Histone Methyltransferase ASH1L Primes Metastases and Metabolic Reprogramming of Macrophages in the Bone Niche

Chenling Meng[1], Kevin Lin[2], Wei Shi[1], Hongqi Teng[1], Xinhai Wan[3], Anna DeBruine[1,4], Yin Wang[1], Xin Liang[1], Javier Leo[1,4], Feiyu Chen[1], Qianlin Gu[1], Jie Zhang[1], Vivien Van[5], Kiersten L. Maldonado[5], Boyi Gan[1], Li Ma[1], Yue Lu[2]*, Di Zhao[1]*

[1]Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[2]Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[3]Department of Endocrine Neoplasia & Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[4]The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, TX 77030, USA
[5]Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

***Corresponding Authors:** Di Zhao, Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, 6565 MD Anderson Boulevard, Houston, TX 77030, USA; email: dzhao2@mdanderson.org; and Yue Lu, Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; email: YLu4@mdanderson.org.

ABSTRACT

Background Bone metastasis is a major cause of cancer death; however, the epigenetic determinants driving this process remain elusive.

Methods We characterized the loss-of-function and gain-of-function effects of ASH1L on cancer invasiveness and bone metastases. Then, we performed high-throughput transcriptomic and epigenetic profiling to dissect the molecular basis of ASH1L's role in transforming invading cancer cells. Besides, we generated a new PCa bone metastasis model in immunocompetent mice, which recapitulates human diseases. Combining it with single-cell transcriptomics, we determined the role of ASH1L in modulating the communication between disseminated cancer cells and host immune cells in the bone niche.

Results Here, we uncover that histone methyltransferase ASH1L is genetically amplified in metastatic diseases and is required for prostate cancer invasiveness and bone metastasis in males. In invading cancer cells, ASH1L rewires methylations at H3K4 and H3K36 and cooperates with transcriptional factor HIF-1α to induce pro-metastatic transcriptome. Leveraging a newly developed syngeneic metastasis model and single-cell transcriptomic profiling, we demonstrate that ASH1L in invading cancer cells induces monocyte differentiation into lipid-associated macrophage (LA-TAM) and maintains their pro-tumoral and anti-inflammatory phenotype in the metastatic bone niche. Mechanistic studies reveal that IGF-2 is a direct target of ASH1L/HIF-1α and mediates LA-TAMs' differentiation and phenotypic changes by reprogramming oxidative phosphorylation. In men with metastatic prostate cancer, ASH1L overexpression is associated with enriched LA-TAMs. As a proof of concept, pharmacologic inhibition of the ASH1L-HIF-1α-macrophages axis elicits robust anti-metastasis responses in preclinical models.

Conclusion This study demonstrates epigenetic alterations in cancer cell reprogram myeloid lineage and metabolic reprogramming, facilitating metastatic outgrowth in bone. It establishes ASH1L as an epigenetic driver priming metastasis and controlling macrophage plasticity in the bone niche, providing a bona fide therapeutic target in metastatic malignancies.

KEY WORDS: ASH1L; Epigenetics; Bone Metastasis; Metastatic Niche; Macrophages; Immunometabolism; Prostate Cancer

Acknowledgments

D. Zhao is a CPRIT Scholar in Cancer Research and has been supported by the CPRIT Recruitment of First-Time Tenure-Track Faculty Award RR190021, NIH/NCI R01 CA275990 and CA278889, Prostate Cancer Foundation Challenge Award FP00016492, and DoD CDMRP IDA award PC230358.

Conflicts of Interest

The authors have declared that no conflicts of interest exist.