Analysis of single cells through time and space by mass cytometry

Prof. Dr. Bernd Bodenmiller

Institute of Molecular Life Sciences, University of Zurich,

Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

bernd.bodenmiller@imls.uzh.ch

Introduction.

Tumors consist of heterogeneous cancer and normal cells that communicate with each other in tumor microenvironments (TME). This communication drives tumor progression, metastasis formation and drug resistance. For an understanding of the processes in the TME, comprehensive investigation of its components and their relationship is necessary. This demands imaging approaches that can simultaneously measure dozens of biomarkers to define cell types, their functional and signaling states, and spatial relationships.

Methods

For highly multiplexed tissue imaging at subcellular resolution, we have coupled immunohistochemical (IHC) methods with high-resolution laser ablation and mass cytometry (MC) (1). In MC, metals are used as reporters on antibodies. Analysis of metal abundances using MC allows determination of biomarker expression. In the presented approach, tissue sections were stained with metal-tagged antibodies using IHC protocols. Antibodies were selected to target readouts relevant to breast cancer. Then the tissue was ablated spot by spot (2), and the ablated material was analyzed using a CyTOF MC instrument. After data preprocessing, 44 isotope signals were plotted as a high-dimensional image of the tissue. Single-cell features were segmented and the single cell marker expression data were extracted for downstream bioinformatics analyses.

Results

Imaging MC provides targeted, high-dimensional analysis of cell type and state at subcellular resolution. The imaging approach enables the simultaneous visualization of up to 120 proteins and their modi-fications. Application to breast cancer samples allowed delineation of cell subpopulations and cell-cell interactions, highlighting tumor and TME heterogeneity. As such it has the potential to yield insights of the TME by exploiting existing large collections of FFPE tumor samples and associated clinical information.

References

(1) Giesen et al. Nat. Meth. 2014

(2) Wang et al. Anal. Chem. 2013