TITLE

Stemness of the Hybrid Epithelial-Mesenchymal State in Circulating Tumor Cells: Phenotypic Plasticity and Cell Fate Decisions in Cancer

ABSTRACT

Nearly 90% of cancer deaths are attributed to distant tumor metastasis. Circulating Tumor Cells (CTCs) are the disseminated cells from primary tumors or metastatic deposits, which shed into blood circulation and constitute as key components of cancer metastasis. An important process involved in tumor metastasis is the Epithelial Mesenchymal Transition (EMT). To examine the fate of CTCs in circulation, we interrogated CTC-specific gene expression profiles that unfolded the pivotal role of the highly significant 'leukocyte extravasation pathway' in tumor cell extravasation during metastasis. Cancer stemness and cellular plasticity with EMT has been linked however cells bearing hybrid E/M phenotype have been referred to as "metastable", reflecting the flexibility of these cells to reverse the EMT process.

CTCs identification and characterization require extremely sensitive and specific methods. Consequently, there is an urgent need for techniques that can successfully expand CTCs. We have devised a microwell-based culture method to assess cancer CTCs from patients undergoing neoadjuvant therapy. Our culture system enabled us to perform deeper characterizations of CTCs, capable of forming tumorospheres following EMT induction and expressing a CD44highCD24low profile was reminiscent of that of CSCs. Further, network-level analysis and bioinformatic scoring methods revealed a wide spectrum of EMT phenotypes in CTCs across many cancers, substantiating the intermediate or hybrid phenotypes of cancer cells in circulation.