Spatial Transcriptomic Delineation of Human Chondroblastoma: Cellular Architecture and Lineage Dynamics

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INTRODUCTION: Chondroblastoma is a rare benign bone tumor that arises in the epiphysis of long bones and is thought to be of cartilaginous origin. The cellular identity of "chondroblasts" and the broader tumor microenvironment remain controversial. A better understanding of the molecular and cellular composition of chondroblastomas is needed to clarify their pathogenesis and identify potential therapeutic targets. We hypothesized that spatial transcriptomics could resolve tumor heterogeneity and reveal lineage trajectories and stromal–immune interactions in human chondroblastoma.

METHODS: Formalin-fixed paraffin-embedded (FFPE) sections (6 µm) from eight histologically confirmed human chondroblastomas were obtained with IRB approval. High-resolution spatial transcriptomic profiling was performed using the 10x Genomics Visium HD platform. Two samples with sufficient RNA quality were analyzed in detail. Dimensionality reduction, pseudotime trajectory analysis, and cell–cell communication inference (CellChat) was integrated with several external bone tumor transcriptomic datasets for comparative evaluation.

RESULTS SECTION: We identified 13 transcriptionally distinct cell clusters, including tumoral chondroblasts, osteoclast-like giant cells, fibroblast-like stromal cells, and diverse immune populations. Tumoral chondroblasts showed aberrant differentiation, characterized by high COL10A1 and CCN2 but low COL2A1 and ACAN expression, consistent with dysregulated cartilage development. Pseudotemporal analysis revealed a trajectory from progenitor-like to osteogenic tumor subtypes, with CD44 signaling and oxidative phosphorylation as key regulators. Osteoclast-like giant cells formed via zonal progression and displayed distinct metabolic and absorptive signatures. Core tumor regions exhibited enhanced extracellular matrix remodeling, high metabolic activity, and strong immune exclusion. Stromal fibroblasts expressing FN1 and COL1A1 formed a physical and molecular barrier surrounding tumor nests and engaged in CD44-mediated interactions with tumor cells.

DISCUSSION: Chondroblastoma is characterized by disrupted chondrogenic differentiation, metabolic reprogramming, and immune exclusion by stromal–tumor interactions. These findings provide mechanistic insights into tumor progression and highlight potential therapeutic pathways. Limitations include the small number of high-quality samples and the need for validation in larger cohorts.

SIGNIFICANCE/CLINICAL RELEVANCE: This study provides the first spatial transcriptomic map of human chondroblastoma, defining tumor, stromal, and immune interactions in situ. The findings improve our understanding of tumor biology and suggest new avenues for therapeutic intervention in cartilage-derived bone tumors.