De novo discovery of phenotypic intratumour heterogeneity using imaging mass spectrometry.

An essential and so far unresolved factor influencing the evolution of cancer and the clinical management of patients is intratumour clonal and phenotypic heterogeneity. However, the de novo identification of tumour subpopulations is so far both a challenging and an unresolved task. Here we present the first systematic approach for the de novo discovery of clinically detrimental molecular tumour subpopulations. In this proof-of-principle study, spatially resolved, tumour-specific mass spectra were acquired, using matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry, from tissues of 63 gastric carcinoma and 32 breast carcinoma patients. The mass spectra, representing the proteomic heterogeneity within tumour areas, were grouped by a corroborated statistical clustering algorithm in order to obtain segmentation maps of molecularly distinct regions. These regions were presumed to represent different phenotypic tumour subpopulations. This was confirmed by linking the presence of these tumour subpopulations to the patients’ clinical data. This revealed several of the detected tumour subpopulations to be associated with a different overall survival of the gastric cancer patients.
(p = 0.025) and the presence of locoregional metastases in patients with breast cancer (p = 0.036). The procedure presented is generic and opens novel options in cancer research, as it reveals microscopically indistinct tumour subpopulations that have an adverse impact on clinical outcome. This enables their further molecular characterization for deeper insights into the biological processes of cancer, which may finally lead to new targeted therapies.