GAVIN PUBLISHERS

Biomarkers and Applications

Jiancheng Hu and Qiang You. Biomark Applic 2017: 103.

Editorial

DOI: 10.29011/BMAP-103. 100103

Biomarkers and Its Application in Cancer Research

Jiancheng Hu[1] and Qiang You[2]

[1]National Cancer Centre Singapore, Duke-NUS Medical School, Singapore

[2]Department of Biotherapy and Immunology, Nanjing Medical University, China

[*]**Corresponding authors:** Jiancheng Hu, National Cancer Centre Singapore, Duke-NUS Medical School, Singapore, Tel: 65+64368355; Email: hu.jiancheng@nccs.com.sg, Qiang You, Department of Biotherapy and Immunology, Nanjing Medical University, China, Email: Qiang.You@live.com

Citation: Jiancheng Hu and Qiang You (2017) Biomarkers and Its Application in Cancer Research. Biomark Applic 2017: 103. DOI: 10.29011/BMAP-103. 100103

Received Date: 5, May, 2017; **Accepted Date:** 6, May, 2017; **Published Date:** 7, May, 2017

Introduction

Biomarkers are defined as alterations in molecular sequence, expression level, structure or function that associates with a specific biological process [1]. The cancer development is an evolutional process in which cancer cells acquire through genetic alterations capabilities of 'sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling explicative immortality, inducing angiogenesis, and activating invasion and metastasis [2]. Cancer biomarkers consist of oncogenic mutations that drive cancer development, proteins with altered expression that adapt cancer cells to malignant growth and metastasis, and micro environmental factors induced by cancer cells, such as molecules that mediate anti-cancer immunity. Cancer biomarkers play critical roles in early detection, treatment, and monitoring disease progression and therapeutic response.

Biomarkers In Early Detection of Cancers

Cancers, especially solid cancers, have a long period of growth before they reach a size large enough to begin metastasis, invasion and producing symptoms. Early diagnosis is still the most efficient method to cure cancer patients by surgical resection, although remarkable progress has been achieved to reduce cancer mortality by other methods in last decades. Accurate early detection of cancers depends on reliable biomarkers. Biomarkers in blood and other biological fluids hold the best promise for diagnosis of cancers before having symptoms [3]. By using genomic/proteomic analysis and other methods, some potential blood-borne biomarkers have been identified, which include (1) tumor-derived proteins/peptides, DNAs, micro RNAs and metabolites, and (2) antibodies, cytokines, and other anti-cancer immune components .In gastric cancer, these potential biomarkers include C9, fibrino peptide A, apolipo, SERPINA1, ENOSF1, several autoantibody signatures, and cell-free DNA/mi RNA signatures [4]. In breast cancer, CEA, glycol proteins of the MUC family, hsp27, 14-3-3ó, C3a, and auto antibodies against HER2/new, MUC1, or endostatin in serum might function as biomarkers for its early detection [3,5]. In pancreatic cancer, GPC1+ circulating exosomes may serve as a potential non-invasive diagnostic and screening tool to detect the early stage cancer [6].In colorectal cancer, MMP9, TMP-1, CEA, sCD26, methylated Septin 9 DNA and auto antibodies against RPH3AL, SULF1, MUC1, or MUC4 in serum have been reported as potential biomarkers [7]. In lung cancer, blood-based protein, auto antibodies, and mi RNA signatures, have been constructed, which might facilitate its pre-clinical examination [8].

In liver cancer, the elevated levels of AFP-L3, DCP, GPC3, OPN and GP73 in serum have a potential to service as biomarkers in its diagnosis at early stage [9,10].Serum PSA has been approved for pre-clinical screening of prostate cancer, while urine NMP22 for that of bladder cancer [11]. Although the identification of these potential biomarkers sheds a light on the early detection of cancers, it is still a long way to develop valuable biomarkers for early detections of most cancers. Firstly, most of potential biomarkers identified so far still need to be validated by using large-scale cohorts. Secondly, few of these biomarkers reach the standard for widely clinical application: high sensitivity and specificity, noninvasive, and cost-effective. Therefore, there are still a lot of works in the discovery of biomarkers suitable for early diagnosis of cancers in future.

Biomarkers Function As Therapeutic Targets In Cancer Treatment

Cancers are driven by oncogenic mutations/alterations that not only function as diagnosis biomarkers but also are frequently used as therapeutic targets. There are many examples that a cancer driver mutation/alteration functions as both biomarker and therapeutic target in literatures. The classical leukemia biomarker, BCR-Abl is a putative therapeutic target and its inhibitors have been extensively applied to the clinical treatment of this disease [12]. The biomarker of poly cythaemiavera, JAK2 (V617) is a dominant driver of malignancy and services as a promising target in current

drug development [13]. EGFR/Her2, a biomarker of non-small cell lung cancer and breast cancer, has functioned as a critical target for clinical therapy [14,15]. BRAF (V600E), a highly prevalent driver and biomarker in melanoma, papillary thyroid cancer and hairy cell leukemia, has been targeted by RAF inhibitors in clinic treatment [16]. The first oncogenic, Ras, is a dominant driver and biomarker in many cancers, and recent studies have indicated that it is a 'druggable' target for cancer therapy [17]. Besides cancer drivers, those biomarkers that are essential for cancer development can also be good targets for cancer therapy. By using synthetic lethal screenings, this kind of biomarkers has been identified in some type of cancers by recent studies. For example, STK33, TBK1, CDK4 and some other molecules have been shown as potential therapeutic targets for K-Ras mutated cancers, whereas GSK-3β, CDK1, and several other molecules for Myc-driven cancers [18].In addition, some specific biomarkers are pivotal targets for cancer immunotherapy. Recently, regression of all intracranial and spinal tumors in a patient with recurrent multifocal glioblastoma was observed after treatment with chimeric antigen receptor (CAR)-engineered T cells targeting interleukin-13 receptor alpha 2 (IL13Rα2) [19]. Together, biomarkers that contribute to cancer pathologic progression but have no/minor effect on normal cell physiology could be used as targets for cancer therapy.

Biomarkers Monitor Cancer Progression And Therapeutic Response

The pathological progression of cancers companies with the accumulation of genetic mutations/alterations. In the progression of non-small cell lung cancer, the mutations/alterations of ERBB2/Kras/Myc occur at the stage of hyperplasia/dysplasia, those of VEGF/Cox2/AMACR arise in primary tumors, and that of MYO18B emerges in invasive and metastatic tumors [20]. During the development of colorectal cancer, the mutations/alterations of Kras/APC/TGF β occur at the initial stages, whereas that of Bax does at the advance stage [20]. These mutations/alterations appearing at specific stages of cancer could function as biomarkers to monitor cancer progression. BRAF and MMP2 have been shown as early-stage biomarkers in melanoma, while p27 as a late-stage biomarker of this disease [21]. γ-Synucle in and the serum levels of CA15-3, CA27-29, and Her2/NEU have been used as biomarkers for assessing breast cancer progression [11, 22]. Other biomarkers that applied to monitor cancer progression include: serum CA19-9 in pancreatic cancer, serum CA125 in ovarian cancer, serum CEA in colorectal cancer, serum thyroglobulin in thyroid cancer, and urine Fibrin/FDP, BTA, and CEA/mucin in bladder cancer [11]. Most of these biomarkers monitoring cancer progression are altered upon drug treatment, and thus can be used to evaluate therapeutic efficacy of cancer drugs. In addition, some biomarkers could also predict therapeutic response in cancer patients. For instance, BCR-Abl (T315I) and EGFR (T790M) emerge as a biomarker of TKI resistance [23], while Ras mutation or RTK up regulation arises as a biomarker of RAF inhibitor resistance in BRAF (V600E)-driven cancers [24].

In summary, biomarkers have a significant effect on all stages of cancer development and contribute to the diagnosis and treatment of almost all cancers. Unfortunately, the discovery and application of cancer biomarkers progressed slowly due to the conventional laboratory research tools in last decades. We believe that the recent advances in technologies, especially novel high-throughput genomics/proteomics methods, and accurate analytic technologies, would accelerate the research and clinic application of cancer biomarkers.

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