Genetic biomarkers: Potential roles in cancer diagnosis

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Abstract: Biomarkers are indicators of pathogenic processes, typical biological processes, or pharmacological reactions to a therapy. It has several potential usages in cancer; differential diagnosis, prognosis, risk assessment, therapeutic response, and monitoring of disease progression. Recently, advances in oncomarkers raised significant opportunities for enhancing management of cancer. Chromosomal aberration, molecular impairment and epigenetic alteration might be applied to diagnose and prognose cancer and its epidemiology. Some oncomarkers are specific and highly sensitive for detection. An oncomarker might be used to see how the body reacts to an intervention or a situation. The present study represents a short review about various genetic oncomarkers with diagnostic and prognostic values.

Key words: Biomarker; Cancer; Diagnosis; Cytogenetic; Molecular genetics; Epigenetic.

Introduction

The World Health Organization (WHO) defines abiomarker as any traceable or measurable material, process, or structure through the body as well as its product that can affect or prognoses the incidence of disease or outcomes (1). It includes all diagnostic examinations, imaging techniques, and any subjective evaluations of the health state of an individual (1). The biomarker in an oncological sense (oncomarker) is defined as a bio-molecule in tissues, whole blood, or other body fluids that have diagnostic values (1,2). It is an exclusive assayable attribute which would be measured as an indicator of abnormality, normal activity or pharmacological responses (3).

Because of new technologies, scientists are able to study several potential genetic markers and discover new oncomarkers (2,4). Personalized biomarker-related medications depend upon diagnosis, prognosis, and therapy (5). Hence, identification and evolution of oncomarkers are one of the foundations of personalized cancer medicine (5). Six significant malignancies have been proposed by the National Comprehensive Cancer Network (NCCN) to identify the optimal examination that will support patient care (4).

Various studies have classified oncomarkers. Generally, a biologically developed entity or process which leads to a cancer identification at the phase of diagnosis or post diagnosis (in treatment course) is potential prospects of a cancer marker (6,7). Different categories of oncomarkers are applied in early detection, risk assessment, diagnosis, therapy and cancer management (8,9). During the past decades, multiple areas of the technology development and biological sciences have cooperatively proposed various ways for classification of oncobiomarkers (1); but these ways should be interpreted contextually because the biomarker detection is one of the main multidisciplinary features in the biomedical science (1). Oncobiomarkers could be classified based upon different parameters including characteristics and function (5). Type 0 biomarkers are applied to measure the natural history of a disease; Type I biomarkers are linked with the efficacy of pharmacological agents, and Type II biomarkers, known as surrogate endpoint biomarkers, are applied to replace clinical endpoints (5). Current oncobiomarkers may be classified into a variety of classes, including cytogenetic, molecular genetics, epigenetic, proteins, glycoproteins, hormones, antigens, receptors and microorganisms. Prediction and screening oncobiomarker might also be utilized for staging or grading that cancer (1). Oncobiomarkers as shown in Fig.1 can be grouped based upon genomic state and disease state (10).

We studied chromosomes, whole genomes, genes, RNA, proteins, and metabolites through high resolution and much more accessible methodology following the rapid progress of high-throughput technologies and their entry into the biomedical field. Various genomic databases were collected from databases, like GEO from US National Center for Biotechnology Informa-
Cytogenetic markers

Cytogenetic is the science of investigating chromosomes and abnormalities at the chromosomal and subchromosomal levels (11). In cancer, genomic mutations might be detected in a cytogenetic resolution analysis (12).

Chromosomal abnormalities as well as numerical and structural aberrations were considered as conventional oncomarkers since the relationship between neoplastic transmutation and chromosomal abnormalities has been well known (2,13). Chromosomal abnormalities are associated with the major kinds of neoplasms, both non-hematological and hematological, including acute lymphoid leukemia (AML), acute myeloid leukemia, chronic myeloid/granulocytic leukemia (CML), lymphomas, solid tumors and others (13). No well and Hungerford enlisted clinical cytogenetic correlations (14); in Philadelphia chromosome (a recurrent abnormality of chronic myeloid leukemia (CML)), t(9;22)) this correlation is confirmed with the development of banding analyzes (14); in AML, a complex bone marrow malignancy t(8;21), the translocation fuses the gene ETO (encoding the protein CBFA2T1) from chromosome 8 to the gene AML1 on chromosome 21(15). Acute promyelocytic leukemia (APL), a subtype of AML, marked by the reciprocal translocation of t(q22;q12) and t(15;17) presenting in the fusion gene RARA-PML and an oncoprotein that damages myeloid distinction (16). Fusion of IGH-CCND1, t(11;14), is chiefly found in mantle cell lymphoma, but also in plasma cell leukemia, in splenic lymphoma with villous lymphocytes, in B-prolymphocytic leukemia, in multiple myeloma and in chronic lymphocytic leukemia (17). The chimeric gene fusion TEL(ETV6)-AML1(RUNX1), produced through the translocation of chromosomes t(12;21) (p13;q22), was the most common fused gene in pediatric cancer (18). Burkitt’s lymphoma (BL), a heterogeneous family of highly mature B-cell malignancies, commonly correlates with the translocation of t(8;14) (19). Le Beau et al. revealed a relevant correlation of chromosome aberration(inv16) and AML M4 (20).

Variations in chromosome numbers, including hypodiploidy, hyperdiploidy, and aneuploidy, as well as translocations and transferences of sister chromatids might cause structural abnormalities (21,22). In these abnormalities, homogeneously stained regions and double minutes, usually determined in tumor cells, might be considered as oncomarkers (21); for example, in aneuploidy somatic mosaicism occurs in most tumor cells. Trisomy 8 in AML and trisomy 12 in CML (23) are two typical cases for the mosaicism. As another examples, the monosomy of the chromosomes 7 and 17 and 18 are related, respectively, to some myeloid disorders, including AML in children, and breast carcinoma (23, 24).

There are a few procedures to detect oncomarkers for cancers. (A) Jiang et al. cloned and characterized a novel p53 and DNA damage-regulated gene named PDRG1. Furthermore, they proved that PDRG1 is highly expressed in multiple human malignancies highlighting its value as a novel tumor marker. (25, 26). (B) Circulating microRNAs (miRNAs) play an essential role in the development and progression of acute myeloid leukemia (AML). However, miR-217 was identified as an independent marker for the diagnosis and prognosis of AML (27).

DNA marker

Cancer is a genetic disorder which would be occurred by mutation(s) in two types of genes: (1) cancer-preventing tumor suppressor genes and (2) cancer-promoting oncogenes (28, 29) so that it misses its duty (ies) and/or gain new function(s) (30). Both the types are critically regulatory genes which encode cell cycle checkpoints and also participate in retaining terminal division and apoptosis entrance (30), so that the impairments result in uncontrolled cell division (30). Both alleles of the gene should be inactivated, through a recessive mutation, to lose the suppressing function completely (30). Functional alterations in the suppressor genes usually result dysregulation in cell cycle and DNA replication, inhibition of apoptosis, or dissociation tumor cells from immune system (28). Functional impairments of the oncogenes, including the signal transmissions and mitogenic signal executions, occur in hyperactive proliferation and cell growth; mutation in only one of the proto-oncogene alleles can affect downstream events (28, 30). Oncogenes generally behave in dominant fashion (30, 31).

Single nucleotide mutants are essential DNA biomarkers in several genes, for example BRCA1, BRCA2, RAD1 and CYP1A1 in breast cancer, XRCC1, p53 and ATM in lung, head and neck cancers, PGS2 in lung cancer (6). Other major DNA biomarkers include heterozygosity loss, copy-number variations, and micro-satellite instability (MSI) (1,2). Nucleotide mutations in tumor suppressor genes (Rb, p16, p19, p53), tumor promoters (Ras, APC), DNA-repair related genes and cell cycles (cyclins) contribute to diagnosis and prognosis of various tumors (2). The APC gene, a tumor silencer, is inactivated in many cancers; 92% esophageal adenocarcinoma cases, 50% esophageal squamous cell carcinoma cases, and 60% colorectal carcinoma cases show this mutation (2).

Beside nuclear aberrations, mtDNA mutations may act as oncombiomarker (2,21). Human mtDNA consists of 16.5 kb and contains 37 genes encoding 16SrRNA,
12SrRNAs, 22iRNAs, and 13 polypeptides (32). The mtDNA mutation rate is higher than the nDNA one due to lacking mtDNA repairment, the histones, and its sensitivity to reactive oxygen (33,34).

mRNA marker

Generally, the analysis of mRNA expressions and dysregulated processes can represent accurately the carcinogenesis process (35). Nevertheless, the carcinogenic roles and functions of many of these genes are poorly known, and others may be among standard genes that don’t participate in tumorigenesis (36). However, this role can act as oncomarkers due to their unique expression patterns (36). Khaǐlany et al. indicated the mRNA expressions as templates for distinguishing histological subgroups of carcinogenic cells, including clear cells, papillary and chromophobes in renal carcinoma (RCC) (34). The techniques applied to determine oncomarkers at the mRNA expression level might contribute to prognosis, diagnosis, and treatment (37, 38). The knowledge on RNA expression levels is highly dynamic; it can integrate both epigenetic and genetic mechanisms of gene regulation and tell us, as an effectual phenotype, about the functional condition of the cell (39).

Protein marker

Cancer proteomics gives details on probably all the processes that occur in carcinogenic cells, cancer tissue microenvironment and cancer cell-host interaction (2,40). Carcinogenic cells release macromolecules and proteins into cellular fluids, which might be probed as oncomarkers (2). Some of the outputs that enter the blood act as serum oncomarkers (1). Few crucial oncoantigens are diagnostic and prognostic oncobiomarkers like prostate specific antigen (PSA), alpha-fetoprotein (AFP), and cancer antigen 125 (1). Cellular biomolecules such as proteins affect the molecular mechanisms in transformed and normal cells; therefore, compared to previous oncomarkers, proteomic biomarkers are more closely related to carcinogenesis commencement and development (1), and they are more significant than RNA- or DNA-based biomarkers (41).

Protein-depend signatures are derived from the polyacrylamide gel electrophoresis and two-dimensional fluorescence difference gel electrophoresis analysis (1). High performance techniques like mass spectroscopy, matrix-assisted laser desorption/ionizing time-of-flight and reverse phase microarray surface enhanced laser absorption ionizing flight time (1). Recently, nano-particles and quantum dots contribute to evaluate the potential proteins for cancer biomarking (1). Protein molecules are the only FDA-approved biomarkers currently available for medicine (1).

Epigenetic markers

DNA methylation marker

Epigenetic dysregulation is progressively recognized as a cancer hallmark (31). Accumulated data over the past decade suggest that not only genetic alterations but also epigenetic changes play significant roles in cancer (42-44). They are inheritable changes in expression of gene in somatic cells that are directed by other modifications in the primary DNA base sequence (45). Epigenetic regulation usually happens through post-replicative methylation (DNA level), RNA interference, and histone modifications (28, 29).

The preliminary epigenetic indications in carcinogenesis were obtained from DNA methylation and gene expression studies (46,47). DNA methylation definitely affects the processes involved in DNA integrity and function, and it supposedly participates in carcinogenesis (48). These alterations are either causally involved in the transformation process or reflecting the changed physiology of quickly dividing cancer cells (49). The 5-carbon methylation on cytosine residues (5mC) in CpG dinucleotide occurs in the major groove of DNA double helix and can interact with some transcription factors to silence gene expression (50). In addition, some methylated DNA-binding proteins, specially MBD and MECP2 family, attach to methylated cytosine nucleotides and reduce gene transcription (50).

CpG island hypermethylation usually happen during malignant transmutation in70% mammalian promoters (46,50). Therefore, hypermethylation markers might diagnose the commencement and development of cancers (50). For instance, the hypermethylation of p16 promoter strongly relates to repeated colorectal cancer (2). The promoter CpG island hypermethylation more than the hypomethylation of transcription regulatory regions in cancer (51,52). On the other hand, in some cases like tumor development in breast cancer, due to hypomethylation of transcription control sequences, the protease urokinase gene coding is overexpressed (51, 53).

Non-coding RNA markers

A Non-coding RNA (ncRNA) is transcribed from a primary DNA sequence, but it would not be translated into proteins (53). Epigenetic related ncRNAs might be divided into two major groups: short ncRNAs and long ncRNAs. In general, ncRNAs control the gene expression transcriptionally and post-transcriptionally (54). Definitely, both the groups apply same function in targeting DNA methylation, heterochromatin formation, histone modification, and gene silencing.

Short non-coding RNA markers

MicroRNAs (miRNAs), short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs) are the three main classes of short non-coding RNAs. miRNA shave 18-24 nucleotides. By interaction with 3’-untranslated region of mRNA, they have translational inductive roles and have crucial functions in the timeliness of progression (55). They finally regulate target gene expression by corrupting the mRNA and/or suppressing its translation (56). For example, deregulations in miRNAs expression have been determined to participate not only in major cancers like lung, breast, and prostate but also in uncommon cancers like waldenstrommacroglobulinemia and cholangiocarcinoma (57).

Abnormal miRNAs expression in cancers is linked to various processes, including chromosomal abnormality, genetic mutation, polymorphism, epigenetic modification in miRNA biogenesis (5). About50% human miRNA genes are usually located in fragile sites and genetic sequences (2), and elevated frequency of genomic shifts in miRNA loci definitely relates to human melanomas, prostate, colon, ovarian, breast, and
lung cancers (58). Statistically, significant differences have been shown between cancer patients and healthy group, such as breast cancer miR-145, prostate cancer miR-141, and colorectal cancer miR-29a (58). miRNAs might be down- or up-regulated in cancer cells (55), based on their downstream signaling impacts on genes and gene derivatives; the down-regulated miRNAs supposedly can suppress tumors, but the up-regulated ones have oncogenic functions (59).

About 20,000 piRNA (PIWI-interacting RNAs) genes exist in the human genome. Unlike microRNAs, piRNAs interact with PIWI proteins, mainly within the nucleus. They are involved in the epigenetic silencing of transposable elements. piRNAs are expressing in a tissue-specific way within a variety of human somatic tissues. Abnormal piRNA expression is a typical feature among various forms of tumors; their basic carcinogenic roles, however, remain unknown (60,61).

**Long non-coding RNA marker**

Long non-coding RNAs (lncRNAs) are transcripts with more than 200 nucleotides but not any translational potential and coding function (62). They have significant regulatory roles; for example, MALAT, HOTAIR, and H19 express abnormally in some tumors and interfere the hallmark events of tumorigenesis, such as apoptosis, proliferation, and metastasis (62,63).

**Histone modification markers**

Histone residues can become phosphorylated, ubiquitinated, methylated, acetylated, ADP-ribosylated, and sumoylated (58). Covalent alterations of histones can control all DNA-dependent processes (58). Definitely, histone alterations affect the chromatin dynamics and regulation as well as gene expression (58). Because of participation in various carcinogenesis stages, histone modifications are potential biomarkers for the diagnosis and progression (59). The modifications as well as the enzymatic machinery that set them as important regulators can control cellular differentiation, plasticity, proliferation, and malignancy (60).

**Oncomarker based on disease states**

These biomarkers might be classified into four kinds; predictive oncomarkers, prognostic oncomarkers, detection oncomarkers and diagnostic oncomarkers (see Table 1) (2).

### Table 1. Cancer biomarker examples based on Detection oncomarkers.

| Detection Oncomarkers | Methods |
|-----------------------|---------|
| Serology              | Enzyme assays |
| Immunology            | Immunochemistry, radioimmunoassay, Enzyme-linked immunosorbent assay |
| Cytology              | Flow Cytometry |
| Cytogenetic analysis  | Fluorescent in-situ hybridization, Spectral karyotyping, Comparative genomic hybridization |
| Genetic analysis      | Sequencing (automated), Reverse transcription, Gel electrophoresis, DNA micro-array analysis |
| Proteomics            | Surface-enhanced laser desorption/ionization |

### Predictive oncomarkers

Predictive (or response) oncomarkers estimate the probability of benefit of an intervention or the different results of two or more treatments, including toxicity (61). Predictive markers entirely evaluate the effect of a specific medication (62). These markers let clinicians to select a collection of chemotherapeutics for special cases (63,64). For instance, K-ras is a gene that encodes a 21-kDa G-protein with GTPase activity. It is a predictive oncomarker in colorectal cancer who has an important role in the signaling of epidermal growth factor receptor (EGFR), which has a pathogenic function in colorectal cancer (65).

So, this gene mutation may cause resistance to anti-EGFR targeting drugs, such as panitumumab and cetuximab, via alteration and mutation of drug targets (66,67).

### Prognostic oncomarker

The prognostic oncomarkers relates to the carcinogenesis likelihood (68,69,70). A prognostic marker (its presence or absence) might be utilized to select a special treatment but not for prediction of the reply to the treatment (67). As most cancer patients are assisted by adjuvant treatments (for example, post-surgical treatment), prognostic markers might be determinative in prescription of systemic anticancer therapy (71).

### Detection oncomarkers

The detection oncomarkers has been classified into following groups (Table 2). The most commonly used detection on co-markers are serological that used enzymes (72-76).

### Diagnostic oncomarker

Diagnostic oncomarkers may be exhibited in any step during carcinogenesis (1). C-C Motif Chemokine Ligand 11 (CCL11) levels with serum PSA (prostate specific antigen) in prostate cancer are an example which would be exhibited in the primary stages of carcinogenesis (64). Furthermore, a diagnostic oncomarker could be tissue, stage, relapse, serum, urine, and age-specific (77). Hui-Jen et al. proposed that matrix metallopeptidase 13(MMP13) is a highly overexpressed secretion protein in breast tissue, and it is a new diagnostic
Oncomarkers can be used at all stages of a cancer. They are being used to screen people, predict prognosis, and monitor for disease recurrence, but none have been reliable enough to be used on their own; rather, they must be paired with additional tests such as imaging. New molecular tools and technologies are allowing researchers to improve the sensitivity and specificity of these existing oncomarkers, increasing their overall impact on cancer care and limiting the number of tests patients must go through during their cancer (79, 80).

Oncomarkers must be sensitive enough to detect disease at an early stage and eliminate false negatives, but also specific enough to limit the number of false positives. To enable screening of large populations, assays using these oncomarkers must also be non-invasive and cost-effective (79, 81).

To date, oncomarkers are not so sensitive or specific enough to be used on its own for particular cancer screening; costly supplemental tests such as ultrasound or MRI must still confirm any findings. Improving the performance of existing oncomarkers and finding new oncomarkers will help limit the number of tests patients require to detect and confirm disease presence, allowing them to start receiving treatment sooner. Here we choose an example of estrogen receptor. Expression of the estrogen receptor has been established as both a predictive and prognostic biomarker for breast cancer. Tissue samples from patient tumors are analyzed histologically for the presence of this protein. In terms of prognosis, estrogen receptor-positive tumors generally have a better outcome than estrogen receptor-negative tumors. As a predictive biomarker, presence of the estrogen receptor can inform treatment decisions. For example, estrogen receptor-positive tumors can be targeted with treatments like tamoxifen that block hormone receptors. This treatment is ineffective for estrogen receptor-negative tumors that do not express (79, 82, 83).

There are still many challenges that must be overcome before biomarkers can be independently relied on for detection, diagnosis, and prognosis of cancer. Important strategies are being developed to address some of the major limitations of current biomarkers. For example, multi-gene or multi-protein panels are being assembled to improve the sensitivity and specificity of biomarker assays. Liquid biopsies are also being investigated for their ability to capture associations with other cellular processes and already obtainable interventions against undesired growing can create new comings, as combined therapies. The need...
to prepare translational physician-scientists who have a more intense biology of cancer, medical understanding, and the clinical business execution is obvious. Nevertheless, translational utilization of biomarker discovery still has to face its ultimate challenge: consolidation into routine clinical practice.

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