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Single cell microfluidics for systems oncology[1]

RONG FAN, Department of Biomedical Engineering, Yale University

The singular term "cancer" is never one kind of disease, but deceivingly encompasses a large number of heterogeneous disease states, which makes it impossible to completely treat cancer using a generic approach. Rather systems approaches are urgently required to assess cancer heterogeneity, stratify patients and enable the most effective, individualized treatment. The heterogeneity of tumors at the single cell level is reflected by the hierarchical complexity of the tumor microenvironment. To identify all the cellular components, including both tumor and infiltrating immune cells, and to delineate the associated cell-to-cell signaling network that dictates tumor initiation, progression and metastasis, we developed a single cell microfluidics chip that can analyze a panel of proteins that are potentially associated inter-cellular signaling network in tumor microenvironment from hundreds of single cells in parallel. This platform integrates two advanced technologies – microfluidic single cell handling and ultra-high density protein array. This device was first tested for highly multiplexed profiling of secreted proteins including tumor-immune signaling molecules from monocytic leukemia cells. We observed profound cellular heterogeneity with all functional phenotypes quantitatively identified. Correlation analysis further indicated the existence of an intercellular cytokine network in which TNFα-induced secondary signaling cascades further increased functional cellular diversity. It was also exploited to evaluate polyfunctionality of tumor antigen-specific T cells from melanoma patients being treated with adoptive T cell transfer immunotherapy. This platform could be further extended to analyze both solid tumor cells (e.g. human lung carcinoma cells) and infiltrating immune cells (e.g. macrophages) so as to enable systems analysis of the complex tumor microenvironment from small amounts of clinical specimens, e.g. skinny needle biopsies. Thus, it could potentially become a clinical tool for patient stratification based upon the inter-cellular signaling network and designing new anti-cancer therapy by targeting microenvironmental components.

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