Ind J Clin Biochem (Jan-Mar 2019) 34(1):1–2
https://doi.org/10.1007/s12291-019-0812-z

EDITORIAL

Single Cell Omics Approach: A Paradigm Shift in Diagnosis and Therapy of Cancer

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Published online: 10 January 2019

Relentless progress in molecular technologies over the decades has now solved the puzzle of carcinogenesis that it is heterogeneous in nature. Heterogeneity in cancer is primarily linked to the genetic alternations, as it is well-known fact that random mutation frequency in human cancer cells is several fold greater than in nearby normal cells. So, it may translate abnormal protein qualitatively or may generate several copy of the same protein in quantities, as per basic mechanisms of central dogma of biology. But, with progression in cutting-edge technologies, now the complexity is unlocked beyond the simple mutation/aberration, now various unknown drivers of cancer have been explored through whole genome analysis. Thus, DNA copy number variation (CNV), methylation analysis, histone-modification, non-coding RNA expression, transcriptional profiling and splicing aberrations have been evident, which are significant contributor in complexity and heterogeneity of the cancer.

All above novel dimensions were added mainly due to the extensive endeavor of The Cancer Genome Atlas (TCGA) project, which was launched with a joint effort of the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI). Molecular studies on homogenous population of tumor cells have revealed that single tumor cell can display remarkable heterogeneity in gene expression, transcripts, protein levels and phenotypic manifestation that results in crucial functional consequences. The earlier studies on cellular heterogeneity were very limited due to technological constrain, were restricted to a few targeted RNAs or proteins but now it has open its horizon, due to advancements in micro-fluidic methodologies for single cell analysis.

Micro-fluidics advancements in form of mass spectrometry, Next Gen sequencing, flow-cytometry and novel advancement in FISH enables researchers to explore exclusive single cell peptides, single cell RNA-Seq, various unique cell surface receptors on individual cells and RNA-Fluorescent in situ hybridization (FISH). This is providing more vivid picture of heterogeneity patterns that have not been reported previously [1, 2].

Single cell analysis in cancer is utmost needed because it is established fact that tumors may initiate in consequence of malignant transformation of even a single normal cell, more probably due to continuous piling-up of genetic mutations and gene expression alterations. Thus, varied subset of tumor cells with distinct characteristics appear, which may further progress to metastatic advancements. So this whole journey of altered single cell from tumor initiation to malignant transformation is resultant of various cascades of genetic and epigenetic changes, which is collectively known as carcinogenesis. Several biotech companies and translational labs like Fluidigm Corporation (San Francisco, CA) and Denovo Sciences (Plymouth, MI) are seeking for developing microfluidic devices to study the heterogeneity of breast CSCs (Cancer Stem Cells) and circulating tumor cells (CTCs) at the single cell level. Our lab is also involved in characterizing heterogeneity of CSCs populations by using cell surface markers CD44+/CD24− and CTCs in breast cancer sample [3–5]. Now researchers have recognized the presence of two types of breast CSCs, which are anatomically distinct, one with EMT (epithelial-to-mesenchymal transition) and other having MET (mesenchymal-to-epithelial transition) gene expression profiles. Additionally,

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they dynamically demonstrate transition between the mesenchymal and epithelial-like states along with their normal counterparts in mammary cells. Interestingly, seed and soil theory of metastasis, also pinpoints its transformation from quiescent mesenchymal state to a proliferative epithelial-like state as a metastatic nodules in distant organs.

As a consequence of genomic sequencing findings, two novel small-molecule drugs, crizotinib and PLX4032, have been progressed to late phase clinical trials for their remarkable anticancer effects on NSCLCs carrying EML4-ALK translocations and metastatic malignant melanomas having V600E mutation of the BRAF gene respectively. Similarly, Trastuzumab, an anti-HER2 antibody, was the first successful targeted therapy offered for treatment of HER2-positive breast cancers. Current clinical practice states anti-HER2 therapy should only benefit to breast cancer patients with HER2 positive primary tumors. Multiplexing and high-throughput assays for proteomic studies performed by using mass cytometry have explored the expression and plenty of proteins key targets under concern conditions. The DVS Sciences mass cytometry technology, CyTOF, (now purchased by Fluidigm Corporation) and likewise other advanced technologies permit cancer researchers to explore many target proteins simultaneously in each single cancer cell. Single cell omics approach including genomics, transcriptomics, methylomics, proteomics and metabolomics will broadly cross-examine the patient tumor and allow investigators to learn and resolve the important aspects of tumor initiation and progression to metastatic and drug resistant phenotypes. Now we are at the horizon of paradigm shift in diagnosis and therapy, where single cell omics is radiating a new hope in better management of cancer.

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