CCBIO Opinion

Text: Lars A. Akslen

Prospects of Next Generation Tissue Profiling

The gold standard for a diagnosis of cancer, following clinical and radiological suspicion, has for a long time been the microscopic analysis of simply stained tissue samples. In addition to studying the criteria of malignancy, more features will be reported, such as histologic grade and detailed stage information. Using breast cancer as an example, the last edition of the TNM classification system (AJCC, 8.ed, 2017) has now included histologic grade (G) and expression status of key biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and HER2 on top of the basic TNM parameters, in a new prognostic stage group concept. This upgrade of the TNM classification is significant.

In recent times, translational efforts have made extensive use of tissue samples for large-scale research purposes including discovery and validation of omics profiles, and biobanks with clinical annotations (TCGA, METABRIC, Human Protein Atlas and many others) have become valuable tools for hypothesis-based studies and more extensive discovery-oriented mapping of different classes of biomarkers. However, some problems are evident. First, many biomarkers are mostly based on samples from primary tumors, whereas metastatic disease represents the real clinical problem. Second, even when considering the primary lesion alone, or the metastatic lesions, tissue heterogeneity as a reflection of biological diversity within a tumor mass adds a significant challenge.

A large majority of biomarker studies on intact tissue samples have focused on individual tumor cell features. There is a need for higher order studies of multiple characteristics, or profiles, or phenotypic patterns, such as those starting to emerge from multiplex immuno-histochemistry or immuno-fluorescence analyses. This will be necessary to build more precise tissue based models of co-expression patterns and functional biomarkers within different tissue compartments, with particular attention to the tumor microenvironment, and including the interacting immune and vascular systems. The use of mass cytometry might be necessary to increase the potential for even deeper learning of the tissue composition as well as proximity patterns and functional tissue domains. To support such ambitious plans, studies will have to be supported by intense bioinformatics and artificial intelligence resources to be successful. Modeling of the tumor-microenvironmental interactions based on studies of solid biopsies, is a challenge in this field. In translational studies, researcher networks will be needed to increase our insight of the complexity and heterogeneity of biological networks in cancer. A deep and integrated understanding of morphology and biology is necessary to obtain better models of how malignancy is driven in the context of tissue landscapes. ••