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Spatiotemporally-Resolved Single-Cell Genomics Reveals Tumor Immune Escape Mechanisms in Glioblastoma

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Our immune system possesses an intrinsic capability to recognize and eliminate malignant cells. Yet, tumors frequently subvert this defense by reprogramming tumor-infiltrating immune cells, driving immune evasion and contributing to therapy resistance. Single-cell genomics bear great potential to enhance our understanding of these processes by generating detailed molecular maps of immune cell states within the tumor microenvironment. However, the destructive nature of most single-cell genomics technologies inherently limits them to static snapshots, lacking the temporal resolution required for a causal understanding of tumor-immune interactions. To overcome this limitation, we developed a novel, temporally-resolved single-cell genomics platform that leverages fluorescent in vivo timestamping of circulating immune cells. Our methodology enables the time-resolved recording of transcriptional dynamics of an immune cell once it has been exposed to the tumor microenvironment and thereby offers the possibility to retrieve tumor-immune interactions in real-time. We extended this approach to single-cell resolved spatial transcriptomics, allowing dynamic tracking of immune cell infiltration into tumor niches across space and time. Applying this technology to a model for glioblastoma, we uncovered dynamic patterns of immune infiltration and adaptation, revealing a previously inaccessible perspective of tumor-immune interactions. Our spatiotemporal analyses identified reported drivers of immune escape in an unbiased, data-driven manner and suggested novel therapeutic vulnerabilities that could be exploited to reinvigorate anti-tumor immunity. Together, we present a novel space- and time-resolved single cell genomics technology with tremendous potential for the rational design of novel immunotherapies.

Preferred type of presentation

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