Spatial Transcriptomic Profiling of Osteosarcoma in Clinically Relevant Mouse Model

Harrison Ho, Sung-Suk Chae, Ranxin Zhang, Hasibagan Borjihan, Abhijith Annasamudram, Rui Yang, David Samuel Geller, Chuanyong Lu, Deyou Zheng, Bang H Hoang

INTRODUCTION: Osteosarcoma (OS) is a common primary bone malignancy. The Rb1/Trp53 double knockout (DKO) mouse model recapitulates the histological and molecular features of human OS, providing a platform for studying disease progression [1]. Spatial transcriptomics combines cellular transcriptomic data with spatial coordinates in tissues, revealing area specific cell interactions and tissue structure. Spatial profiling of metastatic osteosarcoma lung specimens revealed spatial heterogeneity which correlate with five-year survival, highlighting the clinical relevance of spatial organization [2]. In this study we use spatial transcriptomics to characterize the tumor cells and microenvironment heterogeneity in primary tumor and lung metastasis using our mouse model. These findings may help scientists to predict treatment response.

METHODS: Four spatial transcriptomics datasets were generated by sequencing two DKO mice using Visium V2 platform. Formalin-fixed, paraffin-embedded (FFPE) tissue sections from the femur (primary tumor) and lung (tumor metastases) of each mouse were prepared from each mouse and processed as instructed. In collaboration with pathologists, areas of interest were selected, and spot deconvolution data were confirmed. This data was further computationally analyzed.

RESULTS: Spatial transcriptomics analysis revealed distinct tumor heterogeneity in all samples. Computationally identified cell types matched information from histology. For example, in one of the lung metastasis samples, we can clearly see the location of tumor and lung endothelial cells (Fig. 1A). We also see that tumor and lung endothelial cells were computationally identified in distinct spots that match histology data (Fig.1B and C). Further analysis shows that Col1a1 and Col2a1 are found to be spatially differentially expressed markers for tumor cells (Fig.1D). Col2a1 was absent in one of the tumor locations. This indicates the presence of distinct spatial distributions of various tumor subtypes.

DISCUSSION AND CONCLUSION: These findings lay the groundwork for understanding the tumor microenvironment, possible cell-cell interactions, immune modulation, tumor escape, and identifying spatially variable genes. This work is important in the hopes of identifying targeted therapies.
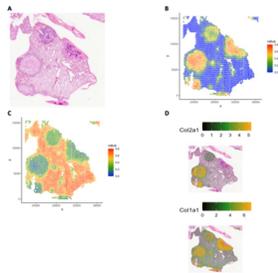
Figures:

Figure 1:
(A) H&E image of the lung tissue with tumor metastases. (B) Pseudo-color image of the proportion of tumor cells at each specific spot, after spatial deconvolution. (C) Pseudo-color image of the proportion of endothelial cells at each specific spot, after spatial deconvolution. (D) Col1a1, osteoblastic osteosarcoma maker is expressed in most tumor metastases while Col2a1, chondroblastic marker is expressed in selective tumor metastases.