Conquer the tumor microenvironment: Phenotypic heterogeneity of human cancer using imaging mass cytometry

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Tumours are highly heterogeneous populations of cells, and measures of intratumoral heterogeneity (ITH) and diversity correlate with worse prognosis in many cancers. Emerging studies are highlighting functional interactions between subclones, as well as among subclones and components of the tumour microenvironment. A growing body of evidence indicates that the tumour microenvironment contributes to tumour growth and viability. However, these studies have focused on soluble factors without interrogating the spatial distribution of subclones defined by activated signalling pathways. In large part, this is due to limitations of currently available technology which does not allow for the detection of complex immunophenotypes in tissue sections. High parameter methods such as gene expression profiling or flow cytometry have been applied to study the tumour microenvironment (TME). However, data on cellular heterogeneity and rare cells is lost with gene expression studies, and the spatial relationship between the tumour and immune cells is lost with flow cytometry. We will circumvent these limitations by undertaking imaging mass cytometry (IMC), which allows for simultaneous measurement of 30-40 antigens while retaining the spatial organization of the sample. Our objective is to develop and optimize highly multiplexed assays for characterization of signalling heterogeneity in tissue microarrays of human tumours and describe the modelling cell signalling heterogeneity in cell line-based models to determine mechanisms of cell-cell interaction and communication in various tumours on the IMC platform. We have constructed an IMC panel of antibodies that combines markers for tissue architecture, tumour and immune cell phenotyping, and signalling pathway activation. Analysis of individual tumours demonstrates unique compositions of cell phenotypes between the edge and core of the tumour. Interestingly, while the tumour cells exhibit distinct phenotypes, the stromal cells are largely indistinguishable from one another. Methods developed here should be applicable for the study of the TME in different tumour types and could be used to identify additional biomarkers of response to immuno-oncology agents.

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