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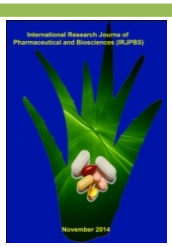

Biomarkers in cancer

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Abstract

Cancer biomarker discovery is eminent due to its anticipated critical role in early diagnosis, therapy guidance, prognosis and monitoring of cancers. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic process, pathogenic process or pharmacologic response to a therapeutic intervention. A biomarker might be either molecule secreted by a tumor or it can be a specific response of the body to the presence of cancer. Recent technological advancement has enabled the examination of many potential biomarkers and renewed interest in developing new biomarkers. This review provides a brief account on various biomarkers for diagnosis, prognosis and therapeutic purposes.

Keywords: Biomarker, Diagnosis, Prognosis, Pathogenic, Therapeutic.

INTRODUCTION

Every year more than 11 million people are diagnosed with cancer. It is estimated that there will be 16 million new cases by the year 2020 [1]. Cancer involves variations in the status and expression of multiple genes that grant a survival benefit and unmitigated proliferative potential to somatic or germinal cells [2]. Cancer cells exhibit a wide range of genetic alterations that include gene rearrangements, point mutations, and gene amplifications, leading to perturbations in molecular pathways regulating cell growth, survival, and metastasis. When such changes testify in most patients with a specific type of tumor, these

can be used as biomarkers for sensing and developing targeted therapies, besides anticipating responses to various treatments [3-5]. Technologies to recognize and understand the signatures of normal cells and how these become cancerous, promises to provide important insights into the aetiology of cancer that can be useful for early detection, diagnosis, and treatment. Biomarkers are therefore priceless tools for detection, diagnosis of cancer, patient prognosis and treatment selection [6]. These are also used to locate the tumour and determine its stage, subtype, and response to therapy.

Biomarkers are referred to every means of tools for quantifiable measurements of biological homeostasis, which distinguish what is abnormal from what is normal [7]. In the simplest form, biomarker also known as molecular marker or signature marker is a molecule that indicates an alteration in physiology from normal. A more practical definition of a biomarker would require clinical utility of this molecule [8]. Cancer biomarkers aids in many areas of cancer biology, for early diagnosis of cancers and also provide important information in cancer therapy such as, verification of cancer staging response to therapy, guidance on therapy, and clinical end points or surrogate end points. Cancer biomarkers lend to the progress in smattering the cancer staging [9]. The United Nations World Health Organization (WHO) defines a biomarker as any substance, structure or process that can be measured in the body or its products and influences or predicts the incidence of outcome or disease (Biomarkers in Risk Assessment: Validity and Validation, Environmental Health Criteria Series, No222, WHO).

The word biomarker was first been used by Karpetsky, Humphrey, and Levy in the April 1977. They reported that the serum RNase level was not a biomarker either for the presence or extent of the plasma cell tumour in the Journal of National Cancer Institute. Part of this success can no doubt be attributed to the fact that the word gave a long overdue name to a phenomenon that has been around at least since the seventh century B.C, when Sushustra, the father of Ayurvedic surgery, recorded that the urine of patients with diabetes attracted ants because of its sweetness. However, although the origins of biomarkers are indeed ancient, it is fair to point out that the pace of progress over the first 2500 years was somewhat less than frenetic [10].

Biomarkers can reduce time factor, cost for Phase I and II clinical trials and are helpful in redefining the diseases and their therapies by moving the vehemence of traditional practices to a more rational objective molecular basis [11]. The pathway related studies are needed for biological identification of cancer. Various complex pathways are responsible for proper regulation of various cell functions need specific attention to particular part of the pathway. In every pathway there are number of component playing role in regulation. Study of only one component is not an easy task what possible is a comparative study with two or more component. In the process of carcinogenesis biomarkers can be identified (Figure 1) and track the event in early stage [10].

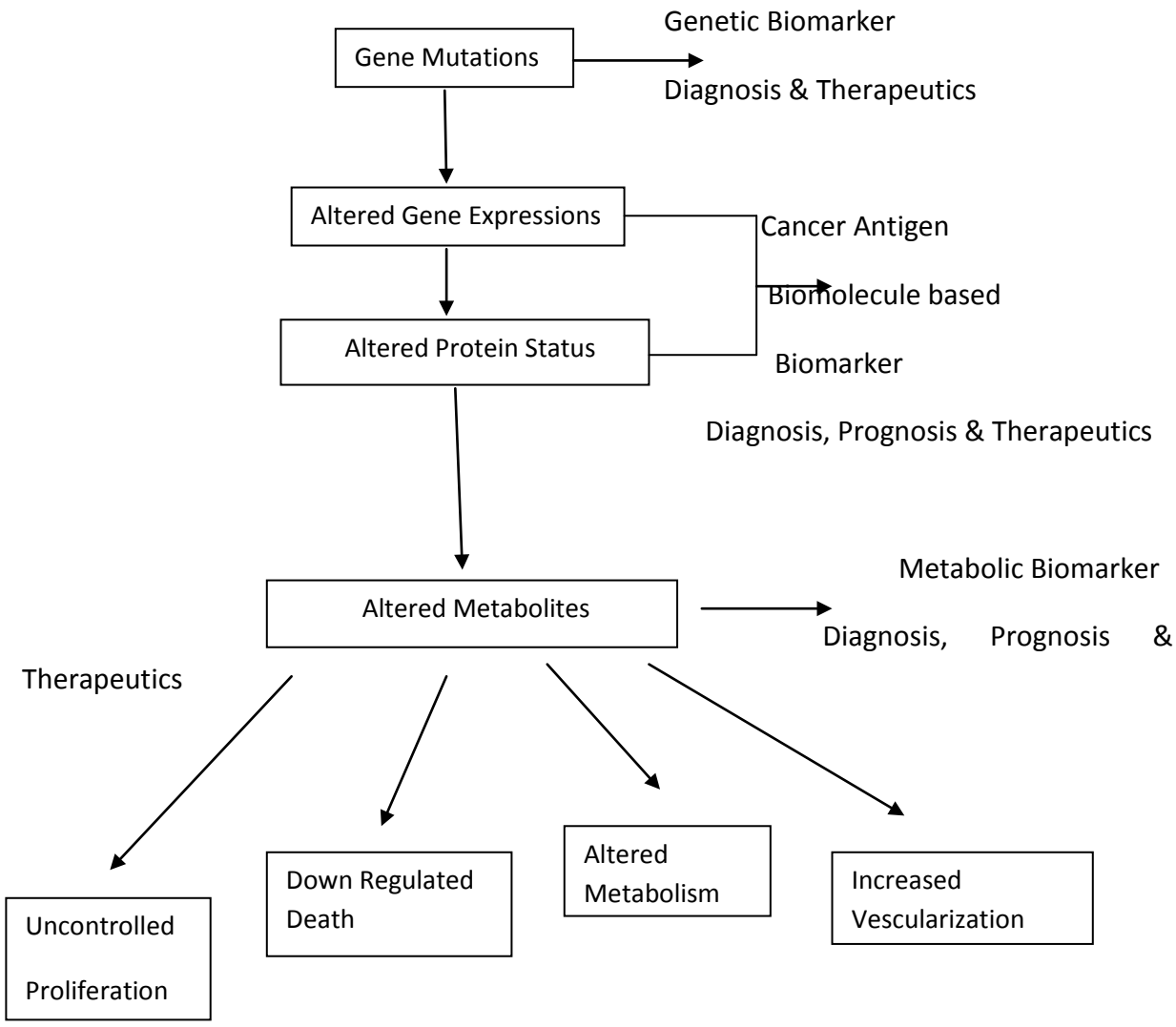

Figure 1: The process of carcinogenesis & possibility for biomarker identification

Biomarkers are broadly used in the development of oncology drugs and many experiments have been performed with interesting results based on biomarkers. The widespread occurrence of the disease is the prima cause that results in the use of cancer biomarkers in drug development and discovery. The demand for cancer biomarkers is also increasing because of their ability to trace the exact type of cancer and to target patient-specific molecular structure.

Biochemistry of biomarker

Biomarkers are used to develop targeted therapies, prognosticate the risk for cancer, and anticipate how well a person is likely to responds to cancer treatment. For example, cholesterol, a fatty substance is a biomarker for heart disease which is produced by the body. A doctor can determine cholesterol level from the blood sample to predict the risk of having heart attack. If doctor recommends anticholesterol medication, the cholesterol level

can be measured to determine whether the drug has lowered cholesterol and reduced the risk for having a heart attack. Biomarkers are used to manage cancers and for other kind of diseases in the same way [12]. Biomarkers are tests that can be used to follow body processes and diseases and to predict how a patient responds to a medicine or whether they are likely to develop a certain disease. For example, the chemical levels in the fluid that surrounds the brain indicate the likelihood that a patient with mild memory problems will develop dementia due to Alzheimer's disease [3]. Various assay methods are needed to measure the biomarker and one biomarker can have multiple assays that are capable of measuring the biomarker assay method performance characteristics which is important. Biomarkers are qualified for a specific context of use a context of use is a comprehensive statement of the manner and purpose of use, including how to apply results to decision making [14]. New biomarkers of impregnability and effectively are becoming powerful tools in drug development. Their application can be exaggerated if an accord can be established about their eligibility for regulatory applications [15]. For the ongoing knowledge in biomarker recognition, an occult is linked with professional debate initiated at the level about whether qualification for specific biomarkers should be discussed. While a biomarker must be defined both as a test measurement as well as a preclinical or clinical interpretation of the result from this measurement, professional debate disorients measurement with interpretation. For example, the detection of a specific molecular species is frequently addressed in isolation from the elucidation of this perception in a particular preclinical or clinical context. The International Life Science Institute Health and Environmental Sciences Institute (ILSI/HESI) formed a technical committee for the development and application of biomarkers of toxicity [16]. This committee has focused on data rendered by its members to better under-stand the analytical and preclinical performance of biomarkers of toxicity, with an initial focus on troponins and biomarkers of nephrotoxicity [17].Working of biomarkers can be understood with CA 125 which is biomarker for Ovarian Cancer). The investigators attached an antibody that binds to the cancer biomarker CA 125. When solutions with known concentrations of CA 125 were applied to the biosensor, the device accurately measured concentrations as low as 1 "enzymatic unit" per milliliter (U/mL) of solution to as high as 1,000 U/mL. The maximal normal blood level of CA 125 is considered to be 35 U/mL. The researchers obtained identical results when they tested human blood plasma for CA 125 levels [18].

Like CA 125 the working mechanism of biomarker C12 protein chip for multi-tumour marker detection system can be understood with the help of Biomarker C12 is based on specific binding of antigens to antibodies; multiple antibodies are immobilized on solid matrix, to capture the specific tumour markers in serum samples. The concentrations of tumour markers are determined quantitatively through a chemiluminescent mechanism [19]. Biochemistry or working of biomarkers are different and can vary case by case like in above situation where working based on antibody antigen interaction.

Classification of Cancer Biomarkers

Several attempts have been made to define and classify cancer biomarkers but general consensus has yet to be established. Different methods have been proposed due to increased knowledge in the field of biomedical sciences and technology development to classify cancer biomarkers [20]. But these classifications should be considered contextual as identification of cancer biomarkers is one of the major multidisciplinary areas of the biomedical field. A schematic for the classification of biomarkers is shown in Figure 2. An attempt has been made to classify cancer biomarkers according to contemporary findings. However some of the biomarkers in the following categories are overlapping in nature, *i.e.*, biomarkers for cancer screening and prediction might also be useful for cancer grading or staging [21].

Biomarkers can be divided into the following categories based on their utility:

1) Early detection – if used for screening patients to find cancer early;
2) Diagnostic – if used to assess the presence or absence of cancer;
3) Prognostic – if used to assess the survival probabilities of patients or to detect the aggressive phenotype and determine how the cancer will behave;
4) Predictive – if used to predict whether the drug and other therapies will be effective, or to monitor the effectiveness of treatment; and
5) Target – if used to identify the molecular targets of novel therapies and which molecular markers' expression were affected by therapy.

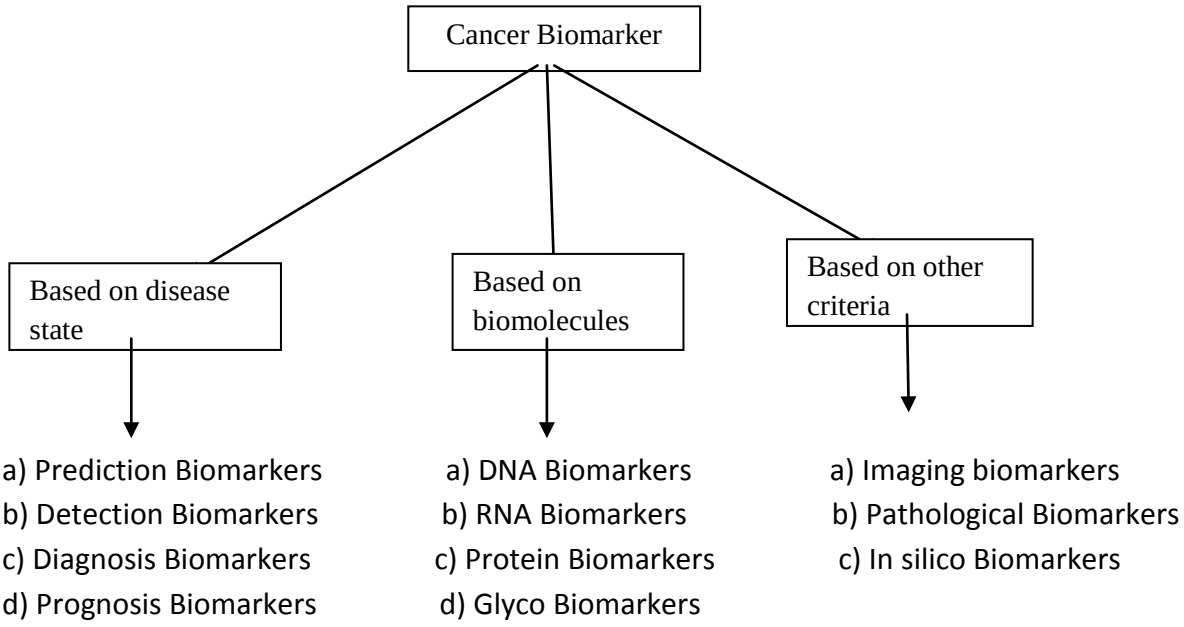

Figure 2: Classification of Biomarkers

Cancer Biomarkers on the basis of biomolecules

1. DNA: Single nucleotide polymorphisms (SNP) are major DNA markers, including *XRCC1*, *ATM*, *p53* (lung, head, and neck cancers); *CYP1A1*, *RAD1*, *BRCA1* and *BRCA2* (breast cancer); and *PGS2* (lung cancer). Other major DNA markers include loss of hetrozygosity (LOH); variation in copy number of genes; chromosomal aberrations at a gross cytogenetic level, such as translocation/fusion (BCR-ABL, PML-RARA translocation in leukemias), micro-satellite instability (MSI), and epigenetic modifications [22]. Mutation(s) in DNA nucleotides in tumor promoters (*Ras*, *APC*), tumor suppressors (*p16*, *p53*, *p19*, *Rb*), cell cycles (cyclins), and DNA-repair related genes (*XRCC*) have been associated with prognosis and diagnosis of different cancers, although their clinical implications have yet to be established. The source of DNA may be from tissue, serum, sputum, saliva, bronchial tear, cerebrospinal fluid (CSF), and tumor cells circulating in the blood, bone marrow, and nipple aspirate [23]. Interestingly, besides nuclear aberrations, alterations in mitochondrial DNA (mtDNA) molecules are also approved as biomarkers for various cancers. Epigenetic modification of nucleic acids and associated proteins (histones and non-histones) are important in carcinogenesis [24]. Histone deacetylation, lysine-specific histone-H3 methylation, and promoter region CpG methylation modulates transcription of tumor-suppressor genes (*CDKN2A*, *TP53*, *APC*, *BRCA1*); DNA mismatch-repair genes (*MLH1* or the *O6-methyl-guanine-DNA methyltransferase gene*, *MGMT*). Gene silencing by CpG methylation is the optimal characterized epigenetic modifications till date [25]. The degree of methylation in prostate cancer tissue, sputum/serum from patients with lung cancer, and saliva in those with oral malignancies are directly implicated in the severity of the lesions.

2. RNA and Micro RNA (miRNA): The methods commonly used to detect cancer biomarkers at the RNA expression level are Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR), Serial Analysis of Gene Expression (SAGE), differential display, bead-based methods, and microfluid card and micro-array analysis [26]. Pure RNA signature acquisitions are attempted by laser capture-based microscopy in different grades and stages of therapy. Comparative analysis of RNA expression in terms of heat maps, supervised-algorithms, and snapshots are coupled with diagnosis and prognosis. Micro RNAs (miRNAs) are small non-coding RNAs whose expression in a tissue- and time-dependent manner is associated with clinical characteristics for several cancer types, such as leukemia, breast, prostate, colorectal, hepatic, lung, and pancreatic cancers [27]. miRNA expression profiles can be used for the classification of human cancers, which also which also advocate that a correlation exists between disease prognosis and therapeutic outcome. The area of metastasis-associated miRNA markers in relation to oncogenesis is expanding rapidly and these markers have recently been referred to as “metastamirs” [28]. miRNA can act as a tumor suppressor as well as an oncogene [29]. For example, miR15a is a suppressor for *Bcl-2* in chronic lymphocytic leukemia (CLL), prostate cancer, and myeloma. let-7 is a suppressor for *RAS* in lung and gastric cancers and mir17 and mir21 clusters modulate *PTEN*, *TGF-RII* and are oncogenic for many lymphomas; blastomas; and prostate, breast, and lung cancers.

The miRNAs are potentially used as biomarkers for diagnosis, prognosis, stage, risk stratification and prediction, and drug- responses in patients with cancer.

3. Protein Markers: Protein-based markers are valuable biomarkers than DNA- or RNA-based markers because proteins are the main executioner bio-molecules in cells [30] . As the protein molecules determines the molecular pathways in normal and transformed cells; therefore, proteomic markers are more pertinant to the disease state initiation and progression. Protein-based signatures are derived from the techniques of classical two-dimensional (2-D) fluorescence difference gel electrophoresis (DIGE); polycarylamide gel electrophoresis (PAGE); and high throughput platforms, such as Mass Spectroscopy (MS), Matrix Associated Laser Absorption Desorption Ionization Time of Flight (MALDI-TOF), Surface Enhanced Laser Absorption Desorption Ionization Time of Flight (SELDITOF), and reverse phase microarray [31]. Quantum dots and nanoparticles are recent additions to the technologies available to assess the potential of protein molecules as cancer biomarkers [32].

Quantitative proteomics have been utilized to discover cancer biomarkers in different organ sites, such as Stable Isotope Labeling with Amino Acids in Cell culture (SILAC) for prostate cancer [33] ; iTRAQ for leukemia [34]; Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS); antibody arrays [35]; bead suspension arrays for cervical and ovarian cancers; and aptamer arrays for breast, lung and colorectal cancers[36].

4. Carbohydrate biomarkers: During the progression of some cancers, the expression of certain N-linked and O-linked glycans changes which serve as candidate biomarkers for cancer detection [37]. Mass spectrometry is generally used to detect disease-associated carbohydrate markers. Tissue samples and biofluids (serum, cerebrospinal fluid, pancreatic fluid, lavage) are worthy for detection of breast, colon, ovarian, pancreatic, lung and colon cancers [38]. Serum glycomics is used to detect esophageal cancer [39]. The glycomarkers (glycoproteins, proteoglycans and glycolipids) are more stable than RNA and proteins, therefore they are highly fitted for epidemiological studies where human populations can be who are highly at risk to develop cancer in their lifetime. Profiling O- and N-linked glycosylation of protein molecules at serine and threonine residues by MALDI-TOF and Electrospray Ionization (ESI) in human sera, tissue and cancer lines are an important approach to detect glycanbased cancer biomarkers. Increased branching and altered terminal structures of glycans are due to modulated expression in glysyltransferases (sialyl and fucosyl-transferases). The most common terminal glycan moieties found in cancer cells are sialyl Lewis x (sLex), sialyl Tn (sTn), Globo H, Lewis y (Ley) and polysialic acid, as described in the literature [40]. Many O-linked glycans are not present in ovarian cancer patients' serum, therefore, it is important to note that neoexpression of glycans as well as altered expression can serve as potential cancer biomarkers [41].

5. Pathogenic cancer biomarkers: Various infectious agents particularly viral infections adds to 15-20% of all human cancers. The presence of viruses with specific tumors makes them highly attractive virus biomarkers [42,43] .The presence of Epstein Bair virus (EBV) is linked with nasopharyngeal carcinoma and lymphoma whereas HPV is associated with cervical , head and neck cancers. The bacterial infection by Hellicobacter pylori (H.pylori) causes a chronic low level inflammation of the stomach lining. H.pylori infection is related to the development of duodenal and gastric ulcers and is an established biomarker for gastric cancer [44,45] .

Biomarker	Tumor	Application
PSA	Prostate cancer	Diagnosis & prognosis
α-Foetoprotein	Hepatocellular carcinoma	Diagnosis & prognosis
Human chorionic gonadotrophin	Ovarian cancer	Diagnosis
Thyroglobulin	Thyroid cancer	Diagnosis & prognosis
Heat shock proteins	Gastric & prostate cancer	Diagnosis & prognosis
Hsp27, Hsp70	Uterine, cervical, bladder cancer	
TGF-β	Malignant tumor	Diagnosis & prognosis
CTC	Breast cancer	Diagnosis & prognosis
Cancer stem cells	Brain tumor, breast & prostate cancer	Therapeutic
APC gene	Stomach, pancreas, thyroid, ovary cancer	Diagnosis & prognosis
FGFR2	Breast cancer	Prognosis
PTEN	Breast cancer	Prognosis
RARA	Breast cancer	Prediction of drug response
STAT3	Breast cancer	Prediction of drug response
PIK3CA	Breast cancer	Prediction of drug response
TIMP1	Breast cancer	Prediction of drug response
B2M	Ovarian cancer	Diagnosis
TP53	Ovarian cancer	Prognosis
M-CSF	Ovarian cancer	Diagnosis
CD34	Ovarian cancer	Prognosis

Table 1: Cancer biomarkers for diagnosis and prognosis of disease

6. Imaging Biomarkers: Current imaging techniques, such as x-ray, computed tomography (CT), ultrasound, radionuclide imaging, and Magnetic Resonance Imaging (MRI), commonly ued for screening and diagnosis of cancer, including disease staging, and determining the effectiveness of cancer therapy and monitoring disease recurrence [46]. Attempts have been made to correlate PSA expression with bioimaging data in prostate cancer. Mammograms are widely used for screening women over age 50 for the detection of breast cancer. According to a recent report from American Cancer Society (ACS), the rate of breast cancer has declined due to screening practice. Colonoscopy is done regularly for screening populations at high risk of developing colon cancer.

Biomarker	Type	Cancer	Clinical use
α-Fetoprotein	Glycoprotein	Testicular	Staging
Human choronic gonadotrophin		Testicular	Staging
CA 19-9	Carbohydrate	Pancreatic	Monitoring
CA125	Carbohydrate	Ovarian	Monitoring
CEA	Protein	Colon	Monitoring
Epidermal growth factor receptor	Protein	Colon	Selection of therapy
Thyroglobulin	Protein	Thyroid	Monitoring
CA15-3	Glycoprotein	Breast	Monitoring
CA27-29	Glycoprotein	Breast	Monitoring
Cytokeratins	Protein	Breast	Prognosis
NMP22	Protein	Bladder	Screening & Monitoring
Fibrin/FDP	Protein	Bladder	Monitoring
BTA	Protein	Bladder	Monitoring
HER2/NEU	Protein	Breast	Prognosis & Monitoring
PSA	Protein	Prostate	Selection of therapy, Screening, Monitoring

Table 2: USFDA approved cancers biomarkers [47]

Cancer Biomarkers for selected organ sites

Breast cancer: Estrogen receptor ER, Human epidermal growth factor 2 are the biomarkers for breast cancer. The oncogene HER2 is the target of monoclonal antibody trastuzumab, and HER2 amplification predicts for a good response to anti HER2 therapy. Ki67, a marker of proliferation has a strong prognostic effect and appears to predict for a good response to systematic chemotherapy. ERα expression is the significant biomarker as it provides the index for sensitivity to endocrine treatment. ERβ has been proposed due to primary down regulation in breast cancer as compared to normal breast tissue [48]. Biomarkers urokinase dependant plasminogen activator system (µPA), plasminogen activator inhibitor (PAI), & the Thomsen- Friedenreich (TF) antigen have also gained significant importance. Biomarkers mammaglobin, osteopontin , snail, twist, Zeb1, fibroblast growth factor receptor (FGFR), Phosphatase & tensin homolog (PTEN) and sirtuins (SIRT) are used for the prediction of metastatic disease [49]. A number of genetic markers such as BRCA1/BRCA2, p53, ras (k-ras), PTEN, MDM2 are associated with breast cancer susceptibility [50] . The evaluation of ER, progesterone receptor (PgR), Ki67 & human growth epidermal growth factor is common in clinical practice for prognostic purposes & treatment decisions [51] .

Ovarian cancer: The cancer antigen 125, CA125/MUC16 is widely used clinical biomarker for ovarian cancer. The USFDA has approved the assay kit having a panel of five biomarkers consisting of transthyretin, apolipoprotein A-1, β-2 microglobulin, transferring & CA-125. Biomarker prostatin /PRSS8 is over expressed in the sera of patients with epithelial ovarian cancer, and the combination of prostatin & CA125 provides detection sensitivity of 92% and specificity of 94% for ovarian tumors. Other serum markers reported to monitor ovarian cancer are MMP, MIF, EGFR, macrophage colony stimulating factor (M-CSF) and follicle stimulating hormone (FSH) [52]. Micro RNS signatures of tumor derived exosomes are used as diagnostic biomarkers for ovarian cancer. mi RNAs frequently over expressed in ovarian cancer are miR93, miR106b, miR155, miR200a/b/c, miR221/221 and miR372/373; that are under expressed miRNAs include miR15/16, miR140, miR145. A marker gaining observance for its potential role in the early diagnosis of ovarian cancer is human epididymis secretory protein 4 (HE4) [53].

Pancreatic cancer: The biomarker approved by FDA for pancreatic cancer is carbohydrate antigen 19-9 (CA19-9) which has been used since 1980s as a marker for recurrence & progression [54]. TGFBI transforming growth factor beta induced, latent transforming growth factor beta binding 2 (LTBP2) and aspirin ASPN were investgated by immunohistochemistry and found to be over expressed in pancreatic cancer tissues. STML2 is a member of oncogenic related protein which is over expressed in several cancers. ANXA4 is suggested to be implicated in proliferation, migration and chemoresistance of cancer cells. CD9 is involved in cel adhesion, signal transduction and also plays role in the suppression of cancer cell motility & metastatisis. Cf nucleosme profiles are also used for the early

detection of pancreatic cancer because of their rich variety of potential epigenetic features available which can allow fine tuning of sensitivity & specificity [55] .

Lung cancer: The protein biomarkers such as CA-125, CA19-9, CEA, CYFRA21, chromogranin A, NSE & TPS are found to be noninvasive & cost effective diagnostic tool for early stage lung cancer. Recently new group Micro RNAs (miRNAs) such as miR-20a, miR-223, miR-21, miR-155, miR145 have been discovered for NSCLC. Small nucleolar RNA (snoRNA), which are expressed in all tumor tissues are used as biomarkers for the early detection of lung cancer [56]. An oncofetal protein, carcinoembryonic antigen CEA is elevated in adenocarcinoma and large cell lung cancer. CEA is used in conjugation with CYFRA. CYFRA-21-1 proteins are indicators of increased level of cytokeratin 19 fragments that implies the presence of lung cancer. Protein releasing peptide ProGRP is lung cancer biomarker for small cell lung cancer. Plasma kallikrein B1 (KLKB1) is a potential biomarker in diagnosis of lung adenocarcinoma. Some studies suggest that TTF-1, Pax-9 and Nkx-8 amplification at DNA level plays a role in lung cancers. Hypermethylation of p16, RARB, DAPK genes may predict development of lung cancer.

Medullary thyroid carcinoma: Plasma calcotonin & CEA are widely used biomarkers for MTC. Germline RET mutations are used in the diagnosis & timing of treatment of hereditary MTC whereas somatic RET mutation may serve as a prognostic biomarker in sporadic MTC [57].

Liver cancer: Cancer stem cell markers are useful for hepatocellular carcinomas in prognostic estimation and for targeted specific therapy. Cancer stem cell markers for hepatocellular carcinoma include epithelial cell adhesion molecule EpCAM, CD133, CD90, CD44, CD24, CD13 and oval cell marker OV6 [58]. micro RNAs, a class of noncoding RNAs made of 15-25 nucleotides are novel biomarkers in the diagnosis & prognosis stratification of HCC. Serum GP73 is a valuable biomarker for patients with HCC. The GP73 level significantly increased in patients with HCC compared with healthy controls, decreased following surgical resection of HCC lesions and increased with tumor recurrence. The plasma miRNA panel (miR122, miR192, miR21, miR223, miR26a, miR27a, miR801) is used for early diagnosis of HCC [59]. Circulating biomarker serum AFP is used for diagnosis & surveillance of HCC and has been suggested as an independent indicator for prognosis. Other circulating factors such as Ang2, VEGF, HGF, TGFβ are also independent factors for prognosis.

Prostate cancer: A number of PCa biomarkers have been known such as α-methylacyl CoA, racemose (AMACR) also known as P504S [60]. Prostate cancer antigen PSA, a 33 KDa serine protease is the most studied biomarker in prostate cancer. Among kallikreins, hK2, hK3 expression is highly restricted to the prostate in males and are therefore used as biomarkers [61]. Normal prostate cancer cells produce serum biomarker PSA in small amounts but higher the PSA in the serum the higher the possibility of prostate cancer. PCGEM1, prostate cancer gene expression marker is the earliest oncogenic lncRNA discovered; plays an important role during carcinogenesis & a specific biomarker for prostate cancer [62]. The

autoantibody biomarkers has recently been developed for the detection of prostate cancer through the use of interative biopanning & phage protein microassays; where multiple autoantibody biomarkers are used for screening prostate cancer [63].

Bladder cancer: A urinary marker seems o be promising tools for diagnosis and follow up of bladder cancer. The expression levels of Aurora-A mRNA in bladder cancer tissues have found to be higher than nontumor tissues. Expression of p16INK4a has been suggested as a sensitive marker for urothelial carcinoma. Several mRNA markers have been proved to be involved in pathogenesis of cancer. Numerous down regulated and up regulated miRNAs have been determined. Several miRNAs including miR145, miR143, miR125b are down regulated in bladder cancer and known to be tumor supressors, while miR183, miR96, miR7-5p & miR20a are up regulted in bladder cancer and have oncogenic properties. USFDA has approved protein biomarkers BTA & NMP22 for detection of bladder cancer. Protein biomarkers including carcinoembryonic antigen CEA, BTA, d-dimer, FAS, interleukin (IL)- IL6, IL8 and vascular endothelial growth factor (VEGF) have shown remarkable different levels in bladder cancer [64] .

Oral squamous cell carcinoma: The prima cellular biomarkers for oral squamous cell carcinoma are epidermal factor receptors (EGFRs), cyclin D1, cyclin B1, Ki67, proliferating cell nuclear antigen PCNA and Akt1. The EGFR family includes four members : HER1, HER2, HER3,HER4. All these biomarkers are cell cycle progression and proliferation biomarkers. Tumor suppression and apoptosis biomarkers for OSCC are p53/p63, p21/p27, Bcl2 family members, the retinoblastoma proteins Rb and survivin. The tumor suppressor p53 is one of the most studied biomarkers and its high expression is detected at advanced stages of carcinogenesis. Survivin is an inhibitor of apoptosis and over expression in most of OSCC indicating a potential biomarker of aggressiveness and invasiveness. The combined expression of EGFR, cyclin D1, p53, cyclin B1 is helpful in anticipting occult cervical lymph node metastasis in OSCC [65].

Colorectal cancer: Biomarkers to improve CRC diagnosis, prognosis and prediction of treatment response therefore represent opportunities to improve patient outcome. Carcinoembryonic antigen CEA is the widely used marker for CRC in clinical practice. Tumor biomarkers identified in CRC tissues have been used to guide chemotherapy regimens and include the Kirsten rat sarcoma viral oncogene homolog (KRAS), v.raf murine sarcoma viral oncogene homolog b (BRAF), micro stallite insability (MSI) and sma and dad related family member 4 (SMAD4) [66].

HIV associated cancer: Kaposi sarcoma is the most common malignancy in HIV patients. HIV associated Kaposi sarcoma is a low grade vascular tumor associated with human herpes virus. The biomarkers used in HIV/KS diagnosis/ prognosis are cyclin D1, Bcl 2, HV8, LANA1, CD31, CD34, oncostatin M, TNF-α, VIL6. The biomarkers used in HIV/NHL diagnosis and prognosis are LDH, CD19, CD20, Bcl6, IL6, CRP, TNFα, B2M, FLC, FOXP1, cMYC, CXCLI3 [67].

CONCLUSION

Discovery and clinical applications on new biomarkers is expected to play a significant role in reshaping life science research and life science industry, thereby influencing the detection and treatment of many diseases and cancer in particular. The resultant panel of biomarkers will not only help in the detection and diagnosis but also answer fundamental questions about biologic behaviours of tumors, resistance to therapy and sensitivity to therapy, besides identifying individuals predisposed to cancer. The future of cancer therapy lie in the use of biomarkers that offer potential to identify and treat cancer before it is either visible or symptomatic. A comprehensive understanding of the relevance of each biomarker will be very important to efficiently diagnose the disease and provide appropriate direction in the multiple therapeutic alternatives currently available that is likely to benefit the unfortunate patients. In closing, biomarkers offer great potential for improving management of cancer at every point from screening and detection, diagnosis, staging, prognosis, and assessment of treatment response.

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