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Cancer molecular markers: A guide to cancer detection and management

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ABSTRACT

Cancer is generally caused by the molecular alterations which lead to specific mutations. Advances in molecular biology have provided an impetus to the study of cancers with valuable prognostic and predictive significance. Over the hindsight various attempts have been undertaken by scientists worldwide, in the management of cancer; where, we have witnessed a number of molecular markers which allow the early detection of cancers and lead to a decrease in its mortality rate. Recent advances in oncology have led to the discovery of cancer markers that has allowed early detection and targeted therapy of tumors. In this context, current review provides a detail outlook on various molecular markers for diagnosis, prognosis and management of therapeutic response in cancer patients.

1. Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries [1] due to the increased adoption of cancer-associated lifestyle choices. As the world population continues to age and developing countries continue to modernize, morbidity and mortality due to cancer are increasing. Lung, liver, colorectal, stomach and breast cancer are the most common causes of cancer deaths each year. Cancer is a complex disease occurring *via* genetic alterations or aberrations that enables transformation of normal cells into tumor cells, which results due to an interaction between the genetic factors and external agents (physical, chemical and biological carcinogens). In addition, cancers can arise *via* the aberration of different combinations of genes, which in turn may be mutated, over expressed, or deleted. During carcinogenesis, alterations in genes or mutations lead to disregard to cell cycle checkpoints which cause a normal cell to grow in an uncontrolled manner. Cancer cells thus have two heritable properties: they and their progeny (a) reproduce in defiance of the normal restraints on cell division and (b) invade and colonize territories normally reserved for other cells. Over the years diverse areas of science have shown to solve the enigma surrounding the initiation of cancer, but irrespective of the knowledge and its clinical application accumulated, a total understanding of the mechanism of cancer development is still required [2]. In recent years, different biomarkers have shown optimistic response and have been utilized for successful prediction of cancer progression. Advances in molecular techniques, genomics, high technology testing have provided

an impetus to the development of novel and valid biomarkers [3]. Likewise, these advancements provide us with a new outlook on the various ways to combat cancer. In this article, we will focus on molecular markers for cancer diagnosis and prognosis.

2. Biomarkers: understanding cancer

Biomarkers are utilized to study the overall process required in the initiation of cancer, i.e. these markers provide a measurement which is helpful in the screening of the cancer. This could be either molecular or clinical utilizing bodily fluids such as saliva or blood. According to the World Health Organization, a biomarker is any substance, structure or process which can be measured so to predict the incidence of outcome or disease [4]. Currently, measurement of gene expression data has been utilized to further classify patients and their disease using biological samples, robust experimental techniques and statistical analytical methods to enhance clinical decision. Furthermore, by analyzing biomarkers, diagnostic study also provides the complete information about the early development of tumors so to detect the cancer at an early stage leading to the management of cancer. The presence-or absence-of a specific biomarker initiates therapeutic options for a patient. Biomarkers are reported to be successful if it diagnosis cancer, predicts or check responses to drugs or therapies and is also helpful in determining cancer remission. Different types of cancer biomarkers are available for detecting, predicting and diagnosing disease. These biomarkers can also assist in personalized prognosis and treatment strategies as well as recurring monitoring of the disease. Presently, scientific and medical

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literature indicates the inadequacy of protein and metabolite biomarkers to detect advanced stage cancers leading to lower survival rates [5]. Advent of novel molecular, genetic technologies is the solution to the above problem as they enhance our ability to predict and detect cancer before it develops at the earliest signs of impending carcinogenic transformation.

Recent progress in developing novel molecular markers for cancer screening has increased *via* genomics, genetic mutations and epigenetic alterations causing initiation of carcinogenic process. Diagnosis of cancer has shifted from the routine diagnostic panel to incorporations of molecular biomarkers; new technologies have allowed high throughput measurements of DNA. These high throughput techniques have provided an impetus to the biomarker research, where mutations, gene expression generate data which are useful for the discovery of biomarkers.

Uncovering the mutations in cancer is the most golden standard method for diagnosing cancer in a patient, thus it has subsequently increased the routine molecular testing of solid tumors. In addition, new insights on acquiring resistance have provided an outlook on the involvement of tumor and personalized treatment options. Molecular testing by far has significantly impacted the basic understanding of the brain tumors as driver mutations in IDH1, chromosomal alterations and DNA epigenetic events have driven the development of routine molecular analysis of brain cancer [5]. Molecular biomarker HER2 (ERB2), a member of the epidermal growth factor receptor (EGFR) is used in clinics for detection of breast cancer [6].

3. Molecular markers: a giant leap

Molecular markers are fragments of DNA, which are genetic signatures for discovering alterations in gene sequences, expression levels and protein structures or functions. Genomics provides a comprehensive study of cancer, which helps in molecular characterization of the tumors. Likewise, advances in molecular techniques have driven cancer biology to next level, such as information's have guided the design of drugs targeted to a relevant molecule. Recent discoveries *via* research projects of International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA) have portrayed molecular markers as a platform for determining various types of cancers through sequencing hundreds of tumors [3].

Development of a molecular marker for cancer requires a good understanding of the type of genes, which are involved in the development of cancer. The process of interrogating these cancer genes necessitates both the requirement of molecular therapeutics and biomarkers leading to the development of medicine for a particular cancer [7]. A recent study has shown that integrating large-scale molecular profiling data to clinical variables yields statistically significant improvements in prognostic estimates for selected cancer patients [8]. Molecular methods have also changed the perspective of how we look on cancer, as these methods have transformed our understanding as well classification based on the microscopic examination. Nowadays molecular analysis of breast cancer is determined *via* molecular portraits which are used to define distinct subtypes

Next-generation sequencing has increased the sensitivity of oncogene panels while maintaining high specificity. Tests assessing the gene expression pattern have shown promising results, with high sensitivity but low specificity.

4. Development of a molecular marker

Molecular markers over the last 10 years have amplified due to the increasing advancements made in understanding the molecular biology of cancer and also the molecular basis of tumor progression and treatment response. There are basically three types of biomarkers which are available: Prognostic markers, Predictive markers and Diagnostic Markers. Prognostic markers evaluate the overall patient's outcome

after standard treatment and it predicts the course of a disease or a response to a therapeutic intervention among patients with the same characteristics, ex. Betatubulin (NSCLC), BRCA1 (Breast Cancer, NSCLC), CA19-9 (Pancreatic Cancer). Predictive markers evaluate the benefit of specific clinical intervention or the differential outcomes of two or more interventions and indicate the sensitivity or resistance to a specific therapy. Ex: EGFR1 (NSCLC, CRC); ER (Breast Cancer). On the otherhand, Diagnostic markers identify whether a patient has a specific disease condition *via* evaluating the sensitivity or resistance to a specific therapy. Ex: A15-3 (breast cancer), CA-125 (ovarian cancer).

Genomic technologies offer the promise of a comprehensive understanding of cancer. These technologies are being used to characterize tumors at the molecular level, and several clinical successes have shown that such information can guide the design of drugs targeted to a relevant molecule [5]. Development of molecular marker is basically based on the DNA sequencing technologies with whole-genome sequence analysis, exome sequencing becoming the most cost-effective method. One of the main barriers to such a progress is identifying the biological indicators or biomarkers, of cancer that predict who will benefit from a particular targeted therapy.

Cancer molecular markers are compared and evaluated using deep sequencing cancer stem cells and circulating tumor cells. Furthermore, molecular markers are assessed for their potential use in clinical settings where, advances in molecular techniques have made it possible to profile and characterize cancer on a molecular basis. This field is revolutionizing cancer treatment and will lead the way to applying these techniques in other disease areas. There are a variety of molecular techniques reported and studied that may be excellent candidates for designing a molecular marker which can monitor and detect early development of the disease. Because of the wide variety of cancers this review is focused on some of the most common cancers.

5. Thyroid cancer

Thyroid cancer represents approximately 3.8% of all new cancer cases and their incidences have increased in the last several decades. It is the most common type of endocrine-related cancer and estimates to 64,330 new cases in 2016 [9]. There are 4 types of thyroid cancer: papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer and anaplastic thyroid cancer. Studies have corroborated that BRAF and RAS point mutations and RET/PTC and PAX8/peroxisome proliferator-activated receptor γ (PPAR γ) rearrangements, constitute to the two most common types of thyroid cancer *viz.*, papillary and follicular carcinoma [10]. Various molecular assays (ThyGenX thyroid oncogene panel, ThyraMIR, ThyroSeq test, ThyroSeq v2) specific for thyroid cancer have been utilized to study and characterize the lesions so to avoid any diagnostic surgery. These include, detection of mutations or gene expression profiles at the transcriptional (messenger ribonucleic acids [RNAs]) or post-transcriptional level (microRNAs).

Most thyroid cancers exhibit somatic point mutations (BRAF) or rearrangements (RET/PTC or TRK) that activate the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3 kinase/protein kinase B pathways [11]. Most well-differentiated thyroid cancers exhibit a single point mutation or chromosomal rearrangement, although two or more mutations are also found in more aggressive tumors [12]. Point mutations like BRAF V600E are very specific where as RAS mutations are also found in benign tumors, limiting their diagnostic specificity. Moreover, genetic alterations in the PI3K/AKT signaling pathway, have a higher prevalence in less-differentiated thyroid carcinomas [13]. Likewise, mutations occurring in TP53 and CTNNB1 genes cause anaplastic carcinomas [14]. TRK proto-oncogenes rearrangement represents another type of chromosomal rearrangement that occurs in papillary thyroid carcinomas [10]. Some of the biomarkers used for thyroid cancer detection are enlisted in Table 1.

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