated to poor prognosis, metastasis, and short survival in breast and skin cancers (Tokuo et al., 2018).

Results of the current study, along with these studies suggest an important role of MYO10 in cancer development. On the other hand, MYOM2 was previously reported to be under- expressed only in the breast cancer cell lines (Fumiichiro and Miyako, 2008).

### 3.3. Survival analysis

Survival analyses were performed and Kaplan–Meier plots were generated using cBioPortal platform. Alterations in Kinesin and Dynain, families’ genes in cancer patients were found to significantly correlate to decreased overall survival (Log rank test p-value 0.0273, 0.0298, respectively). On the other hand, alterations in the Myosin family had no significant relation to overall survival (Log rank test p-value 0.0115) (Fig. 4).

### 4. Therapeutic approaches

The heterogenous nature of cancers and the wide variation in treatment response in clinical practice requires more targeted and personalized therapeutic approaches. Modern cancer therapeutic approaches include more motor proteins -acting drugs that act through several mechanisms. The dynamic equilibrium of tubulin-MT has become an important target in cancer research and drug development. Antitubulin drugs that are able to disturb the MT dynamics are in clinical use and others in clinical trials (Khwaja et al., 2021). Microtubule-targeting agents (MTAs) include classical drugs such as paclitaxel and vincristine and more cancer-specific compounds such as S-Trityl-l-cysteine (STLC) (Yuki et al., 2021). MTAs bind to tubulin dimers or assembled MT triggering cell death by multiple mechanisms, including prolonged activation of the spindle assembly checkpoint (SAC) during mitosis and by inducing senescence in interphase (Teshima et al., 2021).

### 4.1. Kinesin inhibitors

Kinesin inhibitors are mostly small molecules specific for particular Kinesins. For example, monastrol acts as an allosteric inhibitor for one member of the Kinesin-5 family, namely Eg5. Eg5 is a plus- end directed Kinesin- related motor protein which is a crucial regulator in centrosome separation and spindle assembly in mammalian somatic cells. It was shown that monastrol has an antiproliferative effect on human breast cancer cell lines (Marques et al., 2016).

Hybrid analogues of monastrol-1,3,5-triazine were reported to have an anticancer activity in vitro several cancer cell lines. This anticancer activity is suggested to be through several mechanisms including Kenesin inhibition (Wu et al., 2020).
S-trityl-L-cysteine (STLC) is another Eg5 inhibitor, which was reported to have an antitumor activity in neuroblastoma. STLC was found to be able to induce cell cycle arrest and apoptosis in a dose-dependent manner in neuroblastoma. The mechanism of this effect is yet to be clarified. However, it was found that mitogen-activated protein kinase and nuclear factor κB signaling pathways had contributed to STLC mediated cell cycle arrest and apoptosis (Wu et al., 2018).

Another potent Eg5 inhibitor is Dimethylenastron. It has been reported that Dimethylenastron was shown to inhibit Eg5 activity and reduce pancreatic cancer cells migration and invasion (Sun et al., 2011). Dimethylenastron derivatives such as dihydropyrimidin-2(1H)-one are potent Eg5 inhibitors previously reported to target human breast cancer cells in vitro with low cytotoxicity to normal cells. This specificity is a great advantage over many classical drugs commonly used in treatment of cancer. It has been reported that dihydropyrimidin-2(1H)-one has the ability to prevent normal mitotic spindle formation during mitosis resulting in apoptosis of breast tumor cells (Guido et al., 2015). Hence, dihydropyrimidin-2(1H)-one is a promising candidate because of its selective bioactivity in tumor cells.

Other Kinesins inhibitors include paprotrain and its derivatives. BKS0349, a new paprotrain high affinity derivative, is a KIF20A-specific inhibitor (Ferrero et al., 2019). BKS0349 was shown to be a promising anticancer agent in an experimental mouse model of ovarian endometriosis (Qiao et al., 2021).

The Kinesin Spindle Protein (KSP) inhibitor, ispinesib (SB-715992) was reported to act as an antiproliferative and...
apoptosis inducer in several breast cancer cell lines. Moreover, it was found to produce partial responses in a phase II clinical trial in women with metastatic breast cancer (Purcell et al., 2010). On the mechanistic level, it has been reported that the KSP inhibitor SB743921 inhibits growth and induces apoptosis of breast cancer cells through a cascade of reactions affecting p53, Bcl-2, caspases and DTL expression and function (Zhu et al., 2016).

4.2. Dynein inhibitors

Dynein has been a target of anticancer therapy in many studies. Several dynein proteins act as force-producing protein associated with MT and able to bind and hydrolyze ATP (Schmidt and Carter, 2016). One potential Dynein inhibitor is Dynarrestin, which is an inhibitor of the cytoplasmic Dynein 1 and 2 (Khwaja et al., 2021). Also, several Dumpyrazoles derivatives were shown to be
able to modulate dynein’s activity and MT binding. Dynapyrazoles derivatives act mainly as Dynein 1 inhibitor (Santarossa et al., 2021).

Dynamin 2, one member of the dynamin proteins, is an MT-associated force-producing protein involved in producing MT bundles and able to bind and hydrolyze GTP. Dynamin inhibitors like Dynasore, Dyno-4a, MiTMAB, and Dynole-34–2, target some forms of endocytosis (Buri et al., 2021). Dynasore can inhibit cell proliferation, migration, and invasion in osteosarcoma cells via STAT3 signaling pathway (Zhong et al., 2019). Dynasore has also been reported to affect exosome endocytosis in cancer cells and inhibit the uptake of cancer cell-derived exosomes by normal cells in some types of cancer (Sinha et al., 2021). Inhibition of Dynamin by dynole 34–2 has been reported to induce apoptosis following inhibition of cytokinesis in cancer cells (Chircop et al., 2011).

Dynamin 2 could be a potential target in treatment of cancer. For this purpose, different dynamin 2 inhibitors were investigated. It has been demonstrated that dynamin 2 inhibitors were able to significantly reduce cell proliferation, increased apoptosis in Hela cell line (Lee et al., 2016). Dynamin 2 inhibitors had been shown to accelerate degradation of some crucial molecules such as c-Met. c-Met is a tyrosine kinase receptor involved in the development and progression of cancer cells through stimulating the PI3K/AKT, Ras/MAPK, JAK/STAT, SRC, Wnt/β-catenin pathways, among many others. Through increasing degradation of c-Met, Dynamin inhibitors were able to inhibit the c-Met downstream
signaling, leading to increased tumor cell apoptosis (Trochet and Bitoun, 2021).

Dynamins 2 inhibitors were known to inhibit cytokinesis during mitosis, resulting in growth arrest and apoptosis of cancer cells in several cancer cell lines including lung, cervical, and leukemia (Trochet and Bitoun, 2021).

4.3. Myosin inhibitors

Classical Myosin inhibitors such as Paclitaxel are effective anticancer drugs used for the treatment of solid tumors such as ovarian, breast and lung cancers. It acts by stabilizing MT, blocking cell progression through mitosis. Newer Myosin inhibitors’ analogues such as Flutax-1 and Flutax-2 are currently under investigation (Gerasimaite et al., 2021).

Blebbistatin is an inhibitor of non-muscle myosin II activity which was reported to affect cellular migration, invasiveness, and spreading of pancreatic adenocarcinoma in a dose-dependent manner. At higher doses than those required to interfere with migration and invasion, blebbistatin was found to inhibit cellular proliferation (Duxbury et al., 2004).

ABT-751, which is an experimental antimitotic agent, has been shown to exert cytotoxic effects in preclinical studies. Combination of ABT-751 with carboplatin has been reported to have the ability to inhibit the growth of lung cancer in cell lines (Ma et al., 2012).

5. Cytoskeletal inhibitors

Other drug classes targeting intercellular communication include actin and tubulin acting drugs. Several studies have been done to investigate the effects of various mitotic protein inhibitors on cancer progression. The actin-binding marine macrolide latrunculin A was reported to inhibit actin polymerization in human gastric cancer experimentally. Latrunculin A showed a strong anticancer activity against peritoneal dissemination of gastric cancer in mice (Konishi et al., 2009). Also, Cytochalasins (microfilament-directed agents) had showed anticancer activity through impairing the end stages of mitosis. Therefore, cytochalasins could be used in combination with other drugs to improve efficacy and decrease drug resistance (Trendowski, 2015).

Several tubulin acting drugs were also investigated for potential anticancer activity. It is worth noting that colchicine acts through tubulin inhibition and destabilization of MT, resulting in disruption of MT dynamics. This disruption of MT dynamics affects the mitotic spindle regulation resulting in cell cycle arrest. This suggests that colchicine could be able to decrease the risk of prostate and colorectal cancers in male patients with gout (Kuo et al., 2015). Noscapine, which is a natural compound with anticancer properties, was shown to target MT. Novel synthetic noscapine derivatives were of much higher potency, showing promising results in preliminary studies (Nemati et al., 2021).

Another example of tubulin acting drugs is CMPD1. CMPD1 is a Tubulin polymerization inhibitor known to impair spindle organization. It has been shown to inhibit proliferation through inducing apoptosis and G2/M cell cycle arrest in human gastric cancer (Li et al., 2013). Another mechanism by which CMPD1 could be used in cancer therapy is the selective inhibition of MAPK-2 phosphorylation. This mechanism was reported in treatment of non-small lung cancer in vitro (Breindel et al., 2013).

An example of drugs targeting MT and mitosis is harmine (a β-carboline alkaloid), which is a potent inhibitor of several genes important in MT formation, such as DYRK1A, DYRK1A, DYRK3 and DYRK2. Harmine also Inhibits DYRK1A-mediated tau phosphorylation and regulates PPARγ expression. Previous study showed that harmine affects cell proliferation and is capable of inducing apoptosis of human breast cancer cell lines (Ding et al., 2019).

Chaetoglobosin G has also been shown to induce G2/M phase arrest and subsequent inhibition of A549 cell proliferation in EGFR/MEK/ERK/LC3 pathway-dependent manner (Chen et al., 2020). Targeting mitotic proteins with pharmacological inhibitors may be a promising new approach for cancer treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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