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Single-cell RNA-Seq unveils tumor microenvironment

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Keywords: single-cell RNA-Seq; tumor microenvironment; tumor-infiltrating immune cells

Abbreviation: RNA-Seq: RNA sequencing

Running title: Single-cell RNA-Seq unveils tumor microenvironment

Original article

Woosung Chung, Hye Hyeon Eum, and Hae-Ock Lee et al., 2017, Single-cell RNA-seq enables comprehensive tumor and immune cell profiling in primary breast cancer, Nature Communications (8) 15081 doi:10.1038

Abstract

Single cell transcriptome analysis became an essential tool to define cell types or sub-populations within a heterogeneous bulk population. Tumor-associated microenvironment is a complex ecosystem with numerous cell types, supporting the tumor growth, angiogenesis, immune evasion, and metastasis. With the success of checkpoint inhibitors targeting the immune cell compartment, tumor microenvironment is an emerging anti-cancer target and its understanding becomes an imminent issue in the cancer biology.

In the article by Chung, Eum, and Lee et al., Single-cell RNA-Seq was applied for the illustration of tumor-infiltrating immune cells in the primary breast cancer tissues. Tumor heterogeneity in a narrow definition refers to the genetic and non-genetic differences in the tumor cell clone. Characteristics of tumor, however, is highly influenced by tumor microenvironment which is reciprocally shaped by tumor cell itself. Thus tumor associated microenvironment is a central component of the tumor landscape. Single-cell transcriptome analysis is most powerful for the characterization of different cell types, thus diverse cell types within a tumor microenvironment can be identified from. In the past, histology best illustrated the diversity of tumor-associated cell types. The characteristics of each population, however, can be partially glimpsed by conventional histology-associated methodology such as immunohistochemistry. Single cell transcriptomics is potentially the most comprehensive tool for the characterization of tumor landscape including tumor cell itself and associated microenvironment. There is a limit, however, a very critical limit in the application, as cell dissociation required for the current high-throughput analysis of single cell

transcriptome, is far from perfection. Loss of cell types, adherent cells and rare cells in particular, is the huddle in the comprehensive tumor characterization by single cell transcriptome analysis. Immune cells, in its nature are a non-adherent migrant cell type, thus relatively free from loss or damage during cell dissociation. Thus current application of single cell transcriptome analysis best captures tumor associated immune cell compartment in the tumor microenvironment.

Conventionally, characterization of immune cells have relied on the surface marker based separation and their bulk transcriptome analysis. This approach is dependent on the prior knowledge of the subpopulation and limited by the availability of surface markers and detecting antibodies. In the article by Chung, Eum, and Lee et al., previously defined immune gene sets were utilized for the classification of tumor-infiltrating immune cells. Thus, the cell type identification benefitted from prior knowledge of transcriptome data but were not limited by few chosen markers. As a result, Chung, Eum, and Lee et al. provided the full landscape of tumor cells and tumor infiltrating immune cells including T and B lymphocytes and macrophages. In the therapeutic view point, T lymphocytes, macrophages, and tumor cells are all potential targets of immune checkpoint inhibitors as any of them can activate checkpoint on T lymphocytes. In T lymphocytes, multiple checkpoint molecules were identified, the renowned PD-1 and more recently developed targets LAG3 and TIGIT. Those T lymphocytes retained a potential to exert an anti-tumor immunity, judging from their expression of cytotoxic mediators. The non-redundant expression of immune checkpoint molecules suggests that combination of checkpoint inhibitors or screening of the best matching checkpoint inhibitor are necessary for the successful application of immune checkpoint therapy in breast cancer.

The study presented other important findings in intra-tumoral heterogeneity such as multiple subtype composition within a patient, which may confer a mechanism for treatment resistance. The most important finding of the study, however, is the demonstration that single cell transcriptome analysis could enable comprehensive tumor and immune cell profiling. Extension of the study, i.e. high-throughput single cell transcriptome analysis for a large number of patients would reveal the full landscape of tumor and associated immune cells in breast cancer with currently available technology. The full landscape will guide towards better treatment strategies targeting tumor cells and the immune compartment.