Journal of Thoracic Disease 2021 vol.13 N3, pages 1370-1379

Musashi 2 (MSI2) expression as an independent prognostic biomarker in non-small cell lung cancer (NSCLC)

Topchu I., Karnaukhov N., Mazitova A., Yugai V., Voloshin M., Tikhomirova M., Kit O., Frantsiyants E., Kharin L., Airapetova T., Ratner E., Sabirov A., Abramova Z., Serebriiskii I., Boumber Y., Deneka A.

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

Background: Musashi-2 (MSI2) is a member of RNA-binding protein family that regulates mRNA translation of numerous intracellular targets and influences maintenance of stem cell identity. This study assessed MSI2 as a potential clinical biomarker in non-small cell lung cancer (NSCLC). Methods: The current study included 40 patients with NSCLC, of whom one presented with stage 1, 14 presented with stage II, 15 presented with stage III, and 10 patients had stage IV. All patients received standard of care treatments. All patient samples were obtained before treatment started. We used immunohistochemical (IHC) approach to measure MSI2 protein expression in matching specimens of normal lung versus tumor tissues, and primary versus metastatic tumors, followed by correlative analysis in relation to clinical outcomes. In parallel, clinical correlative analysis of MSI2 mRNA expression was performed in silico using publicly available datasets (TCGA/ICGC and KM plots). Results: MSI2 protein expression in patient samples was significantly elevated in NSCLC primary tumors versus normal lung tissue (P=0.03). MSI2 elevated expression positively correlated with a decreased progression free survival (PFS) (P=0.026) combined for all stages and with overall survival (OS) at stage IV (P=0.013). Elevated MSI2 expression on RNA level was confirmed in primary tumor versus normal tissue samples in TCGA dataset (P<0.0001), and positively correlated with decreased OS (P=0.02). No correlation was observed between MSI2 expression and age, sex, smoking, and treatment type. Conclusions: Elevated MSI2 expression in primary NSCLC tumors is associated with poor prognosis and can be used as a novel potential prognostic biomarker in NSCLC patients. Future studies in an extended patient cohort are warranted.

http://dx.doi.org/10.21037/jtd-20-2787

Keywords

Musashi-2 (MSI2), Non-small cell lung cancer (NSCLC), Overall survival (OS), Prediction biomarkers, RNA binding proteins

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.

[2] Howlader N, Krapcho M, Miller D, et al. SEER Cancer Statistics Review, 1975-2016. Available online: https://seer. cancer.gov/csr/1975_2013/: National Cancer Institute. Bethesda, MD2019.

[3] Sakakibara S, Nakamura Y, Yoshida T, et al. RNA-binding protein Musashi family: Roles for CNS stem cells and a subpopulation of ependymal cells revealed by targeted disruption and antisense ablation. Proc Natl Acad Sci U S A 2002;99:15194-9.

[4] Sakakibara S, Nakamura Y, Satoh H, et al. Rna-binding protein Musashi2: developmentally regulated expression in neural precursor cells and subpopulations of neurons in mammalian CNS. J Neurosci 2001;21:8091-107.

[5] Ito T, Kwon HY, Zimdahl B, et al. Regulation of myeloid leukaemia by the cell-fate determinant Musashi. Nature 2010;466:765-8.

[6] Kudinov AE, Karanicolas J, Golemis EA, et al. Musashi RNA-binding proteins as cancer drivers and novel therapeutic targets. Clin Cancer Res 2017;23:2143-53.

[7] Lee J, An S, Choi YM, et al. Musashi-2 is a novel regulator of paclitaxel sensitivity in ovarian cancer cells. Int J Oncol 2016;49:1945-52.

[8] Kang MH, Jeong KJ, Kim WY, et al. Musashi RNA-binding protein 2 regulates estrogen receptor 1 function in breast cancer. Oncogene 2017;36:1745-52.

[9] Guo K, Cui J, Quan M, et al. The Novel KLF4/MSI2 Signaling Pathway Regulates Growth and Metastasis of Pancreatic Cancer. Clin Cancer Res 2017;23:687.

[10] Kudinov AE, Deneka A, Nikonova AS, et al. Musashi-2 (MSI2) supports TGF-beta signaling and inhibits claudins to promote non-small cell lung cancer (NSCLC) metastasis. Proc Natl Acad Sci U S A 2016;113:6955-60.

[11] Hirsch FR, Varella-Garcia M, Fau-Bunn PA Jr, et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. J Clin Oncol 2003;21:3798-807.

[12] Bankhead P, Loughrey MB, Fernández JA, et al. QuPath: Open source software for digital pathology image analysis. Sci Rep 2017;7:16878.

[13] Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6:pl1.

[14] Gyorffy B, Surowiak P, Budczies J, et al. Online survival analysis software to assess the prognostic value of biomarkers using transcriptomic data in non-small-cell lung cancer. PLoS One 2013;8:e82241.

[15] Nagy Á, Lanczky A, Menyhart O, et al. Validation of miRNA prognostic power in hepatocellular carcinoma using expression data of independent datasets. Sci Rep 2018;8:9227.

[16] Barbouti A, Hoglund M, Johansson B, et al. A novel gene, MSI2, encoding a putative RNA-binding protein is recurrently rearranged at disease progression of chronic myeloid leukemia and forms a fusion gene with HOXA9 as a result of the cryptic t(7;17)(p15;q23). Cancer Res 2003;63:1202-6.

[17] Singh A, Settleman J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. Oncogene 2010;29:4741-51.

[18] Fang T, Lv H, Wu F, et al. Musashi 2 contributes to the stemness and chemoresistance of liver cancer stem cells via LIN28A activation. Cancer Lett 2017;384:50-9.

[19] Yang C, Zhang W, Wang L, et al. Musashi-2 promotes migration and invasion in bladder cancer via activation of the JAK2/STAT3 pathway. Lab Invest 2016;96:950-8.

[20] Aly RM, Ghazy HF. Prognostic significance of MSI2 predicts unfavorable outcome in adult B-acute lymphoblastic leukemia. Int J Lab Hematol 2015;37:272-8.

[21] Byers RJ, Currie T, Tholouli E, et al. MSI2 protein expression predicts unfavorable outcome in acute myeloid leukemia. Blood 2011;118:2857-67.

[22] Thol F, Winschel C, Sonntag AK, et al. Prognostic significance of expression levels of stem cell regulators MSI2 and NUMB in acute myeloid leukemia. Ann Hematol 2013;92:315-23.

[23] Chu Y, Corey DR. RNA sequencing: platform selection, experimental design, and data interpretation. Nucleic Acid Ther 2012;22:271-4.

[24] Byron SA, Van Keuren-Jensen KR, Engelthaler DM, et al. Translating RNA sequencing into clinical diagnostics: opportunities and challenges. Nat Rev Genetics 2016;17:257-71.