

Emerging Biology of Circulating Tumor Cells (CTCs) in Cancer Detection and Chemotherapy

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Circulating Tumor Cells (CTCs) are present in the blood of all types of cancer patients, and originate from primary tumors and metastasis. Migration and cell adhesion of these cells determine the future site of cancerous growth in the distant organ. The presence of CTCs in the blood could be used to develop suitable biomarkers to detect cancers that are difficult to diagnose, such as pancreatic, lung, brain and ovarian cancer. Isolating single CTCs from blood combined with molecular profiling using Nextgen sequencing could identify genes, miRNA or noncoding RNA to diagnose any cancer and provide significant clues for its treatment. To eradicate cancer, it is essential to kill all CTCs in the blood of cancer patients. Chemotherapy is the only way to treat them, since tumor surgery and radiation therapy are unable to completely remove them. However, very limited information is available about their biology, molecular mechanisms of spreading, cell adhesion and their overall responsiveness to different types of chemotherapy. Recently, an efflux of report indicates that studying CTCs biology with Nextgen genomic technologies is emerging as an important field for the detection and treatment of cancer.

Isolation of CTCs

Large scale isolation of CTCs is challenging. Their existence in blood is extremely rare, for example, only 8 to 50 CTCs are present in 1 ml of blood of cancer patients, and that number is also reduced after chemotherapy or surgery. Isolation of CTCs is based on the presence of epithelial cell markers since most of these cancers are epithelial in origin. The most commonly used antibody for the surface marker is EpCAM (epithelial Cam-adhesion molecule, CD326), to isolate CTCs from lung, breast, colon and prostate cancer. Any leukocyte contamination could be removed by using the CD45 antibody to select CD45- cells. CTCs in ovarian cancer have been purified using both positives of cells of CD133 and CD44, whereas only CD133 is used for glioma. Recently, Nagrath et al. [1] and Yu et al. [2] developed a microchip technique to isolate CTCs in mouse pancreatic cancer by immobilizing the EpCAM antibody on a plastic surface and flowing blood through it that binds to CTCs. Implementation of this technology in humans to isolate CTCs in cancer patients shows promise in understanding CTC biology in relation to development of biomarkers and therapies. Very recently, Powell et al. [3] developed similar microfluidic techniques to isolate CTCs from breast cancer patients.

Developing a Biomarker from CTCs

Most of the studies of CTCs are limited to breast cancer patients. Dawson et al. [4] compared CTCs and primary tumor DNA from breast cancer patients by Nextgen sequencing and suggested that CTCs are more informative for detecting secondary mutation than primary tumors. Yu et al. [2] used single cell RNA sequencing of CTCs from mouse pancreatic cancer and identified the role of WNT signaling pathways in pancreatic cancer. Using single cell transcription profiling of 87 breast cancer patients, Powell et al. [3] identified heterogeneity among CTCs in different individuals and identified several genes (*NPTN, S100A4, S100A9*) that are overexpressed in CTCs. As more studies are expected to come in the near future, single cell CTCs profiling could provide distinct biomarkers for the detection of cancer.

Understanding Molecular Mechanisms of Cell Adhesion and Metastasis

A subpopulation of CTCs is tumor initiating cells (TICs). TICs have two subtypes, intrinsic cancer stem cells and induced cancer stem cells. Intrinsic cancer stem cells are believed to exist within the primary tumor, and induced cancer stem cells are differentiated cancer cells that undergo epithelial to mesenchymal transition (EMT) (Figure 1). EMT occurs due to genetic and epigenetic modifications of the tumor cells through signaling from the stroma and tumor microenvironment. EMT is considered a pathological mechanism and cells begin to downregulate epithelial markers. After finding a new location for growth, they reverse the procedure and undergo mesenchymal to epithelial transition (MET). Understanding the molecular mechanism of these transitions of CTCs are key factors in developing successful chemotherapy. Cen et al. [5] suggested that genomic profiling of CTCs from pancreatic cancer patients provides important information regarding transition of epithelial to mesenchymal cells and identifies specific molecules driving metastasis and chemoresistance. Powell et al. [3] identified several EMT genes (VIM, TGFß1, ZEB2, FOXC1, CXCR4), using single cell gene expression profiling. Yu et al. [6] also identified EMT regulatory



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genes, including TGFß1 and FOXC1 transcription factors. Although further extensive studies are needed to characterize the role of these genes in EMT and MET, their identification could have a profound effect in understanding cancer cell transformations.

Outcome of Chemotherapeutic Treatment in Cancer Patients

Cassatella et al. [7] predicted that CTCs in breast cancer could be an early marker for disease prognosis. Gazzaniga et al. [8] profiled drug resistance genes in 40 colorectal cancer patients and suggested that MRP5+ CTCs may determine the resistance to the drug 5-FU (5-fluorouracil) and L-OHP (oxaliplatin) based chemotherapy. Gradoline et al. [9] profiled drug resistance genes, such as multi drug resistance genes (MRPs) ALDH1 and ER2 (estrogen receptor alpha) in CTCs of 105 breast cancer patients, and observed that CTCs expressing MRPs and ALDH1 had increased drug resistance compared to CTCs that have little or no expression of these genes. They also suggested that this approach could be a first step of individualization of chemotherapy in cancer patients. In xenograft mouse studies, Barok et al. [10] suggested that CTCs are more responsive to trastuzumab, when a primary tumor is resistant to the drug. Their study indicates that trastuzumab could still be beneficial to breast cancer patients, although primary tumor treatment is nonresponsive.

Conclusion

Given the complexities of cancer, chemotherapy frequently fails for many unknown reasons. Recent technological advances, including single cell genomic technologies, are allowing us to understand the biology of CTCs. Although most of the studies are limited to CTCs of breast cancer cells, more comprehensive studies are expected in coming years for other cancers that would help to develop proper biomarkers for detection and successful therapy.

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