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The mammalian Sterile 20-like kinase 4 (MST4) signaling in tumor progression: Implications for therapy

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Abstract

Cancer is a leading cause of death in humans, with a complex and dynamic nature that makes it challenging to fully comprehend and treat. The Mammalian Sterile 20-Like Kinase 4 (MST4 or STK26) is a serine/threonine-protein kinase that plays a crucial role in cell migration and polarity in both normal and tumor cells via activation of intracellular signaling molecules and pathways. MST4 is involved in tumor cell proliferation, migration and invasion, epithelial-mesenchymal transition (EMT), survival, and cancer metastasis through modulation of downstream signaling pathways including the extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) pathways. Additionally, MST4 interacts with programmed cell death 10 (PDCD10) to promote tumor proliferation and migration. MST4 phosphorylates autophagy related 4B cysteine peptidase (ATG4B) to mediate autophagy signaling, promote tumor cell survival and proliferation, and contribute to treatment resistance. Taken together, MST4 functions as an oncogene and is a promising therapeutic target which deserves further exploration.

Keywords

MST kinases; MST4; EMT; Pathways; Cancer

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Authors' contributions

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Declaration of competing interest

The authors have no competing interests to disclose.

1. Introduction

Cancer is the second most common cause of death in the world, surpassed only by cardiovascular diseases (Cancer Facts & Figures 2022, American Cancer Society). Globally there were nearly 10 million cancer deaths and 18.1 million new cases of cancer in 2020, and the worldwide burden of cancer is predicted to reach 28.0 million new cases and 16.2 million cancer deaths by 2040 *(GBD 2019, Global Burden of Disease Collaborative Network)*. Much has been known about the mechanisms of tumor initiation, progression, metastasis, and therapeutic resistance. However, the complexity, heterogeneity, and dynamic nature of various types of human cancers hinder the research community to clearly understand the biology of cancers and improve efficacies of treatments for patients with cancers.

Dissecting the molecular mechanisms that underly tumor progression, metastatic potential, and therapeutic resistance is an urgent need to save millions of lives and improve patient quality of life. MST4, a recently recognized member of Mammalian Sterile 20-Like Kinase (MST) [1], has been appreciated to play important roles in regulating cell proliferation, apoptosis, cell polarity and migration, EMT, autophagy, and cancer metastasis.

Members of the MST family of kinases have been implicated in the regulation of tissue development, cell proliferation, apoptosis, cell polarity, and migration in both normal and diseased states. Of these kinases, MST4 has garnered particular attention in its role in cancer development. Recent findings have demonstrated its important roles in promoting tumor progression by activating key downstream signaling pathways. Given its importance in cancer pathobiology, there is a need for increased efforts to further explore its mechanism of action and develop inhibitors targeting this molecule. In this review, we aim to provide a brief overview of the MST kinase family members and then focus on the current understanding of the molecular mechanisms of MST4 kinase in tumor progression and metastatic potential. We also highlight the challenges and opportunities for developing MST4-targeted therapies and provide an outlook for future research in this area.

2. Overview of the biology of MST kinases

The Mammalian Sterile 20-like (MST) kinases, belonging to the germinal center kinase (GCK) family of serine/threonine protein kinases, consist MST1 (STK4/KRS2/YSK3) MST2 (STK3/KRS1), MST3 (STK24), MST4 (STK26), and Ser/Thr protein kinase 25 (STK25), each with a conserved N-terminal kinase domain and a C-terminal regulatory domain [2,3] (Fig. 1).

Originally recognized as activating molecules upstream of mitogen-activated protein kinase (MAPK), these kinases are involved in the regulation of cell proliferation, apoptosis, development, cell polarity, and cellular migration in health and diseases including cancer [1,4]. In this section, we briefly summarize the key biological characteristics and functions of these kinases. However, as a more in-depth review is beyond the scope of this work, we recommend readers refer to other comprehensive reviews for additional information [2,5,6].

2.1. MST1 and MST2

These families of serine/threonine kinases are class II germinal center kinases, which are functionally related proteins with conserved amino-terminal kinase domains and carboxy-terminal regulatory domains that contain nuclear localization and export signals (Fig. 1) [7,8]. During apoptosis, caspase-mediated cleavage of MST1/2 removes the inhibitory C terminal regulatory domain, triggering autophosphorylation and activation of the kinase, which is then translocated into the nucleus. Nuclear translocation of the active kinase induces chromatin condensation and other events associated with apoptotic progression [9]. Ubiquitously expressed, MST1 is known as a pro-apoptotic kinase that regulates cellular and tissue stress responses. It has been documented that MST1 is involved in restricting cellular proliferation, promoting cell death, and suppressing tumor growth [10]. MST1/2 is a core component of the Hippo pathway. The Hippo pathway in mammals is made up of a kinase cascade including MST1/2 and large tumor suppressor kinase (LATS1/2) as well as the downstream effectors YAP and TAZ, which serve as transcriptional coactivators. These key elements of the Hippo pathway regulate transcription programs that play a role in cell proliferation, survival, mobility, stem cell maintenance, and differentiation [11]. A loss of function of both MST1 and MST2 leads to increased cell growth and tissue development in an organ-dependent manner. MST1/MST2 knockout mice had an increase in liver size and preferential tumor formation [10,12]. The apoptosis induction and growth inhibition functions of MST1/2 suggest that these molecules may play a tumor suppressive function.

A loss-of-function mutation of MST1 causes immunodeficiency and lymphopenia, but also autoimmune manifestations [13-15]. Of particular importance, MST1/MST2 have shown to maintain a stable T-regulatory cell pool and immune tolerance. This function is essential for the proper infiltration of T-regulatory cells into the immune environment and maintaining their immunosuppressive function, which is critical for tumor resistance and the prevention of autoimmunity [16].

2.2. MST3 and STK25

The family members of class III GC kinases, MST3, MST4, and STK25, share very high homology in the kinase domain (Fig. 1). MST3 (STK24) has two isoforms, including a longer MST3b isoform and a shorter MST3a isoform [17]. The widely expressed MST3a regulates cell motility and apoptosis, as well as neuronal migration during central nervous system development [18]. The brain-specific MST3b is activated by nerve growth factor (NGF) or inosine and localizes to neurons, where it regulates axon growth and regeneration [19].

MST3 phosphorylates and activates protein kinases that regulate cell cycle progression and cell morphology [20]. Autophosphorylation of MST3 at Thr178 is required for its kinase activation, while alteration of this residue inhibits the ability of MST3 to regulate cell migration [21].

MST3 has been implicated in cancer. In gastric cancer, MST3 overexpression predicted a poor patient prognosis, and downregulation of MST3 decreased the growth of tumor cells [22]. Studies by using clinical breast cancer samples showed that MST3 is overexpressed

in breast tumors compared to adjacent normal tissues and predicts poor patient survival in the Kaplan-Meier analysis [23]. Downregulation of MST3 showed an inhibition of proliferation of breast cancer cells in vitro and a reduced tumor growth in vivo [23]. The elevated expression of MST3 in tumor tissues and its role in controlling cellular adhesion, cytoskeletal structure, and tumor cell growth [2,3] suggests that MST3 may play a role in oncogenic processes. Moreover, further research is needed to gain a more complete understanding of the effects of MST3 deregulation in both normal and tumor tissue.

STK25, also known as Ste-20 oxidant stress response kinase 1 (SOK1), is known for its involvement in cell polarity and migration. Localized in and interacting with Golgi apparatus, STK25 has been shown to be activated by environmental stress such as oxidative stress but not by growth factors [24]. Overexpression of STK25 induces apoptosis. When cells are deprived of ATP and exposed to hypoxic stress, STK25 expression increases and is forced to translocate from the Golgi to the nucleus, where it promotes apoptotic cell death [25]. STK25 has also been noted to participate in neuronal cell polarity and dendritic branching and has been implicated in cell migration [26-28]. STK25 has also been found to as a negative regulator of lipid and glucose metabolism in normal and cancer cells [29,30].

2.3. MST4

MST4, a Golgi-localized kinase that is ubiquitously expressed, was discovered twenty years ago by two independent groups [31,32]. MST4 gene is localized to chromosome Xq26 which is a disease-rich associated region. Composed of a C-terminal regulatory domain and an N-terminal kinase domain, this molecule is highly homologous to the mammalian Ste20 kinase family member MST3 (Fig. 1). Both the kinase domain and regulatory domain are required for MST4 to be fully activated. It was appreciated for its high expression in the placenta, thymic tissue, and circulating immune cells, as well as its primary localization in the cytoplasm [31]. MST4 has also been found to be able to promote cell growth and transformation of epithelial cell lines. MST4 is localized in the Golgi apparatus following association with the Golgi scaffold protein, cis-Golgi matrix protein (GM130). Binding to GM130 activates MST4 through autophosphorylation at Thr178 [33].

MST4 regulates cellular transformation by activating intracellular signaling molecules and pathways. It was suggested that MST4 played a role in activating MAPK signaling during cytoskeletal rearrangement, morphogenesis, apoptosis, and other cellular events [34].

MST4 is involved in the maintenance of immune homeostasis during excessive inflammatory conditions, which could otherwise result in tissue damage. For example, Jiao et al. (2015) investigated the significance of MST4 engagement in immune balance during bacterial infection. In their study, MST4 acted as a negative regulator to minimize the degree of inflammation during sepsis. Mechanistically, MST4 suppresses the activity of Tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) [35] by directly phosphorylating it at Thr463/468. TRAF6 is mostly known for being an upstream signaling molecule for the transcription of genes involved in inflammatory responses [36]. Furthermore, in a mouse ischemic stroke model study, MST4 inhibited the inflammatory response in cerebral ischemia-reperfusion injury, which accompanied improvement in neurological deficit symptoms and reduced the size of the cerebral infarction [37]. These findings

suggested that MST4 has a variety of yet under-explored functions in both healthy and disease conditions. Moreover, MST4 is also noted to be involved in the induction of tumor cell growth and transformation, EMT, cell survival, invasion, and cancer cell metastasis by modulation of several downstream signaling pathways, including the Ras/Raf-independent ERK pathway [2].

As an intracellular kinase with diverse and crucial functions, MST4 is under the upstream regulatory influence of both cell intrinsic and extrinsic factors such as microRNAs. Schmitt et al. (2015) showed a novel microRNA (miR), miR-4728-3p, which suppresses the tumorigenicity of MST4 by directly targeting it [38]. This study revealed that miR-4728 has the potential to inhibit cell proliferation, migration, and invasion, reduce tumor cell survival, and that loss of miR-4728 is correlated with poor patient outcome. Mechanistically, this study determined that miR-4728 interferes with MAPK signaling by directly targeting MST4, suggesting the potential role of this microRNA in the diagnosis and treatment of cancer. In addition, another microRNA miR-124-3p has also been implicated in suppressing MST4 expression. This microRNA is downregulated in gastric cancer cells, which leads to the enhanced expression of MST4, thereby promoting activation of pro-tumor downstream signaling [39].

Collectively, these evidence suggest that MST4 is an important tumor-promoting kinase that deserves further investigation in cancer and potentially can be therapeutically targeted.

3. MST4 in EMT and cancer progression

3.1. EMT and cancer

EMT is an essential process during development whereby epithelial cells acquire mesenchymal and fibroblast-like properties and display reduced cell-cell and cell-basement membrane adhesion and increased motility [40]. This is a critical feature of normal embryonic development in which several developmental milestones, including gastrulation, neural crest formation, and cardiac morphogenesis, rely on the plastic transition between epithelium and mesenchyme [41].

Epithelial cells exhibit both apical and basal polarity features and form a contiguous sheet in which cells are linked by cell-cell adhesion molecules (CAMs), including E-cadherins. Typical epithelial markers include E-cadherin (CDH1), Desmoplakin (DSP), Tight Junction Protein 1 (TJP1), and Zonula Occludens Protein 1 (ZO). The basal portion of epithelial cells is attached to the extracellular matrix (ECM). However, unlike mesenchymal cells, epithelial cells do not have the capacity to invade the ECM. On the other hand, mesenchymal cells do not have apical-basal polarity [42]. They usually express mesenchymal markers such as Vimentin (VIM), N-Cadherin (CDH2), Snail (SNAI), Slug (SNAI2), SRY-Box 2 (SOX2), TWIST1, having short-lived contacts with neighboring cells, and they downregulate the expression of CAMs which help to elongate through the ECM [42].

Mesenchymal cells are highly motile and invasive through the ECM. They can produce enzymes that aid in the digestion of ECM and promote invasiveness. It is important to mention that uncontrolled epithelial cell proliferation and angiogenesis are hallmarks of

the initiation and early growth of primary epithelial cancers [43]. Adopting the EMT biological phenotype, in which stable epithelial cells transform into highly mobile and invasive mesenchymal cells, is essential for the migration, invasion, and distant metastases of tumor cells [44]. The reverse transformation (mesenchymal-to-epithelial transition, MET) is also required to regain the epithelial phenotype to form secondary tumors [45].

3.1.1. MST4 and cancer progression—MST4 has emerged as a tumor promoting gene in recent years. We [38,46] and others [39,47-50] showed that MST4 is overexpressed in several cancer types and MST4 enhances tumor progression including breast cancer, prostate cancer, colorectal cancer, gastric cancer, and hepatocellular carcinoma. Recently, we have also reported that overexpression of MST4 in breast cancer promotes cell growth and mediates migration/invasion phenotypes of cancer cells [46]. In an aggressive pituitary tumors MST4 has been implicated in the tumor proliferation and pro-survival effect. Notably, in hypoxic tumor microenvironment, MST4 promoted colony formation in soft agar via effects on cell proliferation and survival [51].

In support of these findings, public database analyses clearly show a significant overexpression of MST4 in tumor tissues compared to normal tissue, and it is correlated with cancer progression and a poor patient prognosis. Data from The Human Protein Atlas (HPA) (accessed on December 16, 2022) presents that MST4 is widely expressed in a variety of cancer cell types (Fig. 2), and among them hematopoietic cancer and testis cancer show the highest levels of MST4 expression.

Analyzing The Cancer Genome Atlas (TCGA) database of breast cancer patients, we showed that MST4 gene expression is increased compared to adjacent normal tissues with the highest expression in stage II (T2) of breast cancer [52]. In another dataset (*Tang_2018)*, the Kaplan-Meier survival analysis showed a positive correlation between the expression of MST4 at protein level with poor patient prognosis (Fig. 3, left). Moreover, the increased expression of MST4 at the mRNA level is significantly correlated with the poor overall survival of lung cancer (Fig. 3, middle) and hepatocellular carcinoma (Fig. 3, right) patients.

Collectively, these publicly accessible databases clearly show that MST4 expression at both the mRNA and protein levels is associated with a poor patient prognosis in various types of cancer. MST4 can be exploited further and potentially be used as a therapeutic target to treat cancer or as a biomarker for diagnosis and prediction of patient outcome.

3.1.2. Mechanistic insights of MST4 in cancer progression—Several lines of research have suggested that MST4 plays a role in tumor growth, migration/invasion, and EMT [48,50]. The ERK/MAPK pathway is one of the most important regulators of cell proliferation, and many growth factors and oncogenes transduce signals to promote growth and proliferation through this cascade [53]. Studies provide evidence to show that the oncogenic functions of MST4 are associated with the Ras/Raf-independent activation of the ERK pathway [31,34,53].

In addition to the ERK1/2 pathway, we and others recently discovered that MST4 can phosphorylate Ezrin at Thr567 and activate the AKT signaling pathway, which mediates

EMT by downregulating E-cadherin but upregulating EMT-promoting molecules such as N-cadherin, snail, and slug in breast cancer [39,46]. In addition, in vivo and in vitro studies revealed that MST4 promotes cytoskeleton rearrangements, EMT, invasion, and metastasis of gastric cancer cells by increasing Ezrin activity [39].

In pituitary adenocarcinomas, MST4 has been noted to promote tumor growth while decreasing the tendency of cells to undergo apoptosis under hypoxia. Mechanistically, Xiong et al. (2015) established the link between MST4 and Hypoxia-inducible factor 1 (HIF1). They showed that the MAPK, AKT, and hypoxia-inducible factor-1 (HIF-1) pathways are downstream of MST4 [51]. In their study, MST4 promotes cell proliferation via MAPK/AKT cascades. Intriguingly, HIF-1 activation by MST4 is independent of the MAPK and AKT pathways. They conclude that MST4 helps the tumor cells adapt to hypoxia via HIF1-mediated upregulation of glucose transporter type 1 (Glut1) and Lactate dehydrogenase (LDH). This result suggests that MST4 may also play an important role in regulating glucose metabolism as Glut1 and LDH are key molecules involved in glucose metabolism and utilization in tumor cells [54].

Autophagy-related 4B cysteine peptidase (ATG4B), a cysteine protease that is part of the autophagic machinery, has been postulated as a biomarker and potential therapeutic target in cancer [55]. Autophagy is a dynamic cellular process that involves the removal of intracellular proteins and damaged organelles in a lysosome-dependent manner to maintain the homeostasis of the cell [56,57]. In tumor cells, autophagy promotes tumor cell proliferation and survival. Autophagy was shown to help tumor cells adapt to hypoxia and nutrient deprivation; therefore, cells thrive in these stressful tumor microenvironments [58,59]. In addition, autophagy-mediated replenishment of fuel sources [60] helps tumor cells sustain treatments and contribute to therapeutic resistance [61]. As an autophagic mediator, a deficiency in the level of ATG4B has been implicated in the impairment of autophagic activity [62], thus it can potentially be therapeutically targeted in cancer cells [63]. ATG4B is a substrate for MST4. A study done by Huang et al. (2017) revealed that overexpression of MST4 mediates the phosphorylation of Ser383 residue in ATG4B protein. This study determined that MST4-induced activation of ATG4B is essential for autophagic activity, tumorigenicity, and resistance to radiation therapy in human glioblastoma (GBM) [64].

Under normal conditions, MST4 is involved in the regulation of the orientation of Golgi apparatus and controls the polarity and direction of cell migration. Studies uncover that PDCD10, also known as cerebral cavernous malformation-3 protein (CCM3) interacts with MST3/MST4 and increases their kinase activity to regulate cell migration and normal cellular structure [65]. Using two-hybrid screening system and immunoprecipitation assay, Ma et al. (2007) unveiled the interaction between MST4 and PDCD10 [53]. Further functional studies demonstrated that PDCD10 physically interacted with MST4 to promote cell growth and transformation by modulating the ERK pathway.

β-Catenin, a key molecule at the heart of Wnt signaling pathways, has been linked to embryonic development, cellular homeostasis, and a wide range of diseases, including cancer. Wnt/β-catenin pathway alterations have been linked to a variety of cancers,

including hepatocellular carcinoma, colon cancer, and lung cancer [66,67]. The cytoplasmic stabilization and accumulation of β-catenin, followed by translocation to the nucleus, is critical for its oncogenic role [66]. MST4 can phosphorylate β-catenin. A recent study demonstrated the importance of MST4 involvement in Wnt/β-catenin signaling in colorectal tumor development. MST4 phosphorylates β-catenin at the position of Thr40, preventing glycogen synthase kinase 3 (GSK3) mediated degradation of β-catenin [49]. This allows β-catenin to accumulate in the cytosol and translocate to the nucleus, where it induces the transcription of tumorigenic genes. MST4/β-catenin signaling was found to be significantly increased in colorectal carcinoma and is associated with poor patient outcome [49] implying that this functional link can be therapeutically targeted.

It is important to mention here that, in contrast to the findings above, Dian et al., reported conflicting results showing MST4 played a tumor suppressive role in hepatocellular carcinoma cells [68]. Given the contrasting observations and the potential pro-tumor and antitumor effects of MST4, it is important to investigate in-depth on the roles and its underlying mechanisms in different cancer types.

4. Current progress in MST4 inhibitor development

Despite evidence indicating the important role of MST4 in cancer development and its potential as a target for cancer therapy, the development of MST4 inhibitors has lagged behind. Efforts towards developing MST4 drugs are scarce and there are currently no highly effective and specific inhibitors available.

In a study by Xiong et al., hesperidin was identified as a potent and selective inhibitor of the MST4 kinase [69]. This study showed that hesperidin inhibited MST4 at nanomolar concentrations and prevented the MST4-induced proliferation and colony-forming ability of pituitary tumor cells. In a non-cancer setting, hesperidin attenuates autophagy by blocking the MST4 mediating phosphorylation of AKT and decreased the edema of brain following experimental intracranial hemorrhage [70]. However, hesperidin has previously been described as an Aurora kinase inhibitor and its specificity still needs to be further investigated.

In a separate study, the serine/threonine kinase inhibitor neratinib was found to degrade MST4 through autophagy. This inhibition of MST4 is crucial for deactivating the PI3K, ERK1/2, and YAP/TAZ signaling pathways [71]. There is currently a phase I/II clinical trial evaluating the combination of neratinib and divalproex sodium (Valproate) in patients with advanced solid tumors (https://clinicaltrials.gov/ct2/show/NCT03919292). However, it should be noted that neratinib was originally discovered as an irreversible inhibitor of ERBB1/2/4, so its specificity for MST4 remains uncertain. Thus, developing MST4-specific inhibitors has become an obstacle for MST4 research and drug development.

5. Conclusion and future perspectives

MST4 has been reported to promote tumor cell proliferation by activating several downstream signaling pathways, promoting tumor cell migration/invasion and metastasis by activating EMT-associated molecules, and improving tumor cell survival and resistance to

therapeutics (Fig. 4). It has emerged as a promising potential oncogene and therapeutic target for cancer treatment. However, there are still many unanswered questions and challenges that need to be addressed in future research. There are several unmet challenges need to be addressed to move the field ahead.

1. Lack of understanding of the precise role of MST4 in cancer: Although MST4 has been implicated in promoting cancer cell proliferation and invasion, the precise mechanisms by which it exerts these effects are still not fully understood. Whether MST family members complement each other on impacting cancer development? Whether the spatial and temporal localization of MST4 impact its function?

2. The role of MST4 in different cancer types and stages of cancer progression is not well-defined, and more studies are needed to establish its context-dependent functions in cancer. What are the exact roles of MST4 in different types and progressing stages of cancers?

3. Inconsistent findings on the prognostic value of MST4: The prognostic significance of MST4 expression in various cancer types is still a matter of debate, as some studies have reported that higher MST4 expression is associated with poor prognosis, while others have reported the opposite. This inconsistency may be due to differences in study design, patient selection, and methodology, highlighting the need for more standardized and rigorous studies to establish the clinical value of MST4 as a prognostic biomarker.

4. Limited knowledge of MST4-regulated downstream pathways: Although the MAPK, Akt and Hippo pathways have been implicated in mediating the effects of MST4 in cancer, the downstream targets of MST4 in these pathways are not fully known. Identifying these targets could provide insights into the molecular mechanisms by which MST4 promotes cancer progression and help identify novel therapeutic targets.

5. Lack of selective MST4 inhibitors: Despite the potential of MST4 as a therapeutic target in cancer, there are currently no specific inhibitors of MST4 available. This is a major obstacle in developing targeted therapies that specifically inhibit MST4 without affecting other signaling pathways. Future research efforts are needed to develop and optimize MST4-specific inhibitors that can be used in preclinical and clinical studies.

In conclusion, further research is necessary to fully comprehend the biological characteristics and pathological roles of MST4 in cancer. Given its importance in cancer pathobiology, there is a need for increased efforts to further explore its mechanism of action and develop inhibitors targeting this molecule.

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List of abbreviations

AKT	Protein Kinase B
ATG4B	Autophagy Related 4B Cysteine Peptidase
ECM	Extracellular Matrix
EMT	Epithelial-Mesenchymal Transition
ERK	Extracellular signal-regulated kinase
GCK	Germinal Center Kinase
Glut1	Glucose transporter 1
HPA	Human Protein Atlas
LDH	Lactate dehydrogenase
MAPK	Mitogen-Activated Protein Kinase
MST4	Mammalian Sterile20-Like Kinase 4
PDCD10	Programmed Cell Death 10
TRAF6	TNF receptor associated factor 6

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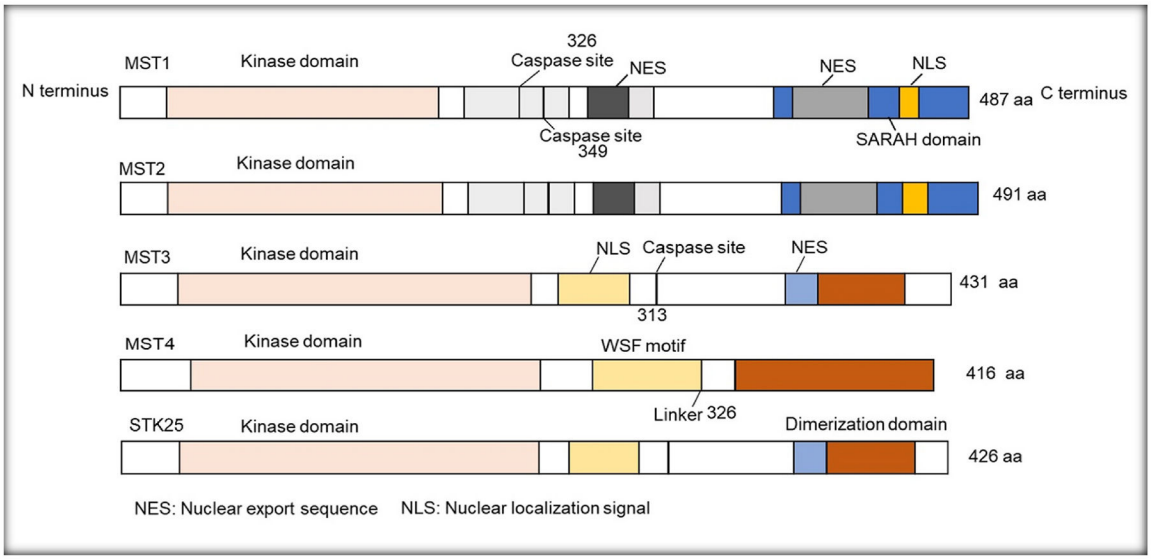

Fig. 1. A representative structure of the MST family kinases.

The name and location of the most prominent features have been given for MST1, MST3 and MST4 based on the available evidence. Each of the kinases contains a N-terminal kinase domain, following with a linker region, which contains a Tarp-Ser-Phe (WSF) motif, and a regulatory domain at the C terminus containing nuclear localization and export signals.

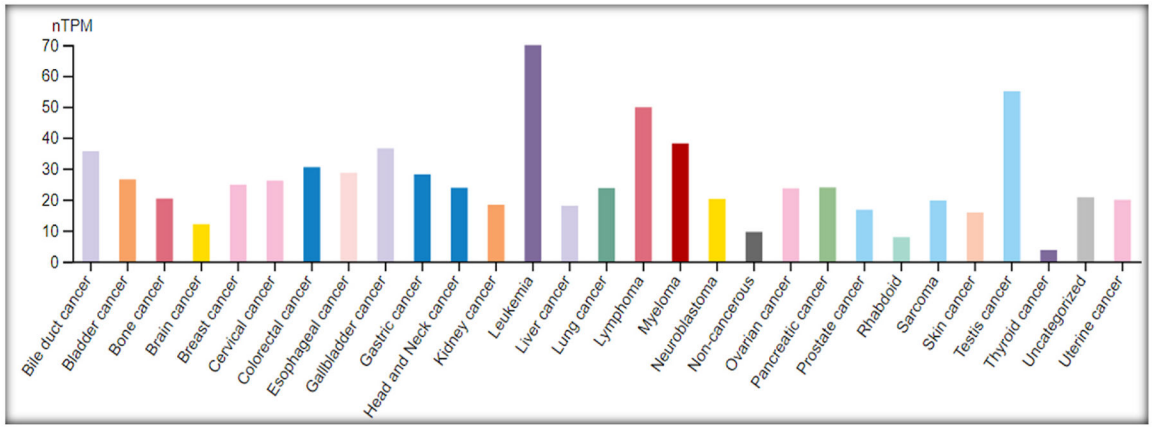

Fig. 2. Distribution and expression cluster analysis of MST4 gene expression across multiple tumor types.

Source: The Human Protein Atlas (HPA)/accessed on December 16, 2022.

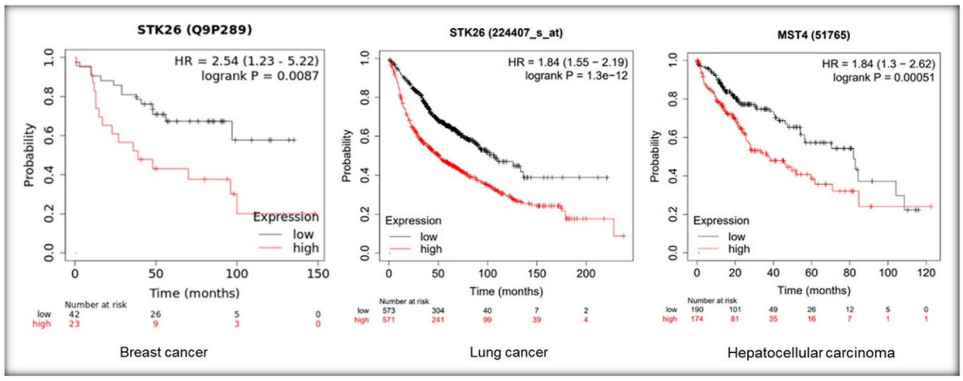

Fig. 3. MST4 expression and overall patient prognosis.

The Kaplan-Meier plots showing the correlation between level of MST4 expression and overall patient survival. Source: Kaplan-Meier Plotter (https://kmplot.com/analysis/), accessed on January 11, 2023.

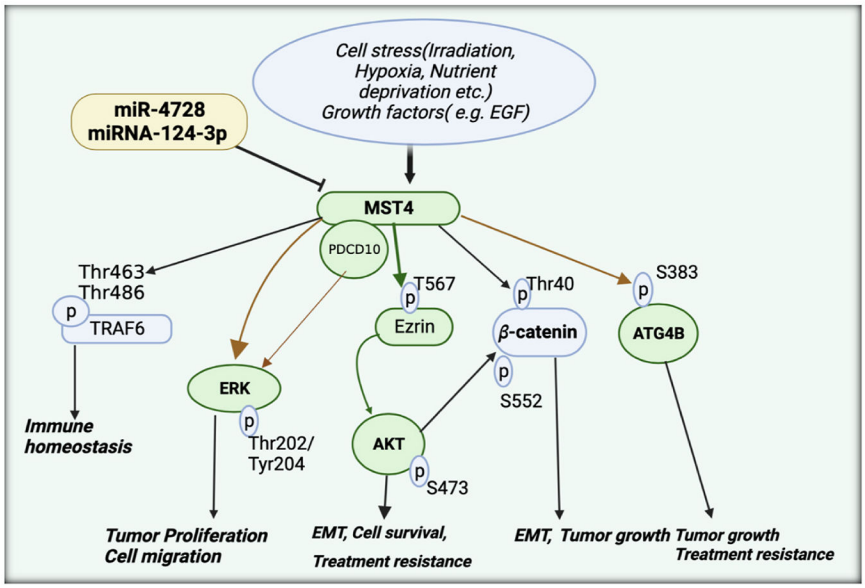

Fig. 4. Mechanisms of MST4 induced tumor progression and treatment resistance.

Through the activation of several downstream signaling pathways, MST4 is contributing to tumor cell proliferation, promoting migration/invasion and metastasis of tumor cells with the activation of EMT associated molecules, and enhance tumor cell survival and resistance for therapeutics.