Molecular diagnostics and molecular targeted therapy of cancer

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Cancer is one of the leading causes of morbidity and mortality worldwide. It has become a major public health problem. Cancer develops from the transformation of normal cells into tumour cells in a multistage process that can affect any part of the body. Generally, there are six hallmarks of cancer, which includes sustaining proliferative signalling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis and resisting cell death. Research suggests two additional hallmarks which are emerging hallmarks (deregulating cellular energetics and avoiding immune destruction) and two enabling characteristics (tumour-promoting inflammation, and genome instability and mutation).

Cancer is one of the complex non-communicable and multifaceted diseases, and it is tied to powerful global trends which are not easily reversed. Some people believed that cancer is a curse due to its complexity. It is impossible to tackle this complex disease without proper diagnosis and therapy. The advancement of technology has allows us to understand a particular disease at the molecular level and the current oncology practice is rapidly undergoing a change. The term “one size fits all” is no longer applicable. Similarly, cancer diagnosis is currently undergoing a paradigm shift with the integration of molecular biomarkers in the diagnostic panel.

The use of precise targets for the diagnosis of cancer is crucial in the era of precision medicine since specific drug therapies will be targeted against these molecules. In precision medicine, treatment modalities in cancer patients are no longer solely based on anatomic location and the phenotype of the tumour. An understanding of the pathogenetic evolution of cancer that leads to the discovery of alterations in several molecules such as DNA, RNA, mRNA, miRNA and proteins occurring within the cancer cells at molecular level has paved the way for personalized oncology. Recent research has demonstrated that advances in chemistries and instrumentation, including automation, integration and throughput such as real-time quantitative PCR, digital PCR, next-generation sequencing (NGS), mass spectrometry, microarray, bead-based suspension array, microfluidic chip, flow cytometry and electrically magnetic-controllable electrochemical biosensors to detect molecular markers, can assist in early and accurate diagnosis, predict prognosis and monitoring of cancer development in patients. In addition, a comprehensive detection panel of molecular alterations can provide a “signature” specific for each tumour and condition, termed as “molecular signature”, which can then serve as a template for personalized onco-pharmacogenomics.
The revolution of the “omic” in cancer diagnostics, which includes (Whole) Genome (WGS), Exome (WES), methylome, transcriptome (including the miRnome), microbiome, metabolome, proteome and topome, has led to the emergence of a new field termed as “Molecular Oncodiagnostics”. Thus, tumours are no more just diagnosed at the histomorphological level. Cancer diagnostics based on molecular biomarkers are part of the precision medicine because such molecules hold promise not only in the early diagnosis of cancer but also in risk-stratification and prognosis. These molecules need to be detected in a wide variety of clinical specimens such as liquid biopsies and tissues both fresh-frozen and paraffin-embedded. These molecules (DNA, RNA, mRNA, miRNA and proteins) could be limited on their detection to certain specimens of the patient. Therefore, the selection of sensitive approach is crucial. Some of the approaches can be classified as companion diagnostics while others as complementary diagnostics. For instance, based on the WHO classification of haematological malignancies, genomic alterations are part of cancer diagnosis. In addition, FDA has approved PD-L1 IHC 28-8 pharmDx assay as an Opdivo (nivolumab) companion diagnostic for both tumour cell PD-L1 expression for non-squamous, non-small cell lung cancer (ns-NSCLC) and melanoma. Recently, FDA also approved Oncomine Dx Target Test as the first NGS-based companion diagnostic that screens tumour samples against panels of biomarkers to identify patients who may respond to one of three different treatments for non-small cell lung cancer.

Mechanism-based targeted therapies to treat human cancers has been indicated as one of the success of three decades of research into the mechanism of cancer pathogenesis. The therapeutic targeting of the hallmarks of cancer includes: cyclin-dependent kinase inhibitors for evading growth suppressors, immune-activating anti-CTLA4 mAb for avoiding immune destruction, telomerase inhibitors for enabling replicative immortality, selective anti-inflammatory drugs for tumour promoting inflammation, inhibitors of HGF/c-Met for activating invasion and metastasis, inhibitors of VEGF signalling for inducing angiogenesis, PARP inhibitors for genome instability and mutation, pro-apoptotic BH3 mimetics for resisting cell death, aerobic glycolysis inhibitors for deregulating cellular energetics, and EGFR inhibitors for sustaining proliferative signalling. On the other hand, drug resistance in anticancer therapy could be critically affected at the molecular level of drug targeting. New anticancer drugs that target oncogenic signalling pathways have been developed to address alterations influenced by drug resistance. Recently, third-generation EGFR inhibitors, such as osimertinib, olmutinib and rociletinib were developed to target T790M. These specific EGFR-TKIs exhibited effectiveness in overcoming T790M-mediated resistance in patients with NSCLC.

In conclusion, the diagnosis of cancer has undergone a paradigm shift and the search for more novel molecular targets (DNA, mRNAs, miRNAs and proteomic) are essential. Cancer is no longer diagnosed only based on morphological parameters, and tumour may not be characterized by a single-gene alteration but by a panel of “signature” genomic or proteomic alterations. Overall, the correct molecular diagnostic tools with advances of instrumentations and chemistries provide accurate diagnosis and have extended their application as prognostic risk factors. Thus, the identification of appropriate drug and right dosage to every patient who receives precision medicine will be possible.

**Conflict of Interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

**References**


