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Heterogeneity of circulating tumour cell neoplastic subpopulations interrogated by single-cell transcriptomics Heterogeneity of circulating tumour cell neoplastic subpopulations interrogated by single-cell transcriptomics

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Fatal metastasis occurs when circulating tumor cells (CTCs) disperse through the blood to initiate a new tumor at specific sites distant from the primary or metastatic tumor. CTCs have been classically defined as nucleated cells positive for epithelial-cell adhesion molecule and select cytokeratins (EpCAM+/CK+/DAPI+), while negative for the common lymphocyte marker CD45 ("classic" CTCs). The enumeration of these CTCs has also allowed the estimation of the overall metastatic burden of breast cancer (mBC) patients, however challenges regarding CTC heterogeneity and metastatic propensities persist and further CTC decryption could improve therapy effectiveness. To this end, we applied a four-pronged experimental approach consisting of interrogating peripheral blood mononuclear cells isolated from blood of mBC patients. We combined: 1) the use of multi-parametric flow cytometry sorting Lin+ (CD45+) and Lin- cell populations from the same patient, 2) the performance of RNASeq of Lin+/Lin- cell populations from 66 mBC patients of distinct subtypes, 3) employing 10x Genomics Chromium platform for the unbiased and comprehensive transcriptional profiling of Lin+/Lin- cell populations on a cell-by-cell basis and from distinct mBC patients and 4) the capture and analysis of "classic" CTCs using the RareCyteTM Cytefinder II platform. Of relevance, single-cell transcriptomic analyses of Lin- vs. Lin+ cell populations isolated from blood of mBC patients identified a unique and heterogeneous cluster of neoplastic cells including not only those expressing EpCAM/CK ("classic" CTCs) but also ones possessing an array of genes not previously associated with CTCs. This study put forward notions that the identification of these genes and their interactions will promote novel areas of analysis by dissecting properties underlying CTC survival, proliferation and cross-talks with immune system cells. It improves upon abilities to measure and interfere with CTC states and plasticity and functionalities of CTC subsets to identify vulnerabilities and interfere with CTC states for impactful therapeutic interventions.

References

1. Molecular Interplay between Dormant Bone Marrow-Resident Cells (BMRCs) and CTCs in Breast Cancer.
2. Application of liquid biopsy for prognostic status of cancers and drug response
3. PMN-MDSCs enhance CTC metastatic properties through reciprocal interactions via ROS/Notch/Nodal Nodal signaling.

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