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Molecular characterization of circulating tumor cells in pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy in humans due to high recurrence rates and early systemic dissemination.1–3 This major health burden leads to tremendous research efforts to decipher the metastatic cascade of PDAC.11,152–156 CTCs, as a well-known intermediary step between primary and secondary tumors, have been a lasting research topic for decades.60,102,157–160 Although exponentially increasing numbers of publications are investigating CTCs, there has been no consensus marker for CTCs in the past decades, most likely as a result of CTC heterogeneity. Universally, researchers applied EPCAM for immunoaffinity isolation of pancreatic CTCs to harvest a particular CTC; however, this subpopulation is controversial and may not represent the metastasis-initiating subfraction of CTCs.60 GEMMs are valuable tools to investigate pancreatic CTCs.60,133 Since they retain histopathological features, consistent transcriptomics alterations, and the mutational landscape of human PDAC,44,55 the CTCs derived from GEMMs should resemble human pancreatic CTCs closely. Previous pioneering research already attempted scRNA-seq of pancreatic CTCs from KPfC mice. The re-analysis was performed on their dataset (GSE51372) with Seurat. Three heterogeneous clusters of CTCs with distinct biologic phenotypes were identified. In this study, the Gas2l1 exhibited better CTC identification than Epcam, Cd45, Sparc, and absence expression in peripheral blood mononuclear cells. Probably, pancreatic CTCs realize migration through Gas2l1 guiding microtubules to focal adhesions. Notably, few pieces of the literature demonstrated that Gas2l1 is in murine platelets. This reflects the possibility that pancreatic CTCs cloak with platelets. Regardless, GAS2L1 shows significant over-expression in PDAC compared to normal pancreatic tissue and a remarkable indicator value of relapse-free survival in the PDAC cohort (The Cancer Genome Atlas Program). Future immunocytochemistry and single-cell RT-PCR in lineage-traced pancreatic CTCs are necessary to validate its efficiency. Generally, stem markers were used to identify CTCs with stem-like features. In case a single marker distorted the stem-related classification, a pool of phenotypic markers was applied on the same murine pancreatic CTC dataset (GSE51372). Combined with the following principal component analysis and hierarchical clustering, Murine pancreatic CTCs were divided into with and without stem-like features groups. Both over-representation analysis and weighted gene co-expression network analysis revealed that the adherens junction pathway is significantly enriched in pancreatic stem-like CTCs. Transcription factor, Klf4 was found to have a significant association with stem-like population. Reasonable speculation is that the stem fraction CTCs regain intercellular junction and form cell clusters through actin cytoskeleton remodeling. However, further transcriptomic comparisons between CTCs and CTC clusters, genetic manipulations are alternative solutions for validations. In summary, pancreatic CTCs are vital components of hematogeneous metastasis. The emerging scRNA-seq techniques and corresponding bioinformatic toolkits accelerated the development of CTC research. Despite limitations existing, these two in silico analyses of scRNA-seq data of pancreatic CTCs derived from GEMM and explored biomarkers and stem-like populations of these CTCs. As scRNA-seq technology is evolving rapidly, the dawn of uncovering more secrets of CTCs is breaking.