AJBS Asian Journal of Biological Sciences

OPEN ACCESS

Mammalian Ste20-Like Kinase 4 (MST4) in Tumor Autophagy

[1,2]*Latif Reshi*

[1]*Graduate Institute of Biomedical Sciences, China Medical University, Taichung 406040, Taiwan*

[2]*Toma Biotechnology Co. Ltd., Taipei, Taiwan*

INTRODUCTION

Autophagy is a conserved intracellular reaction in eukaryotic cells that selectively breaks down intracellular components to maintain homeostasis in response to cellular stress or damage. Autophagy in both tumor and normal cells can encourage cell death and maintain cell survival. The MST4 is a member of the mammalian sterile 20-like (STE) serine/threonine kinase (STK) family, whose activities have been linked to both healthy development and pathological conditions including cancer. The MST4, as an autophagy-associated protein, potentially induces cell death by increasing protein content in radiotherapy. Both autophagy and Mammalian Ste20-like Kinase 4 (MST4) have been linked to diseases like cancer and inflammation. Autophagy has mostly been characterized in oncology as a mechanism of resistance to many cancer treatments, including immunotherapy, targeted therapy, chemotherapy and more. The discovery of drugs that target autophagy for the treatment of cancer has been hampered by the complexity and incomplete understanding of autophagy's role in cancer. In the brief description, the clinical significance of MST4 in cancer and further the relationship between MST4 and tumor autophagy are explored. However, the exact role of MST4 in tumor autophagy has yet to be demonstrated.

DESCRIPTION

The mechanisms behind tumor start, development, metastasis and resistance to treatment are well understood. The research community's ability to comprehend the biology of malignancies and enhance the effectiveness of cancer patient treatments is hampered by the complexity, heterogeneity and dynamic nature of the different forms of human cancers. To save millions of lives and enhance patient quality of life, it is imperative to analyze the molecular pathways behind tumor development, metastatic potential and therapy resistance. Recently identified as a member of Mammalian Sterile 20-Like Kinase (MST)[1], MST4 is crucial in controlling apoptosis, cell polarity and migration, EMT, autophagy, cancer metastasis and cell proliferation.

Mammalian sterile-20-like kinase 4 (MST4), also known as STK26, is a member of the germinal center kinase (GCK) group III family. It consists of three proteins, MST3, MST4 and STK25, located upstream of the MAPK-related kinase. The signaling pathways that control cell mitosis, homeostasis, polarity, migration, apoptosis, proliferation and cellular differentiation are all influenced by MST4, which is highly expressed in human tissue. By phosphorylating ezrin's regulatory T567 residue, it contributes to correct cell polarity. Additionally, MST4 controls tumor cell motility via binding to the Golgi matrix protein GM130[1].

ISSN: 1996-3351 (Print)
https://doi.org/10.3923/ajbs.2025.556.559

Received: 17 Dec. 2024
Accepted: 21 Jan. 2025
Published: 30 Jun. 2025

Poor prognoses for several cancers, including hepatocellular carcinoma, breast cancer, choriocarcinoma and prostate cancer, are associated with overexpression of MST4. On its role in gastric cancer, there is disagreement. According to some research, MST4 inhibits GC carcinogenesis by reducing YAP activation via a non-canonical signaling route[2], while other studies contend that it increases tumor cell metastasis by promoting EMT[2]. Although MST4 is a direct target of miRNA 4728 in human breast cancer, its function and connection to breast cancer are yet unknown.

Early research suggested that autophagy has two roles in cancer and current research is helping us better understand the fundamental processes by which autophagy affects the development and spread of cancer. Although it is now well acknowledged that autophagy inhibits the development of new tumors, there is evidence that autophagy mechanisms in existing tumors are necessary to sustain unchecked cell proliferation and elevated metabolic activity, which results in autophagy dependence for tumor maintenance[3]. Additionally, autophagy plays significant roles in the surrounding stroma (extrinsic) and within cancer cells (intrinsic), both of which have an impact on treatment resistance and tumor progression. All things considered, the effects of autophagy seem to be influenced by the stage of the tumor, particular oncogenic mutations and the cellular environment.

Regulatory mechanisms of MST4 in cancer: The MST4 is comparatively well-studied compared to the other members of this family (MST4, 1, 2, 3) and is implicated in cancer metastasis, cell proliferation and polarity[4]. It is known that MST4 plays several context-dependent roles in carcinogenesis[5]. By triggering the p-ERK pathway, MST4 is known to have accelerated the development of prostate cancer, EMT and tumor metastases of gastric and hepatocellular carcinoma (HCC) cancer[6,7]. The MST4-MOB4 complex, created when MST4 and MOB4 interacted, antagonized the MST1-MOB1 complex and positively regulated YAP activity, hence boosting cell migration and proliferation in pancreatic cancer[8]. Inhibition of MST4 inactivated ATG4B, which in turn reduces tumorigenicity and autophagy of cancer cells in glioblastoma[9]. Additionally, MST4 can contribute to inflammatory reactions through TRAF6-28 phosphorylation. One well-known mechanism in carcinogenesis is the PI3K/AKT signaling pathway[10]. The MST4 expression in glioblastoma is linked to the stimulation of tumor autophagy and may result in tumorigenesis[9]. Its precise function and underlying molecular pathways in many cancers are still unclear, though.

The MST4 carries out its functions by encouraging gastric cancer autophagy. Prior research had demonstrated the connection between MST4 and autophagy to pinpoint the precise mechanism of MST4 in gastric cancer. In BGC-823 and SGC-7901 cells overexpressing MST4, autophagic activity is inhibited by the autophagy inhibitor chloroquine (CQ) (10 μm). The MST4 overexpression in BGC-823 and SGC-7901 cells reduces p62 and raises LC3BII/LC3BI, indicating improved autophagy. Although not at control levels, CQ partially undid the decline in p62 brought on by MST4[7]. Additionally, CQ enhanced the expression of LC3BII/LC3BI in gastric cancer cells and further CQ treatment reduced the ability of MST4-overexpressing BGC-823 and SGC-7901 cells to proliferate and invade.

The study explores the significance of MST4 phosphorylation of ATG4B at S383 in autophagy, taking into account the critical roles of ATG4B in autophagy. The autophagy is indicated by the development of endogenous LC3 puncta and the production of autophagosome membranes. When certain shRNAs cut down endogenous MST4 or ATG4B, p-ATG4B decreases boosted the autophagy substrate p62/SQSTM1 and decreased LC3-II conversion[9]. The study also discovered that MST4 or ATG4B knockdown prevented ATG4B from cleaving the YFP-CFP-LC3B fusion protein. The MST4 or ATG4B depletion dramatically decreased autophagic vacuoles in Glioma stem cells (GSCs). The researchers overexpressed MST4 in GSC 528 and JK42 spheres, which contain low levels of endogenous MST4, to better understand the function of MST4 in autophagy induction. The MST4 overexpression caused YFP-CFP-LC3B cleavage, p-S383 of ATG4B, increased LC3-II conversion, LC3B puncta and autophagosome formation[9].

The cellular signaling pathways that MST4 regulates in breast cancer cells were the subject of earlier investigation. It was discovered that MST4 overexpression raised the phosphorylation of GSK3 and Ezrin, two proteins implicated in the invasion of cancer cells and the advancement of EMT. However, there was less phosphorylation of these proteins in the cells harboring the kinase-defective mutant MST4/T178A. Additionally, MST4 elevated AKT and BAD phosphorylation, indicating that it controls cell survival via the Akt/BAD signaling pathway. Through the MST4-AKT-BAD or MST-AKT-GSK3 signaling cascade, MST4 is essential for cancer cell survival and EMT and it is necessary for the activation of AKT and its downstream signaling pathway in breast cancer cells[1].

According to a study by Dent *et al*.[11], MST4 is broken down via autophagy by the serine/threonine kinase inhibitor neratinib, which is crucial for deactivating the PI3K, ERK1/2 and YAP/TAZ signaling pathways. Neratinib's specificity for MST4 is still uncertain, though, as it was first shown to be an irreversible inhibitor of ERBB1/2/4. As a result, developing inhibitors that are specific to MST4 has become a hurdle for MST4 research as well as drug growth and development.

According to a different study, hesperidin inhibited MST4 at nanomolar doses and stopped pituitary tumor cells from proliferating and colonizing when MST4 was present[12]. Hesperidin reduces brain edema after experimental intracranial bleeding and inhibits autophagy in a non-cancer context by blocking the MST4 that mediates AKT phosphorylation[13]. Hesperidin has been identified as an Aurora kinase inhibitor in the past, but more research is required to determine its specificity.

Conclusion and future perspectives: One of the most important aspects of treating human tumors is autophagy, which is essential for tumor cell survival. Autophagy is induced by several cytotoxic chemotherapeutics, including TMZ and targeted inhibitor treatments, which can result in recurrence and treatment resistance. It has been demonstrated that tumor cells become more susceptible to the effects of cytotoxic therapy when the autophagic response is blocked by autophagy inhibitors such as CQ or HCQ. Clinical trials targeting autophagy in combination therapy have shown promising results, but associated toxicities have limited their utility in treating cancer patients. The MST4 is a potential oncogene and a new therapeutic target for cancer treatment. Its interaction with STRIPAK and TRAF6 phosphorylation has been linked to metastasis and inflammation. However, the exact role of MST4 in tumor autophagy remains unproven. However, several unanswered questions and challenges need to be addressed. These include the lack of understanding of the precise role of MST4 in cancer, the inconsistency in prognostic values, limited knowledge of MST4-regulated downstream pathways and the lack of selective MST4 inhibitors. The prognostic significance of MST4 expression in various cancer types is still debated and the downstream targets of MST4 in MAPK, Akt and Hippo pathways are not fully known. Additionally, there is no specific inhibitors available for MST4, making it challenging to develop targeted therapies without affecting other signaling pathways.

REFERENCES

1. Arora, R., J.H. Kim, A.A. Getu, A. Angajala and Y.L. Chen *et al*., 2022. MST4: A potential oncogene and therapeutic target in breast cancer. Cells, Vol. 11. 10.3390/cells11244057.
2. An, L., P. Nie, M. Chen, Y. Tang and H. Zhang *et al*., 2020. MST4 kinase suppresses gastric tumorigenesis by limiting YAP activation via a non-canonical pathway. J. Exp. Med., Vol. 217. 10.1084/jem.20191817.
3. Reshi, L. and S.H. Juen, 2024. Modulating autophagy as an attractive strategy to treat renal cell carcinoma. Asian Sci. Bull., 2: 290-297.
4. ten Klooster, J.P., M. Jansen, J. Yuan, V. Oorschot and H. Begthel *et al*., 2009. Mst4 and ezrin induce brush borders downstream of the Lkb1/Strad/Mo25 polarization complex. Dev. Cell, 16: 551-562.
5. Thompson, B.J. and E. Sahai, 2015. MST kinases in development and disease. J. Cell Biol., 210: 871-882.

6. Lin, Z.H., L. Wang, J.B. Zhang, Y. Liu and X.Q. Li *et al*., 2014. MST4 promotes hepatocellular carcinoma epithelial-mesenchymal transition and metastasis via activation of the p-ERK pathway. Int. J. Oncol., 45: 629-640.
7. Li, T., L. Deng, X. He, G. Jiang and F. Hu *et al*., 2019. MST4 predicts poor prognosis and promotes metastasis by facilitating epithelial-mesenchymal transition in gastric cancer. Cancer Manage. Res., 11: 9353-9369.
8. Chen, M., H. Zhang, Z. Shi, Y. Li and X. Zhang *et al*., 2018. The MST4-MOB4 complex disrupts the MST1-MOB1 complex in the Hippo-YAP pathway and plays a pro-oncogenic role in pancreatic cancer. J. Biol. Chem., 293: 14455-14469.
9. Huang, T., C.K. Kim, A.A. Alvarez, R.P. Pangeni and X. Wan *et al*., 2017. MST4 phosphorylation of ATG4B regulates autophagic activity, tumorigenicity, and radioresistance in glioblastoma. Cancer Cell, 32: 840-855.e8.
10. Vara, J.Á.F., E. Casado, J. de Castro, P. Cejas, C. Belda-Iniesta and M. González-Barón, 2004. PI3K/Akt signalling pathway and cancer. Cancer Treat. Rev., 30: 193-204.
11. Dent, P., L. Booth, A. Poklepovic, J. Martinez, D. von Hoff and J.F. Hancock, 2020. Neratinib degrades MST4 via autophagy that reduces membrane stiffness and is essential for the inactivation of PI3K, ERK1/2, and YAP/TAZ signaling. J. Cell. Physiol., 235: 7889-7899.
12. Xiong, W., C.J. Matheson, M. Xu, D.S. Backos and T.S. Mills *et al*., 2016. Structure-based screen identification of a mammalian Ste20-like kinase 4 (MST4) inhibitor with therapeutic potential for pituitary tumors. Mol. Cancer Ther., 15: 412-420.
13. Wu, X., J. Wu, W. Hu, Q. Wang and H. Liu *et al*., 2020. MST4 kinase inhibitor hesperadin attenuates autophagy and behavioral disorder via the MST4/AKT pathway in intracerebral hemorrhage mice. Behav. Neurol., Vol. 2020. 10.1155/2020/2476861.