ICFO Colloquium MEHMET TONER 'Bioengineering & Clinical Applications of Circulating Tumor Cells'

MEHMET TONER

November 04, 2013

Monday, November 4, 2013, 12:00. ICFO?s Auditorium

MEHMET TONER

BioMEMS Resource Center & Department of Surgery, Massachusetts General Hospital, Harvard Medical School

Harvard-MIT Division of Health Sciences & Technology, UNITED STATES

Viable tumor-derived circulating tumor cells (CTCs) have been identified in peripheral blood from cancer patients and are probably the origin of intractable metastatic disease. However, the ability to isolate CTCs has proven to be difficult due to the exceedingly low frequency of

CTCs in circulation. We introduced several microfluidic methods to improve the sensitivity of CTC isolation, a strategy that is particularly attractive because it can lead to efficient purification of viable CTCs from unprocessed whole blood. The micropost CTC-Chip (?pCTC-Chip) relies on laminar flow of blood cells through anti-EpCAM antibody-coated microposts, whereas the herringbone CTC-Chip (HbCTC-Chip) uses micro-vortices generated by herringbone-shaped grooves to efficiently direct cells toward antibody-coated surfaces. These antigen-dependent CTC isolation approaches led to the development of a third technology, which is tumor marker free (or antigen-independent) sorting of CTCs. This recently developed isolation strategy combines the strengths of microfluidics for rare cell handling while incorporating the benefits of magnetic-based cell sorting. After the magnetic labeling of cells in whole blood, this capture platform integrates three sequential microfluidic technologies: (i) debulking by separation of nucleated cells, including CTCs and white blood cells from red blood cells and platelets using deterministic lateral displacement chip; (ii) alignment of nucleated cells within a microfluidic channel using inertial focusing; and (iii) deflection of magnetically tagged cells into a collection channel. We call this integrated microfluidic system the CTC-iChip, based on the inertial focusing strategy, which allows positioning of cells in a near-single file line, such that they can be precisely deflected using minimal magnetic force. This integrated microfluidic platform is compatible with high-definition imaging and single-cell molecular analyses, as well as standard clinical cytopathology. We applied these three microfluidic platforms to blood samples obtained from metastatic lung, prostate, breast, colon, melanoma, and pancreatic cancer patients. We isolated CTCs from patients with metastatic non-small-cell-lung cancer and identified the expected EGFR activating mutation in CTCs. We also detected the T790M mutation, which confers drug resistance, in CTCs collected from patients with EGFR mutations who had received tyrosine kinase inhibitors. We also applied microchip to isolate CTCs from blood specimens of patients with either metastatic or localized prostate cancer, and showed the presence of CTCs in early disease. Remarkably, the low shear design of the HBCTC-chip revealed micro-clusters of CTCs in a subset of patient samples. Microscopic CTC aggregates may contribute to the hematogenous dissemination of cancer. More recently, we used microfluidic capture of CTCs to measure androgen receptor (AR) signaling readouts before and after therapeutic interventions using single-cell immunofluorescence analysis of CTCs. The results support the relevance of CTCs as dynamic tumor-derived biomarkers, reflecting "real time" effects of cancer drugs on their therapeutic targets, and the potential of CTC signaling analysis to identify the early emergence of resistance to therapy. We also characterized epithelial-to-mesenchymal transition (EMT) in CTCs from breast cancer patients. While a few primary tumor cells simultaneously expressed mesenchymal and epithelial markers, mesenchymal cells were highly enriched in CTCs, and most importantly, serial CTC monitoring suggested an association of mesenchymal CTCs with disease progression suggesting a role for EMT in the blood-borne dissemination of human breast

cancer. Currently, the work is focused on dissemination of the technology to multiple clinical centers as well as the development of approaches for high sensitivity detection of CTCs for early detection of cancer. This presentation will share our integrated strategy to simultaneously advance the engineering and microfluidics of CTC-Chip development, the biology of these rare cells, and the potential clinical applications of circulating tumor cells.

Monday, November 4, 2013, 12:00. ICFO?s Auditorium

Hosted by Prof. Romain Quidant