HETEROGENEITY IN Glioblastoma Tumor Microenvironment: Strategies for Cancer-Associated Fibroblast Targeting

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Background Glioblastoma (GBM) is the most common and aggressive form of brain tumor, characterized by a poorly accessible microenvironment that renders it notoriously hard to treat. The insufficient treatment success is, in large parts, due to its tremendous molecular heterogeneity, which affects the overall prognosis and response to therapies. The significant intra- and inter-tumor microenvironment (TME) composition heterogeneity plays a crucial role in GBM progression. Mostly due to this high, multifactorial immunosuppression occurring in the microenvironment, the efficacy of immunotherapy in GBM is low. Focusing on characterizing the components of different TMEs to evaluate their molecular and cellular component heterogeneity has a significant advantage to target group of cancer patients that would normally be resistant to immunotherapy.

Methods Deep spatial transcriptomics profiling was performed on non-treated glioblastoma human tissue microarrays (TMA) using NanoString’s GeoMx Digital Spatial Profiler (DSP). 6 tumor tissues from 6 different patients were hybridized and analyzed with the Whole Transcriptomic Atlas (WTA) panel that includes 18,000 genes. Three regions of interest (ROIs) were selected per tissue sample. All the statistical analysis were performed with GeoMx DSP Analysis Suite. Cell deconvolution using the SpatialDecon® algorithm (NanoString®) was then performed to estimate mixed cell type abundance in the spatially-resolved gene expression defined segments.

Results Spatial transcriptomic analyses revealed that glioblastoma tumors varied dramatically in their global gene expression profiles and suggested the existence of differential gene expression among the tumors highlighting the inter-tumors heterogeneity of glioblastoma. Interestingly, different areas of the same tumor did not display distinct molecular profiles. Upregulation of stromal collagen genes was significantly detected in some patients specifically the fibrillar collagens type I, III and VI. Those findings indicated excessive collagen deposition in the surrounding of the tumor for some patients characteristic of tumor progression and involvement of cancer associated fibroblasts (CAFs) in the dysregulated collagen turnover leading to tumor fibrosis.

Conclusions As a cold tumor, malignant glioma has strong immunosuppression and immune escape characteristics. The TME provides the “soil” for the survival of malignant tumors, and recent studies have highlighted a major role for cancer-associated fibroblasts (CAFs) in promoting immunotherapy resistance by excluding T cells from tumors in the TME. Here the spatial transcriptomic analyses allowed a better phenotypical stratification of the cancer patient. In some, targeting CAFs would improve the TME and enhance the efficacy of immunotherapy.