

TARGETING LCP1-MEDIATED METASTASIS IN CHONDROSARCOMA WITH OROXYLIN A

Ava Strohmeyer¹, Caleb Watson¹, Nicholas Guardino², Aron Mebrahtu³, Ariana Matarangas¹, Ananya Dutta⁴, Kevin Betsch⁵, Jason Somareli^{3,4}, Benjamin Alman^{4,5}, Julia Visgauss^{4,5}

¹Duke University, ²Stanford University School of Medicine, Stanford, ³Duke University School of Medicine, ⁴Duke Cancer Institute, ⁵Duke University School of Medicine Department of Orthopaedics

Objective: Chondrosarcoma, the second most common bone sarcoma, is chemo/radiotherapy-resistant. Standard treatment, en-bloc resection, is often ineffective for metastatic disease, highlighting an urgent need for new therapies. Our lab linked dysregulated actin-binding protein LCP1 to metastatic cell behavior. We aimed to validate LCP1 as a metastatic driver and assess LCP1 inhibition, specifically with oroxylin A, to suppress chondrosarcoma metastasis.

Methods: To confirm LCP1's role, two patient-derived high-grade metastatic chondrosarcoma cell lines (725 & 731) underwent CRISPR/Cas9 LCP1 knockout (KO), confirmed by western blot. LCP1 KO effects were assessed via in vitro assays (viability, wound healing, invasion). In vivo, metastatic mouse models compared lung tumor burden and bioluminescent signaling (14 weeks post-tail-vein injection) of luciferase-labeled wild-type (WT) vs. KO cells in immunodeficient mice. Pharmacologic inhibition with 50 μ M oroxylin A was assessed in WT cells via functional assays.

Results: In vitro, LCP1 KO significantly impaired chondrosarcoma cell migration and invasion without affecting viability. Scratch wound assays showed reduced motility (725: $p=0.0003$; 731: $p<0.0001$). Invasion assays showed reduced invasive potential (725: $p<0.001$; 731: $p<0.01$). In vivo, LCP1 KO tumors showed reduced bioluminescent signal ($p=0.0026$) and lower lung metastatic burden at 14 weeks. Oroxylin A similarly suppressed migration ($p<0.0001$) and invasion ($p<0.0001$) without affecting viability.

Conclusion: LCP1 is a key mediator of chondrosarcoma metastatic migration and invasion, in vitro and in vivo. Pharmacologic LCP1 inhibition with oroxylin A effectively mimicked LCP1 KO's anti-metastatic phenotype, crucially without impacting cell viability. LCP1 is a druggable driver of chondrosarcoma metastasis. Oroxylin A is a promising therapeutic candidate to prevent or delay metastatic disease progression.

Significance/Clinical Relevance: Chondrosarcoma is resistant to conventional therapies, and the lack of effective treatments for metastatic disease represents a major clinical challenge. This study identifies LCP1 as a novel and druggable driver of metastasis in preclinical models. The successful inhibition of metastatic behavior with oroxylin A provides a strong foundation for future translational studies and offers a promising new therapeutic strategy to prevent or delay disease progression in patients.

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Figures available in supplementary document