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PAPER OF THE MONTH • SEPTEMBER 2024

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Science Advances

Blocking tumor-intrinsic MNK1 kinase restricts metabolic adaptation and diminishes liver metastasis

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Dysregulation of the mitogen-activated protein kinase interacting kinases 1/2 (MNK1/2)-eukaryotic initiation factor 4E (eIF4E) signaling axis promotes breast cancer progression. MNK1 is known to influence cancer stem cells (CSCs); self-renewing populations that support metastasis, recurrence, and chemotherapeutic resistance, making them a clinically relevant target. The precise function of MNK1 in regulating CSCs, however, remains unexplored.

In this study, we sought to expand our understanding of how MNK1 contributes to breast cancer stem cell (BCSC) properties. Our results suggest that MNK1 affects BCSC function to affect tumor growth rates in vivo.
We performed protein and gene expression analyses, 13C metabolite tracing, and bioenergetic profiling to uncover that MNK1 supports tumor cell glycolysis. Furthermore, we determined that genetic and pharmacologic inhibition of MNK1 restricts tumor cell metabolic adaptability and increases their energetic reliance on oxidative phosphorylation (OxPhos), resulting in suppressed metastasis to the liver, but not the lung, in breast and pancreatic tumor models.

Last, by interrogating mass spectrometry (MS)–derived protein data from The Cancer Genome Atlas (TCGA) PanCancer Atlas Breast Invasive Carcinoma dataset, we demonstrate that MNK1 expression positively correlates with the expression of glycolysis-related enzymes.

Together, our findings document the metabolic consequences of disrupting MNK1 in breast cancer cells and highlight the potential utility of MNK1/2 inhibitors as therapeutic agents in targeting tumor metabolism to reduce metastasis. Future studies are needed to assess how to effectively combine MNKi and OxPhos inhibition and to determine at what stage of the metastatic cascade these drugs could be applied for clinical benefit.

In conclusion, this study supports the utility of targeting metabolic pathways as strategies to reduce metastasis. We have gained an increased understanding of the contribution that MNK1 kinase makes in controlling CSC populations, while further identifying reduced glycolysis as a previously unknown functional consequence of targeting MNK1/2. Better understanding of the metabolic dependencies of metastatic tumor cells in tissue-specific microenvironments may prove useful in identifying vulnerabilities that can be exploited, through use of MNK-targeting therapeutics, to improve therapeutic efficacy.

https://doi.org/10.1126/sciadv.adi7673