A Mass Spectrometry Imaging-based multiomics approach to map the tumour-immune landscape of clear cell Renal Cell Carcinoma and gain insights into resistance to immunotherapy

SpT-26-4

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The advent of Immune Checkpoint Inhibitors (ICIs) has revolutionised cancer treatment, but despite this significant advancement, the efficacy of ICIs is confined to inherently immunogenic cancers, and effectiveness of response varies from patient to patient. Many hypotheses regarding the primary or acquired resistance mechanisms to ICIs revolve around the tumour microenvironment (TME), which involves the presence on Tumor Infiltrating Lymphocytes (TILs), as well as further heterogeneous sets of cell populations, whose presence is known to correlate with tumour response to treatment. In this context, the opportunity to investigate which immune cells characterise this environment, along with the ability to delve deeper into the molecular and spatial interactions which occur in their native spatial context, could be crucial in comprehending the mechanisms that influence the response to ICI treatment. To achieve this goal, a MALDI-HiPLEX-IHC based approach was employed to explore the TME of clear cell Renal Cell Carcinoma (ccRCC) and leverage this multi-omics workflow for the for the subsequent mapping of the lipidome, multiplexed imaging of targeted immune cells and lastly proteome on a single formalin fixed paraffin embedded tissue section of patient-derived ccRCC. This exploration allowed the tissue distribution of TILs and further immune cells to be mapped and to determine their interface of interaction. Moreover, by correlating MALDI data with LC-MS identifications, it underlined which aberrant molecular mechanisms may be involved in immune-tumour cell communication. Concurrently, advanced co-culture cellular models were established and treated with ICIs to confirm the hypothesis formulated based on ex-vivo tumour resections, and provide deeper insights into the factors that play a role in therapy resistance. Advancements in this realm can provide insights into the metabolic pathways steering the immunogenic environment and influencing resistance to immunotherapy.

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