Elucidating and targeting the resistant leukemia stem cell niche using high-resolution in situ protein interactomics and surfaceomics in human bone marrow tissue

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Abstract**:** Outcomes for acute myeloid leukemia (AML) patients remain poor due to a high rate of primary and acquired resistance to current treatments. Leukemia stem cells (LSCs) are considered to be a primary cause for relapse, because of their ability to escape treatment by maintaining a quiescent state. Growing evidence has established the bone marrow (BM) niche as a leukemia permissive environment which can act as a reservoir of these resistant cells. Surface proteins on quiescent LSCs and protein-protein interactions at leukemia cell / BM cell synapses therefore represent potentially promising targets for the eradication of resistant AML cells. However, LSC surfaceomes and interactomes in the BM niche remain unmapped because methods for surfaceome and protein interactome characterization in BM tissue, and human tissue more broadly, have not been reported. We propose to establish a broadly useful single-cell resolved spatial protein interactomics technology, scμMap, and use it to functionally investigate treatment-resistant AML stem cells in their physiological BM niches by combining fluorophore-based label retention for the identification of LSCs and optically-controlled photocatalytic proximity labeling at membrane proteins. This method enables protein interaction mapping in rare cells in situ, applicable both to primary human patient specimens and laboratory models for the functional evaluation of identified hits. We expect that LSC-defining molecules discovered directly in human AML patient tissues will be enriched in translationally actionable targets for eradicating resistant AML malignancies, and that scμMap will be a broadly useful approach for directly characterizing spatial proteomes in patient tissues across many cancer types.